Published in final edited form as:
Adv Virus Res. 2012 ; 83: 219–298. doi:10.1016/B978-0-12-394438-2.00006-2.

Bacteriophage Protein–Protein Interactions

Roman Häuser[*,†], **Sonja Blasche**[†], **Terje Dokland**[‡], **Elisabeth Haggård-Ljungquist**[§], **Albrecht von Brunn**[‖], **Margarita Salas**[¶], **Sherwood Casjens**[#], **Ian Molineux**[**], and **Peter Uetz**[††]

Peter Uetz: peter@uetz.us

[*]Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Karlsruhe, Germany

[†]Deutsches Krebsforschungszentrum, Heidelberg, Germany

[‡]Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama, USA

[§]Department of Genetics, Microbiology and Toxicology, Stockholm University, SE-106 91 Stockholm, Sweden

[‖]Max-von-Pettenkofer-Institut, Lehrstuhl Virologie, Ludwig-Maximilians-Universität, München, Germany

[¶]Centro de Biología Molecular “Severo Ochoa” (CSIC-UAM), Cantoblanco, Madrid, Spain

[#]Division of Microbiology and Immunology, Pathology Department, University of Utah School of Medicine, Salt Lake City, Utah

[**]Molecular Genetics and Microbiology, Institute for Cell and Molecular Biology, University of Texas–Austin, Austin, Texas, USA

[††]Center for the Study of Biological Complexity, Virginia Commonwealth University, Richmond, Virginia, USA

Abstract

Bacteriophages T7, λ, P22, and P2/P4 (from *Escherichia coli*), as well as ϕ29 (from *Bacillus subtilis*), are among the best-studied bacterial viruses. This chapter summarizes published protein interaction data of intraviral protein interactions, as well as known phage–host protein interactions of these phages retrieved from the literature. We also review the published results of comprehensive protein interaction analyses of *Pneumococcus* phages Dp-1 and Cp-1, as well as coliphages λ and T7. For example, the ≈55 proteins encoded by the T7 genome are connected by ≈43 interactions with another ≈15 between the phage and its host. The chapter compiles published interactions for the well-studied phages λ (33 intra-phage/22 phage-host), P22 (38/9), P2/P4 (14/3), and ϕ29 (20/2). We discuss whether different interaction patterns reflect different phage lifestyles or whether they may be artifacts of sampling. Phages that infect the same host can interact with different host target proteins, as exemplified by *E. coli* phage λ and T7. Despite decades of intensive investigation, only a fraction of these phage interactomes are known. Technical limitations and a lack of depth in many studies explain the gaps in our knowledge. Strategies to complete current interactome maps are described. Although limited space precludes detailed overviews of phage molecular biology, this compilation will allow future studies to put interaction data into the context of phage biology.

Correspondence to: Peter Uetz, peter@uetz.us.

I. INTRODUCTION

Bacteriophages have been extremely important model systems in molecular biology. They were critical to many breakthrough discoveries, such as the nature of the genetic material (Hershey, 1952), the structure of genes and genomes and the first genome sequence (Sanger *et al.*, 1977), recombination (Kaiser and Jacob, 1957), transcriptional regulation (e.g., Roberts, 1969), and many others. In addition, phages have become important technical tools in molecular genetics and nanobiology, but these aspects are not reviewed here.

A great deal of work has been invested in learning the mechanistic details of the life cycles of a number of phages, including those described in this chapter. Although phages are tiny biological systems, surprisingly, not even the biology of main "model system phages" is completely understood. Despite a plethora of papers, few comprehensive summaries exist of the molecular interaction events that occur in both phage gene regulation and virion assembly. As in all organisms, protein–protein interactions (PPIs) play a fundamental role in phage biology. PPIs are important in all virus-related processes, including host infection, transcriptional regulation, DNA replication, virion assembly, and lysis. Current protein interaction databases (Lehne and Schlitt, 2009) have consistently neglected phage interactions. For instance, Intact, one of the most comprehenisve databases for protein–protein interactions, listed only 22 interactions for Caudovirales, the only phage group represented at the time of this writing (April 2011). We have thus attempted to compile such information for several phages that infect Gram-negative hosts, including λ, T7, P22, and P2/P4, as well as others that infect Gram-positive bacteria, specifically ϕ29, Dp-1, and Cp-1 (Table I). Coliphage T4 is one of the best understood of all the obligate lytic phages. T4 has been an outstanding model for phage biology, particularly for DNA replication, control of transcription, and virion assembly. Unfortunately, this chapter cannot discuss the extensive T4 PPIs here for reasons of space. Many of the small DNA phages, such as ϕX174 or M13, have been very well studied, but because of their tiny proteomes they do not have many protein–protein interactions. It would be highly desirable to establish their PPIs so that more comprehensive analyses of phage systems biology would be possible. Nevertheless, it is hoped that this chapter proves useful to the phage community and encourages similar compilations for other phages. The interactions collected for this chapter are available in Intact (http://www.ebi.ac.uk/intact/) for easy access.

II. METHODS USED TO DETECT PROTEIN–PROTEIN INTERACTIONS

A. Genetic detection of interactions

Methods used to study protein–protein interactions in phages have evolved over the decades. A few important methods are illustrated in Figure 1. In the beginnings of phage molecular biology, detection of genetic interactions dominated. For instance, certain mutants in the λ *J* gene abolished virion binding to host *Escherichia coli* cells. Similarly, mutants of the *E. coli* gene *lamB* made the cells resistant to λ infections. From such experiments it was concluded that J protein bound to LamB and that LamB was the λ receptor. This hypothesis has been confirmed by isolating compensatory mutations in both genes that regenerate the interaction (Werts *et al.*, 1994).

B. Electron microscopy

Another important method for the investigation of physical relationships between phage components is electron microscopy, especially in combination with genetic analysis. Mutants often have an aberrant morphology. If certain structures are missing in the mutant virion, it can be concluded that the mutated gene encodes this structure or is at least involved in its assembly. For instance, many laboratory strains of λ harbor a frameshift mutation in the *stf* gene, and these mutants lack side tail fibers (Hendrix and Duda, 1992). Many such

studies not only showed which genes encode which proteins, but also indicated how the proteins interact (e.g., when particular structures could be “removed” from the virion by defined gene knockouts).

More recently, many bacteriophage capsids and phage protein complexes have been analyzed by cryoelectron microscopy and three-dimensional reconstructions. This technique gives resolutions approaching that of X-ray crystallography, especially for proteins present in symmetric arrays in the virion, and has proven ideal for analyzing protein–protein interactions in large complexes, especially in combination with high-resolution structural data from other techniques, such as X-ray crystallography.

C. Yeast two-hybrid screens

More recently, the yeast two-hybrid system (Y2H) has become an important method to detect pairwise protein interactions. Interaction screens of phage proteins can be carried out easily by cloning all open reading frames in appropriate vectors and then testing these in a systematic pairwise fashion. This has been done for several phages, including coliphages T7 (Bartel *et al.*, 1996) and λ (Rajagopala *et al.*, 2011), as well as *Streptococcus pneumoniae* phages Cp-1 and Dp-1 (Häuser *et al.*, 2011; Sabri *et al.*, 2010). The whole process can also be automated.

One disadvantage of the Y2H system is that a typical pairwise screen, also called an “array screen” because of the systematic arrangement of clones in microtiter plates, may only detect 20–30% of all interactions. That is, the rate of false negatives is on the order of 70–80%. This can, in theory, be overcome by using multiple vectors that differ in the structure of the fusion proteins, for instance in the production of N- or C-terminal fusion proteins (Stellberger *et al.*, 2010). A combination of multiple vectors can achieve interaction detection rates of up to 80% (i.e., false negative rates as low as 20%) (Chen *et al.*, 2010).

Y2H also suffers from false positives that can only be understood with additional experimentation. Nonetheless, a multivector Y2H strategy can help in the recognition of false positives. For instance, if multiple vector combinations are used, interactions found in all or most cases are more likely to be “true positives,” whereas interactions detected in a lower fraction of cases are less reliable and may be false positives.

D. Protein complex purification and mass spectrometry

Whole phage virions can be purified, typically by CsCl density gradient centrifugation. Proteins from purified phage can then be denatured and separated on polyacrylamide gels or subjected directly to trypsin digestion and subsequent liquid chromatography (LC) and mass spectrometry (MS). The mass of peptides determined by MS can usually identify the corresponding proteins unambiguously, and thus composition of the phage particles. Once all proteins in a virion are identified, at least some can be assigned easily to known structures, such as the icosahedral capsid or tail sheath. Typically, only a fraction of all phage-encoded proteins are represented in the mature virion (e.g., less than 20 of the ≈70 phage λ proteins). Especially for little-studied phages it can be extremely helpful to know which proteins are in the virion. For example, in an analysis of *Streptococcus* phage Dp-1, only 8 of the 72 predicted proteins were identified by LC/MS and were thus confirmed structural proteins (see later).

E. Biochemistry of protein complexes

Biochemical approaches often involve the purification of protein complexes and thus yield protein interaction information. This approach can be made technically easier if individual proteins are affinity tagged. For instance, phage-encoded proteins can often be fused to

affinity column-binding proteins such as glutathione-*S*-transferase or oligohistidine without affecting their function. Such tagged proteins and proteins bound to them can then be purified using affinity reagents. The untagged proteins in the complex can then be identified by mass spectrometry or immunoblotting (if antibodies against specific proteins are available). A range of experimental techniques is available for the characterization of phage protein complexes and their activities; a comprehensive overview cannot be given here. For instance, chemical cross-linking of interacting proteins is used frequently to spatially locate physically associated proteins, and variable spacer lengths can determine the steric proximity of the binding partners. Other tests include activity assays (e.g., proteases or other modifying enzymes that may be required for phage assembly), replication, or other processes. Some examples of such activities are described here.

F. X-ray crystallography and nuclear magnetic resonance

Only atomic structures of all phage proteins and their interactions will give a mechanistic understanding of phage biology, and progress in this area has been accelerating. Individual proteins and protein complexes, if not the whole phage particle, can be crystallized and the structure of such proteins solved by X-ray analysis. Alternatively, protein structures can be solved by nuclear magnetic resonance (NMR) if high enough concentrations can be achieved. Unfortunately, size restrictions on NMR structural determinations limit the analysis of large protein complexes, but monomeric structures can be extremely useful in devising testable models for the interactions proteins may undergo. However, many phage proteins are refractory to structural analysis (especially those involved in virion assembly, as they often assemble only at high concentrations), and even in classical model systems such as phage λ less than a third of all phage-encoded proteins have been crystallized—most of these as pure proteins rather than as protein complexes (Rajagopala *et al.*, 2011;Yura *et al.*, 2006).

III. PROTEIN–PROTEIN INTERACTIONS OF BACTERIOPHAGES

A. Coliphage T7

Bacteriophage T7 was defined in 1945 as a member of the seven Type (“T”) phages that grow lytically on *E. coli* B (Demerec and Fano, 1945), although it is probably identical to phage δ, used earlier by Delbrück; a close relative of T7 was likely studied by d’Herelle in the 1920s (d’Herelle, 1926). Relatives of T7 exhibit high synteny across their entire genomes, with the closest relatives differing primarily only by the number and location of homing endonucleases or other selfish elements not known to have any role in phage development. These phages therefore will exhibit life cycles and PPIs that parallel T7 itself, modified only by the resources available in their host organisms.

1. Growth physiology—T7 grows on rough strains of *E. coli* (i.e., those without full-length O-antigen polysaccharide on their surface) and some other enteric bacteria, but close relatives have been described that infect smooth and even capsulated strains (Molineux, 2006a). In such phages, tail fibers present on T7 are replaced with tailspikes with enzymatic activity that degrades the O- or K-antigens on the cell surface. T7 has a short latent period of 17 min at 37°C, which has resulted in most physiological studies being conducted at 30°C where infected cells lyse after 30 min. However, adaptation of T7 to high fitness with an excess of an *E. coli* K-12 strain growing under optimal conditions at 37°C in rich media results in a phage with a latent period of only ≈11 min. This adapted phage can undergo an effective expansion of its population by more than 10^{13} in 1 hr of growth (Heineman and Bull, 2007). There is no obvious subtlety in the T7 developmental pathway: the early region of its genome is transcribed efficiently by the host RNA polymerase, leading to synthesis of a phage-specific RNA polymerase and the concurrent inhibition of the host enzyme. Thus,

T7 rapidly takes control of the transcriptional capacity of the infected cell. As *E. coli* mRNAs are also intrinsically unstable, T7 therefore also gains control of the translational capacity of the cell. Further, because T7 uses nucleotides derived from the host chromosome for its own replication, more than 80% of the DNA in progeny is derived from the bacterial chromosome and only a small burst is observed after infection of DNA-free minicells. T7 development is not known to be dependent on host chaperones, although it does code for two proteins that have been suggested to have chaperone activity in capsid and tail assembly. Aside from host components used for phage adsorption, plus general biosynthetic processes and the translational apparatus, T7 development is remarkably independent of host proteins: only *E. coli* RNA polymerase, thioredoxin—the cofactor for T7 DNA polymerase —and (deoxy)cytidine monophosphate kinase are known to be essential.

2. Early steps in infection—T7 is a member of *Podoviridae*, possessing only a short stubby tail that needs to be extended functionally in order to span the cell envelope, which thus allows its genome to be translocated into the cell. Tail extension is affected through internal head proteins that are ejected into the cell at the initiation of infection prior to or concomitant with transport of the leading end of the genome (Chang *et al.*, 2010; Kemp *et al.*, 2005). A schematic of the T7 virion is shown in Figure 2. In T7, the core consists of several copies each of three proteins (gp14, gp15, and gp16), which must interact, albeit perhaps loosely, with themselves and each other, in the phage capsid. However, during their ejection into the cell they must at least partially dissociate and also partially unfold in order to pass through the narrow channel through the portal and tail (Molineux, 2006b). The N-terminal domain of gp16 refolds spontaneously in the periplasm of the infected cell to form an enzyme with lytic transglycosylase activity (Moak and Molineux, 2000, 2004). This muralytic activity is only conditionally essential for T7 infection (Moak and Molineux, 2000).

The C-terminal residues of gp16, likely together with a more central portion of gp15, also refold in the periplasm and then insert spontaneously into the cytoplasmic membrane, completing the channel across the cell envelope for DNA translocation into the cell. Likely the last of the core proteins to exit the phage head, gp14 is found exclusively within the outer membrane of the infected cell. Using energy derived from the membrane potential, these proteins then ratchet the leading 1 kb of the T7 genome into the cell (Chang *et al.*, 2010; Kemp *et al.*, 2005). In both T7 and T3, genome internalization by this process stops, and the remainder of the DNA is normally pulled into the cytoplasm as a consequence of host and then phage RNA polymerase-catalyzed transcription (Garcia and Molineux, 1995, 1996; Kemp *et al.*, 2004). Several strong promoters lie on this leading 1-kb segment of the T7 genome.

3. Early genes—Transcription from T7 early promoters not only internalizes the remainder of the genome but also leads to expression of early T7 genes, some of which interact and inhibit or modulate the activity of host proteins (Molineux, 2006a). Of the early proteins, only T7 RNA polymerase is essential for phage growth. The first T7 protein to be synthesized is gp0.3, an anti-type I restriction protein (Studier, 1975). The structure of gp0.3 reveals that it resembles double-stranded DNA, and the protein binds to the specificity subunit of the heteropentameric EcoKI enzyme, preventing both it and the cognate modification enzyme from recognizing its target sequence (Atanasiu *et al.*, 2001, 2002; Kennaway *et al.*, 2009; Murray, 2000; Stephanou *et al.*, 2009). T7 gp0.3 is active against all type I enzymes and thus T7 grows normally on B, C, and K-12 strains of *E. coli* regardless of its previous host. However, the protein affords no protection against type II and little, if any, against type III enzymes. Gp0.3 proteins of different T7-like phages fall into two distinct groups with no sequence similarity; both have anti-restriction activity but the group typified by T3 gp0.3 also has SAMase activity (Studier and Movva, 1976). The second

major early protein whose function is known is gp0.7, a serine-threonine kinase (Rahmsdorf *et al.*, 1974) that is also responsible for the shut off of host transcription. The two activities are separable (Simon and Studier, 1973). Gp0.7 phosphorylates several host proteins, including RNA polymerase (Severinova and Severinov, 2006; Zillig *et al.*, 1975), the translational apparatus including EF-G and the small ribosomal subunit protein S6 (Robertson and Nicholson, 1990, 1992; Robertson *et al.*, 1994), and both RNase III (Marchand *et al.*, 2001) and RNase E (Mayer and Schweiger, 1983). T7 shuts down translation of host mRNAs but it remains unclear whether EF-G or S6 is involved directly. An unknown T7 late gene also modulates the specificity of RNase E (Savalia *et al.*, 2010). Although it is likely that others do so, only 1 other of the 10 early T7 proteins is currently known to interact with host proteins. Gp1.2 binds to *E. coli* dGTPase, converting it into a rGTP-binding protein (Huber *et al.*, 1988; Nakai and Richardson, 1990); gp1.2 also binds to the membrane protein FxsA and the F plasmid protein PifA (Cheng *et al.*, 2004; Schmitt and Molineux, 1991; Wang *et al.*, 1999).

4. T7 RNA polymerase—The hallmark of T7 is of course its phage-encoded RNA polymerase, which, together with its regulator T7 lysozyme, is responsible for most T7 gene expression. It is also essential for synthesizing RNA primers at the primary origin of replication (Fujiyama *et al.*, 1981) and for initiation of DNA packaging (Zhang and Studier, 1997, 2004). In addition to several complexes containing a promoter and product RNAs (Cheetham and Steitz, 1999; Cheetham *et al.*, 1999; Kennedy *et al.*, 2007; Tahirov *et al.*, 2002; Yin and Steitz, 2002, 2004), the crystal structure of the RNA polymerase–lysozyme complex has been determined (Jeruzalmi and Steitz, 1998). Many mutants in both RNA polymerase and lysozyme have been characterized that affect their functional interaction, but it is not obvious from the crystal structures how the mutations affect the regulation of transcription. Lysozyme is thought to target the initial transcribing complex in a promoter strength-dependent manner and have no effect on transcription elongation (Huang *et al.*, 1999; Stano and Patel, 2004; Zhang and Studier, 1997, 2004). Lysozyme is, however, important in pausing or terminating transcription at the class II terminator CJ, where it probably interacts directly with the T7 terminase protein gp19 and thus directs the packaging machinery to create the DNA terminus (Lyakhov *et al.*, 1997, 1998; Zhang and Studier, 2004).

After T7 RNA polymerase has been synthesized, there is no further requirement for the host polymerase and it actually becomes inhibitory to phage development. Inactivation is caused by the T7 gp2 protein, which binds to the β′ subunit and inhibits transcription by interfering with strand separation of the open complex at most promoters (Camara *et al.*, 2010; Nechaev and Severinov, 1999). *In vivo*, the only T7 promoter that must be inhibited by gp2 is A3 (Savalia *et al.*, 2010). Gp2 was found to interact with T7 endonuclease gp3 by a yeast two-hybrid screen (Bartel *et al.*, 1996). An interaction between gp2 and gp3 (albeit not necessarily direct) was suggested earlier (Mooney *et al.*, 1980), but the idea has not yet been critically evaluated experimentally.

5. DNA replication—T7 has been one of the primary model systems for understanding the biochemistry of DNA replication. Central to T7 replication is T7 DNA polymerase, which comprises a heterodimer of gp5 and the host thioredoxin. Binding of gp5 to thioredoxin is strong, with the latter serving as the processivity factor for DNA replication, increasing the length of DNA synthesized per binding event 100-fold. The interface between the two proteins also provides the docking site for binding of the other two proteins, SSB (gp2.5) and the primase–helicase gp4, which are central to T7 replication *in vivo*. The process of T7 replication *in vitro* has been reviewed recently (Hamdan and Richardson, 2009).

Two other proteins in the DNA replication cluster are known to interact with host proteins. The gene *5.5* product binds to the abundant nucleoid-associated protein H-NS (Ali *et al.*, 2011) and *in vitro* relieves its inhibition of both *E. coli* and T7 RNA polymerase-catalyzed transcription (Studier, 1981). *In vivo*, T7 *5.5* mutants direct reduced rates of DNA replication and exhibit a small plaque phenotype (Lin, 1992; Liu and Richardson, 1993; Studier, 1981). However, the phenotype persists in *hns*-defective strains, although an *hns* mutant that renders gene *5.5* essential has been isolated (Liu and Richardson, 1993). Gp5.5 also interacts with the λ proteins of RexAB system; it is not known whether this is a direct protein–protein interaction or whether gp5.5 interacts with a product of RexAB activity. A gene *5.5* missense, but not a null mutant, makes T7 sensitive to Rex-mediated exclusion. The product of gene *5.9* inhibits the *E. coli* RecBCD nuclease in a comparable manner to λ Gam protein; this interaction is also nonessential as mutants lacking gene *5.9* grow normally in *rec(BCD)*$^+$ hosts (Lin, 1992).

The assembly of T7 virions involves several symmetry mismatches and many protein–protein interactions, some of which may be helped by other T7 proteins that potentially have a chaperone-like activity (Kemp *et al.*, 2005). Note that, GenBank annotations notwithstanding, gp13 is not a structural component of the virion (Kemp *et al.*, 2005). Assembly is thought to initiate with oligomerization of the portal protein gp8 to form a dodecameric ring, although both 12- and 13-mers are observed following overexpression of gene *8* (Cerritelli and Studier, 1996b; Kemp *et al.*, 2005; Valpuesta *et al.*, 1992, 2000). The pathway of prohead formation may then involve assembly of the internal core (gp14, gp15, and gp16) on the inner surface of the portal, perhaps concomitant with the recruitment of capsid protein gp10 hexamers bound to scaffolding protein gp9. Subsequent recruitment of gp10 pentamers and hexamers results in shell formation around a scaffold of gp9 (Cerritelli *et al.*, 2003a). The 12-fold symmetrical portal protein faces a symmetry mismatch with the 5-fold vertex of the icosahedral capsid shell. The internal core of T7 contains 4 copies of gp16, 8 copies of gp15, and either 10 or 12 copies of gp14 (Agirrezabala *et al.*, 2007; Cerritelli *et al.*, 2003b; Kemp *et al.*, 2005). These proteins are ejected into the infected cell in order to transport the phage genome into the cytoplasm, and the protein–protein interactions in the mature virion are likely quite different than those found in the infected cell. Gp14 lies at the base of the internal core and is therefore juxtaposed to the 12-fold symmetrical portal protein. Complicating our understanding of the T7 virion is the identification of ≈18 copies of the small gp6.7 protein, which is ejected into the outer membrane of the infected cell at the initiation of infection (Kemp *et al.*, 2005). It is not known where gp6.7 is located; it likely forms part of the internal core or lies within the portal channel.

6. Tail—The outer face of the portal is the site of assembly of the sixfold symmetrical stubby tail. The tail is composed of three proteins—gp7.3, 11 and 12—to which six trimers of the tail fiber protein gp17 are attached. Each trimer consists of three domains: an N-terminal third that binds to the tail; this domain is conserved in phages related to T7 that have a different host range. This domain is followed by a triple-stranded coiled-coil of ≈120 residues and then a C-terminal half consisting of globular domains that interacts with the cell surface lipopolysaccharide (Steven *et al.*, 1988). The body of the tail consists of 12 copies of gp11, 6 copies of gp12, and ≈30 copies of the small protein gp7.3 (Kemp *et al.*, 2005). How these proteins are arranged is unknown. It has been suggested that gp7.3 functions as a tail assembly protein that remains with the mature virion; the protein is ejected into the outer membrane of the infected cell (Chang *et al.*, 2010; Kemp *et al*, 2005). Host range mutants of T7 suggest that all three proteins interact directly with the lipopolysaccharide of the host cell.

7. Interactome screening—T7 was the focus of the first genome-wide screen for phage protein–protein interactions using the yeast two-hybrid assay (Bartel *et al.*, 1996). As proof

of principle, T7 was a good choice: the extensive genetic, molecular biology, and biochemical studies that had been performed on T7 provided a solid basis for evaluating the accuracy and completeness of the approach. Twenty-five interactions were identified in the screen, 15 of which were intramolecular. Many of these are to be expected as even monomeric polypeptides fold into a three-dimensional structure. Virion assembly clearly involves extensive protein–protein interactions, but as discussed by the authors, many of those that were known or plausibly expected from known structures were missed in the screen (Bartel *et al.*, 1996). Conversely, screen-predicted interactions involving gp1.7 that were confirmed subsequently by its purification as an oligomer (Tran *et al.*, 2010) and the predicted interactions between the spanin proteins gp18.5 and gp18.7 predated the discovery of a heterodimer even in phage λ (Casjens *et al.*, 1989). Six intermolecular interactions were predicted that have not yet found confirmatory support, and our current understanding of T7 suggests that some are implausible. Improved screening procedures should help resolve these outstanding issues and, if more intermolecular interactions can be found that are consistent with, in particular, the pathways of virion assembly, the utility of those screening procedures in predicting the protein interactome of lesser-studied phages will be enhanced greatly. All published T7 interactions are summarized in Table II.

B. Coliphage λ

Phage λ may be the best-studied temperate phage and has been under investigation since the early 1950s. There are probably thousands of papers that have been published on phage λ and its closer relatives N15, HK97, and P22. For instance, there are more than 400 citations in a review of lambdoid phages that do not even focus on the genetic switch of λ, the paradigm for gene regulation (Hendrix and Casjens, 2006). The switch has been described in detail by many other papers and in its own book (Court *et al.*, 2007; Ptashne, 2004). This section summarizes current knowledge of the interactions among phage λ proteins. Finally, a summary of interactions with its host, *E. coli*, is given. For a more detailed description of phage λ biology and regulation, the authors refer the reader to other reviews (Calendar, 2006; Court *et al.* 2007; Hendrix and Casjens, 2006; Hendrix *et al.*, 1983; Oppenheim *et al.*, 2005; Ptashne, 2004).

1. The λ virion—The phage λ genome and virion are shown in Figure 3. Note that the virion contains tail fibers that are not visible in most λ micrographs. The variant of λ used in most laboratories around the world, λPaPa, has a frameshift mutation in the structural *stf* gene and lacks the long “side tail fibers” of λ, Ur-λ, that comes directly from the original *E. coli* K-12 lysogen. It is still not entirely clear how many different proteins are in the λ particle but 12 are known with confidence and 2 more (gpM and gpL) are possibly in the particle in very low numbers. A current model of the particle with its known proteins is shown in Figure 3. Based on this model, we can predict at least 23 PPIs in the virion (Table III), although several are inferred from genetic experiments and remain to be detected by biochemical or biophysical methods. The virion adsorbs to sensitive cells through an interaction between the tail tip protein gpJ and the host LamB outer membrane protein. DNA is then released through the tail into the cytoplasm.

2. Assembly of virion head (Fig. 4)—λ encodes 10 proteins required for head assembly, of which 6 end up in the mature virion. Head assembly starts with assembly of the portal, which requires the host GroEL/S chaperone for folding. It is thought that the portal serves as the nucleus for assembling the remaining capsid. However, the mechanistic details of assembly are not well understood. GpC is involved as a head maturation protease that becomes attached covalently to E, the main capsid protein. The resulting fusion proteins subsequently get trimmed to make slightly shortened products named X1 and X2 (Hendrix and Casjens, 1974). The authors note, however, that attempts to identify X1 and X2 were

unsuccessful and thus X1 and X2 may be artifacts (Medina *et al.*, 2010). GpNu3 acts as putative scaffolding protein that aids coat shell assembly and is removed from the capsid by proteolysis before DNA is packaged. Structures of the procapsid and mature λ capsid have been solved by cryo-EM, showing the T=7 arrangement of capsid protein gpE clustered into hexamers and pentamers (Dokland and Murialdo; Lander *et al.*, 2008). Trimers of the decoration protein gpD bind to the capsid at trivalent interaction points between the capsomers and stabilize the capsid (Sternberg and Weisberg, 1977). Comparison of the procapsid with the mature capsid reveals the considerable structural transitions that occur upon capsid maturation and DNA packaging, but this process is not well understood mechanistically.

3. Assembly of virion tail (Fig. 5)—Tail assembly begins with the antireceptor protein gpJ. Proteins gpI, gpK, gpL, and gpM assemble around gpJ in that order, although no mechanistic or structural details are known about this process. In parallel events, gpH, gpG, and gpG-T (the frameshifted form of gpG including the *T* reading frame) form a complex that binds the tail tip and the major tail protein (gpV). The tape meassure protein gpH determines the length of the phage tail (Katsura, 1990). Once the correct length is achieved, gpV assembly stops and the proximal tail protein gpU is added. Protein gpZ somehow facilitates head–tail joining without being assembled into the final virion.

4. Lysogeny and induction—After phage DNA ejection, circularization, and ligation by the host DNA ligase, the earliest genes to be expressed include *N, O*, and *P*, as well as *cII* and *cIII*, which play a key role in the lysis/lysogeny decision (Echols, 1986). Both CII and CIII can interact with and be cleaved by the bacterial FtsH (HflB) protease directly, which in turn is complexed with the host HflK and HflC proteins at the cytoplasmic membrane. HflD, a cytoplasmic membrane protein, also binds CII, making it both more susceptible to FtsH and less able to bind DNA (Kihara *et al.*, 2001; Parua *et al.*, 2010). As a substrate for FtsH, CIII acts as a competitive inhibitor of CII degradation and, as the half-life of CII protein increases, leads to an increase in CI repressor synthesis (Datta *et al.*, 2005a; Herman *et al.*, 1997; Kobiler *et al.*, 2007). Except when cIII is overexpressed, lysogeny is only established when the activity of these proteases (FtsH, Lon, and perhaps others) is low. Once established, lysogeny is a stable state until lysogens are exposed to ultraviolet light or other DNA-damaging agents that lead to the activation of RecA, which in turn accelerates autocleavage of the λ repressor CI. Loss of CI leads to prophage induction and the lytic cycle. The mechanism by which phage λ decides whether to grow lytically or become a lysogen is reviewed elsewhere (Court *et al.*, 2007; Friedman and Court, 2001; Gottesman and Weisberg, 2004; Ptashne, 2006). However, Table IV contains the host–phage protein–protein interactions critical for gene expression and thus the genetic switch of phage λ.

5. Anti-termination—*Escherichia coli* RNA polymerase transcribes λ DNA starting from the immediate early promoters P_L and P_R, which leads to expression of the *N* and *cro* genes, among others. As soon as the gpN-binding sites (*nut* sites) are transcribed, gpN modifies the transcription complex by recognizing a stem-loop structure in the mRNA and by binding to host Nus proteins [note that gpN interacts with *nut* RNA (not DNA)]. This modified complex is capable of overriding the termination signal that normally stops immediate early transcription. Because gpN is continually being degraded by the Lon protease, ongoing anti-termination requires continual transcription of the *N* gene (Fig. 6). In addition to the anti-terminator for early lytic genes (gpN), a second anti-terminator, gpQ, is required for late gene expression. GpQ anti-termination differs from that of gpN in that gpQ binds to the “Q binding element” (QBE, also known as the *qut* site) of the $P_{R'}$ promotor (i.e., unlike the gpN protein, gpQ binds DNA). When RNA polymerase (RNAP) initiates transcription at the $P_{R'}$ promotor, it almost immediately pauses at a pause-inducing sequence. Pausing allows gpQ

to contact σ^{70} in the RNAP, which causes a conformational change in the enzyme that enables gpQ to bind the β subunit (RpoB). The gpQ-containing RNAP is then able to override the termination signal at $t_{R'}$ (Deighan *et al.*, 2008; Nickels *et al.*, 2002).

6. Replication—After λ gene *O* and *P* protein synthesis, replication of the phage genome is initiated (Fig. 6). Replication initiation starts with dimeric gpO bound to the four 18-bp direct repeats of the λ origin, located within the sequence of the *O* gene. Each repeat binds a gpO dimer, leading to a total of eight monomers bound directly to the DNA, in addition to non-DNA-bound gpO that associates with the complex solely by PPIs (Dodson *et al.*, 1986). This large nucleoprotein complex is called the O-some. GpP extracts the host DnaB helicase from its native complex with DnaC (Zylicz *et al.*, 1989). The DnaB helicase is inactive as long as it is tightly associated with gpP. The gpP–DnaB pair is then added to the O-some through interactions between gpP and gpO. Three host heat shock chaperone proteins—DnaK, DnaJ, and GrpE—are subsequently recruited (DnaK through direct interaction with gpP and gpO) and activate the DnaB helicase by liberating it from its inhibitory interaction with gpP. Finally gpP and the chaperones are released, and replication starts with the help of the host DnaG primase, DNA polymerase III, gyrase, and single-stranded DNA-binding (SSB) proteins (Dodson *et al.*, 1986; LeBowitz and McMacken, 1986). The RNA polymerase β subunit was shown to interact directly with gpO (Szambowska *et al.*, 2010). Even though not yet fully understood, how *E. coli* RNA polymerase activates λ *ori* seems to be far more complex than the original idea that it simply changed DNA topology.

Studies on λ *ori*-dependent plasmids have revealed interactions with even more host proteins, including the DnaJ homolog CbpA (Wegrzyn *et al.*, 1996), and through transcriptional activation of origin activity, perhaps also with DnaA and SeqA (Potrykus *et al.*, 2002; Wegrzyn and Wegrzyn, 2001, 2002). As λ *ori*-dependent plasmid maintenance and copy number are very sensitive to changes in host physiology, interactions of the O-some with additional proteins may yet be revealed.

7. The λ interactome—A λ Y2H interactome analysis has been completed (Rajagopala *et al.*, 2011). All λ open reading frames (ORFs) were cloned and tested in all possible pairs for interactions, using three different Y2H vectors. These screens identified 97 interactions among 68 tested λ proteins, of which 16 were known previously. Notably, because only 33 interactions had been reported previously, this screen found more than 50% of all previously published interactions in a single experiment! At least 18 of the newly observed Y2H interactions seem to be plausible, based on the functions of the interacting proteins, indicating that even in λ many new discoveries can be made. Interestingly, relatively few interactions involving morphogenetic proteins were revealed, and possible reasons for the still significant fraction of apparent false negatives are discussed later.

C. *Salmonella* phage P22

P22 infects *Salmonella enterica* serovar Typhimurium and was originally isolated by Zinder and Lederberg (1952). It is a temperate member of *Podoviridae*. Its virion proteins are not particularly closely related to other tailed phage groups, but its early genes and overall lifestyle are very closely related to phage λ. For this reason, it is often placed in the "lambdoid" phage group. Phage P22 is also a very important tool for those who use *Salmonella* genetics, as it is particularly easy to handle in the laboratory and is a very good generalized transducing phage (i.e., it packages a significant amount of host DNA by accident and can be used to move host alleles from one *Salmonella* strain to another).

1. P22 life cycle—The early operons of P22 are organizationally similar to those of λ and carry parallel prophage repressor, Cro, recombination, DNA replication, and transcription

anti-termination functions (Susskind and Botstein, 1978). The P22 repressor has a different DNA operator target specificity from that of λ repressor and encodes nonhomologous types of recombination and replication proteins, but its late operon anti-termination protein is 97% identical to that of λ and has the same target specificity. Unlike λ, in addition to its prophage repressor (C2) and lysogeny control proteins (C1, C3, Cro), P22 carries an "*immunity I*" region that encodes an anti-repressor protein, Ant, that binds to the prophage repressor and blocks its ability to bind its operator. Two additional repressors, Mnt and Arc, regulate Ant synthesis (Susskind and Botstein, 1975; Vershon *et al.*, 1987a,b). Also, instead of a protein that recruits the host DnaB protein to the replication origin, P22 encodes its own DnaB homologue (Backhaus and Petri, 1984; Wickner, 1984). The repressed P22 prophage encodes several "lysogenic conversion" genes, several of which encode a set of three Gtr (glucose transfer) proteins that modify the host O-antigen polysaccharide by glucosylation (Broadbent *et al.*, 2010; Makela, 1973; Vander Byl and Kropinski, 2000). Finally, P22 has been studied as a prototypical headful DNA packaging phage, which is different from the packaging strategies used by the other phages discussed here; unlike these other phages that package DNA between two specific nucleotide sequences in the DNA substrate, P22 packages DNA until the head is full and the nucleotide sequence at the termination point does not matter (Casjens and Hayden, 1988; Jackson *et al.*, 1978; Tye *et al.*, 1974).

2. P22 virion assembly—The P22 virion is assembled by proteins encoded by 14 genes in its late operon (Fig. 7) (Botstein *et al.*, 1973; Eppler *et al.*, 1991; King *et al.*, 1973; Poteete and King, 1977; Youderian and Susskind, 1980). Some P22-like phages, for example, phages ε34 and L, have a 15th virion assembly gene, *dec*, at the promoter proximal end of the cluster, whose encoded protein "decorates" the outside of the head and stabilizes it (Gilcrease *et al.*, 2005; Tang *et al.*, 2006; Villafane *et al.*, 2008). The P22 late operon encodes lysis proteins very similar to those of λ; however, the virion assembly genes are not closely related to λ or to any other tailed phage type. P22 virion assembly is best known for the fact that its head-assembling scaffolding protein was the first to be discovered and studied (Cortines *et al.*, 2011; King and Casjens, 1974; Prevelige *et al.*, 1988; Weigele *et al.*, 2005). The P22 procapsid assembles as a complex of 415 coat protein molecules, 12 portal ring subunits, and about 250 scaffolding protein molecules. At about the time when DNA is packaged, all 250 scaffolding proteins are released intact from the procapsid and are reused with newly synthesized coat protein in subsequent rounds of procapsid assembly. Thus, the P22 scaffolding protein acts catalytically in head assembly and individual molecules can participate in at least five rounds of procapsid assembly. A particularly high-resolution asymmetric cryo-EM reconstruction of the virion has been determined (Lander *et al.*, 2006; Tang *et al.*, 2011), and because assembly of the four proteins of its short tail has also been quite well studied [X-ray structures are known for three tail proteins and the portal protein (Olia *et al.*, 2006, 2007; Steinbacher *et al.*, 1997)], the P22 virion is perhaps the best understood of all tailed phage virions. The details of P22 virion assembly have been reviewed in light of its evolution and genome mosaicism (Casjens and Thuman-Commike, 2011), and the authors refer the reader to this review for further details. The published PPIs of phage P22 are summarized in Table V. Interactions between P22 and its host are much less well studied than those of λ and are mostly understood by homology arguments in the case of proteins that are similar in the two phages. Known P22–host interactions are listed in Table VI.

3. Comparison of P22 and λ interactomes—As noted earlier, comparison of P22 and λ is a particularly informative way to understand the kinds of relationships among the proteins of different tailed phages. The "lambdoid" phages all encode similar functions and have similar gene organization, but these "similar functions" can be of several different types. Because these phages undergo a significant amount of horizontal transfer of genetic

information (especially if they are “closely” related), their functions can be homologous or even nearly identical (Casjens, 2005; Hendrix, 2002). For example, the two “gpQ” late operon control anti-termination proteins of the two phages are nearly identical and can replace one another in function. A second kind of relationship is represented by the prophage repressors. These proteins from the two phages have weak but recognizable homology and similar folds, and probably interact with host proteins the same way, but have different operator-binding specificity. Thus, one repressor cannot functionally replace the other without additional changes in the DNA-binding sites of the protein. A third kind of relationship is that of the virion coat, terminase, and portal proteins, λ gpE, gpA, and gpB and P22 gp5, gp2, and gp1, respectively. These proteins have the same functions in the two phages—coat protein and DNA packaging nuclease/motor ATPase and procapsid DNA entry channel, respectively (summarized in Hendrix and Casjens, 2006). These cognate proteins are not recognizably similar in overall amino acid sequence between the two phages, although the two ATPase proteins have similar ATP-binding motifs. However, the two proteins almost certainly have the same basic fold. Thus, gpE and gp5 and gpA and gp2, as well as gpB and gp1, are all very likely ancient homologous pairs that have diverged beyond the point of having recognizable sequence similarity. Finally, similar functions are performed by nonhomologues in the two phages. Examples of this relationship are the (i) nonhomologous Exo (λ) and Erf (P22) proteins that catalyze homologous recombination in completely different ways (Little, 1967; Poteete and Fenton, 1983); (ii) the endolysin proteins gpR and gp19, where the λ protein is a transglycosylase and the P22 protein is a true lysozyme that both cleave the same peptidoglycan bond (Bienkowska-Szewczyk *et al.*, 1981; Rennell and Poteete, 1989); (iii) the gpW and gp4 proteins, which bind between the portal ring of the head and the tail and yet have no recognizable homology or structural similarity; and (iv) the λ receptor binding “fiber” (gpJ and STF) and P22 tailspike (gp9), which have no homology, recognize different structures, and act in different ways [the P22 gp9 enzyme cleaves its polysaccharide receptor (Iwashita and Kanegasaki, 1976)]. Thus, there are potentially a number of different ways in which parallel λ and P22 functions might interact with the hosts of these two phages, and it will be interesting to understand these in detail in both cases. But are there very similar phage proteins that have different host interactions? Do very different phage proteins that have the same function have equally different host interactions? Although no such situations have been identified to date, it remains possible. A comparison of PPIs in λ and P22 is given in Tables VII and VIII.

D. Enterobacteriophage P2 and its satellite phage, P4

Bacteriophage P2 was originally isolated from the Lisbonne & Carrère strain of *E. coli* by Bertani in 1951 and is a member of the *Myoviridae* family of viruses. It has an icosahedral head and a contractile tail and is a 33.6-kb double-stranded DNA genome (Bertani, 1951; Bertani and Six, 1988; Nilsson and Haggård-Ljungquist, 2006). P2-like prophages are common in the environment (Breitbart *et al.*, 2002) and are present in about 30% of strains in the *E. coli* reference collection (Nilsson *et al.*, 2004).

Bacteriophage P2 has attracted much interest as a “helper” for bacteriophage P4, an 11.6-kb replicon that can exist either as a plasmid or integrated into the host genome as a prophage (Briani *et al.*, 2001; Deho and Ghisotti, 2006; Lindqvist *et al.*, 1993). P4 lacks genes encoding major structural proteins, but can utilize the structural gene products encoded by P2 for assembly of its own capsid (Christie and Calendar, 1990; Lindqvist *et al.*, 1993; Six, 1975). An overview of the P2 structural biology and a summary of its interactions are shown in Figure 8 and Table IX.

1. Gene control circuits—The decision whether to grow lytically or form a lysogen after P2 infection is dependent on the levels of two repressors: the immunity repressor gpC,

which blocks lytic growth, and Cox, which blocks the expression of the genes required for lysogenization. GpC acts as a symmetric dimer, and its three-dimensional structure has been determined (Eriksson *et al.*, 2000; Massad *et al.*, 2010). Cox is multifunctional and acts as a repressor, as well as an excisionase, thereby coupling the transcriptional switch that controls lytic growth versus formation of lysogeny with the integration/excision of the phage genome in or out of the host chromosome. Cox is a tetramer in solution that self-associates to octamers in the absence of DNA (Eriksson and Haggard-Ljungquist, 2000). The transcriptional activator Ogr is required to turn on late gene transcription. Ogr is a Zn finger-containing protein that interacts with the α subunit of the *E. coli* RNA polymerase, recruiting it to the late promoters (Ayers *et al.*, 1994; Fujiki *et al.*, 1976; King *et al.*, 1992; Sunshine and Sauer, 1975; Wood *et al.*, 1997).

Some P2 prophage genes are not blocked by the action of gpC and instead are expressed from the prophage providing the host cell with new properties. Among these “lysogenic conversion” genes, P2 has three genes, *old, fun*, and *tin*, that block superinfection of unrelated phages, but only gpTin is known to have a PPI. P2 gpTin excludes phage T4 by binding to and poisoning T4 gp32 (SSB), thereby inhibiting DNA replication (Mosig *et al.*, 1997).

Satellite phage P4 has to get access to the morphogenetic genes of its helper P2 to grow lytically. This is accomplished by P4-encoded functions during coinfection with P2. The P4 antirepressor Epsilon derepresses the P2 prophage by interacting with gpC, leading to the expression of P2 lytic genes (Eriksson *et al.*, 2000; Geisselsoder *et al.*, 1981; Liu *et al.*, 1998). P4 also has the capacity to *trans*-activate P2 late genes in the absence of Ogr using the transcriptional activator Delta. Delta contains two Ogr-like domains and recognizes the same DNA sequence as Ogr. Like Ogr, Delta interacts with the α subunit of *E. coli* RNA polymerase (Christie *et al.*, 2003; Julien *et al.*, 1997; Souza *et al.*, 1977).

2. P2 DNA replication—After infection, the linear DNA molecule is circularized by ligation of the cohesive (*cos*) ends by the host DNA ligase, and if P2 enters the lytic pathway, DNA replication is initiated by the *cis*-acting gpA that creates a single-stranded cut at the origin. GpA remains linked covalently to the 5′ end of the cleaved strand (Liu and Haggard-Ljungquist, 1994). Replication occurs via a modified rolling-circle mechanism that generates a double-stranded monomeric circle that is the packaging substrate (Pruss *et al.*, 1975). The cleavage/joining reactions are promoted by two tyrosine residues interspaced by three amino acids in gpA (Odegrip and Haggard-Ljungquist, 2001). The host Rep helicase is required for all DNA replication (Calendar *et al.*, 1970), while the phage-encoded gpB is a helicase loader that interacts with the *E. coli* DnaB helicase required for lagging strand synthesis (Funnell and Inman, 1983; Odegrip *et al.*, 2000).

3. Head structure and assembly—The main structural proteins involved in P2 capsid assembly are gpN, capsid protein; gpO, internal scaffolding protein; and gpQ, connector or portal protein (Chang *et al.*, 2008; Lengyel *et al.*, 1973; Linderoth *et al.*, 1991). P2 capsids are assembled as empty precursor procapsids consisting of 415 copies of the gpN capsid protein arranged with T=7 icosahedral symmetry and clustered in hexamers and pentamers that make trivalent interactions (Dokland *et al.*, 1992) (Fig. 9). GpQ forms a dodecameric ring that is incorporated into the capsid at one fivefold vertex and through which the DNA is subsequently packaged (Doan and Dokland, 2007; Rishovd *et al.*, 1994).

GpO plays a dual role in the assembly process as both a protease and a scaffolding protein (Chang *et al.*, 2009; Dokland, 2011). The full-length, 284 residue gpO protein is associated with procapsids at early times (Marvik *et al.*, 1994), but is cleaved autoproteolytically between residues 141 and 142, leaving an N-terminal fragment, gpO* (formerly known as

h7), that remains inside the mature capsid (Chang *et al.*, 2008; Lengyel *et al.*, 1973). Concomitantly, gpN and gpQ are cleaved—presumably by gpO—to their mature forms, gpN* and gpQ*, by removal of 31 and 26 residues, respectively, from the N terminus (Rishovd and Lindqvist, 1992; Rishovd *et al.*, 1994). The protease activity of gpO resides in its N-terminal domain, which binds tightly to gpN and constitutes a serine protease similar to that of the herpesviruses (Chang *et al.*, 2009; Cheng *et al.*, 2004; Dokland, 2011). The C-terminal 90 amino acids comprise a scaffolding domain, which is necessary and sufficient for promoting capsid assembly (Chang *et al.*, 2008, 2009; Wang *et al.*, 2006). It too presumably binds to gpN during assembly, but any interaction is transient (Chang *et al.*, 2009). Both N- and C-terminal domains form dimers in solution (Chang *et al.*, 2009).

Circular P2 genomic DNA substrates are packaged into empty procapsids by the terminase complex, which consists of the small and large terminase proteins (gpM and gpP, respectively). Terminase recognizes and cleaves P2 DNA at the *cos* sites (Bowden and Modrich, 1985; Ziermann and Calendar, 1990). DNA packaging is associated with major structural transitions that lead to a larger, more angular and thin-shelled, mature capsid (Chang *et al.*, 2008; Dokland *et al.*, 1992). A head completion protein, gpL, is added (Chang *et al.*, 2008), and tails, which are assembled via a separate pathway, are attached to the unique gpQ-containing portal vertex (Lengyel *et al.*, 1974).

4. Tail structure—The 135-nm-long tail is composed of an inner tube and a contractile sheath (Lengyel *et al.*, 1974). The head-proximal end of the free tail has two disc-like structures of different thickness and diameter. In the complete phage, only the thinner disc is seen outside the head. The distal end of the tail contains a baseplate with a spike and six fibers. Sixteen essential tail genes have been identified located in three transcription units. GpFI and gpFII constitute the tail sheath and tail tube, respectively, and there are about 200 copies of each protein per tail (Temple *et al.*, 1991). RpR and gpS are involved in tail completion, as *amber* mutations in the respective gene produce giant tails and giant tail sheaths (Linderoth *et al.*, 1994). GpV is the tail spike, which forms a trimer in solution (Haggard-Ljungquist *et al.*, 1995; Kageyama *et al.*, 2009). GpW copurifies with gpV and is thus thought to be part of the baseplate, while gpJ localizes to the edge of the baseplate or proximal part of the tail fiber by immunoelectron microscopy (Haggard-Ljungquist *et al.*, 1995). GpH is believed to be the distal part of the tail fiber because it contains regions similar to tail fiber proteins of phages Mu, P1, λ, K3, and T2 (Haggard-Ljungquist *et al.*, 1992). A region of gene *H* is highly similar to the variable part of the *S* gene (*Sv*) of phage Mu and the variable part of gene *19* (*19v*) of phage P1, in both cases in the (+) orientation of the invertible segments. P2 does not have an invertible segment, but it contains a sequence identical to the left repeat of the Mu invertible G segment located within the *H* gene and upstream of the region with a high similarity to Mu *Sv* and P1 *19v*, indicating that the P2 *H* gene has been frozen in the (+) orientation, probably by a deletion covering the right inverted repeat and the invertase. This region is therefore inferred to constitute the receptor-binding tip of the tail fiber. By its similarities to gpU and gpU′ of phages Mu and P1, and gp38 of phages T4, Tula, and Tulb, gpG is probably required for fiber assembly. GpT is likely the tape measure, as it is the only protein long enough to span the length of the tail shaft (Christie *et al.*, 2002). Function of the products of genes *X, I, E, E′* (programmed -1 frameshift extension of E), *U*, and *D* remains unknown.

5. P4-induced redirection of P2 capsid assembly—Satellite phage P4 cannot form phage particles by itself, but in the presence of phage P2, P4 genomes are packaged into phage particles using structural proteins supplied by P2 (Six, 1975). However, the P4 capsid is smaller than P2 and contains only 235 copies of gpN, arranged on a T=4 icosahedral lattice (Dokland *et al.*, 1992) (Fig. 9). This size control is affected by the P4 gene product Sid (size determination)(Barrett *et al.*, 1976), which forms an dodecahedral cage-like

scaffold around the outside of P4 procapsids (Marvik *et al.*, 1995). Sid self-associates into trimers and dimers that interact with gpN only in two hexamer subunits near the twofold symmetry axes (Wang *et al.*, 2000; Dokland *et al.*, 2002). Gene *N* mutants, called *sir* (*sid* responsiveness), render the capsid protein unable to form small capsids even in the presence of Sid (Six *et al.*, 1991). Conversely, the so-called super-*sid* or *nms* (*N* mutation sensitive) mutations in *sid* act as second-site suppressors of the *sir* mutations and enable the formation of small capsids (Kim *et al.*, 2001). Although well-formed small procapsids can be assembled from Sid and gpN alone (Dokland *et al.*, 2002), gpO is required for the formation of viable P4 phage (Six, 1975). Presumably this is because its protease activity is essential, and gpO may also facilitate incorporation of the portal. Indeed, *sid* complements the P2 *Oam*279 mutant, which produces a 237 residue N-terminal fragment of gpO that includes the protease domain but lacks scaffolding activity (Agarwal *et al.*, 1990). The P4 genome contains P2 *cos* sites and is packaged into small capsids using the P2 terminase (Ziermann and Calendar, 1990). The P4-encoded protein Psu is a suppressor of Rho-dependent transcription termination (Pani *et al.*, 2009; Sauer *et al.*, 1981); it also functions as a decoration protein that binds to gpN hexamers and stabilizes the P4 capsid (Dokland *et al.*, 1993; Isaksen *et al.*, 1993).

E. *Pneumococcus* phage Dp-1 and Cp-1

The lytic bacteriophages Dp-1 and Cp-1 infect the Gram-positive bacterium *Streptococcus pneumoniae*, which colonizes the mucosal surface of the upper respiratory tract and causes serious invasive infections such as pneumonia, meningitis, and sepsis (van der Poll and Opal, 2009). Dp-1 was the first isolated *Streptococcus* phage and is an unassigned member of the *Siphoviridae* (Fig. 10) (McDonnell, Lain and Tomasz, 1975). It was reported that the Dp-1 virion surprisingly contains lipids that might be arranged as a bilayer surrounding the capsid (Lopez *et al.*, 1977), a feature not reported for any other phage belonging to the *Caudovirales*. The lytic enzyme Pal of Dp-1 has been studied intensively because it kills virulent streptococci efficiently and has been used as an enzybiotic to cure pneumococcal infections in animals (Loeffler *et al.*, 2001; Rodriguez-Cerrato *et al.*, 2007). The podovirus Cp-1 lytic enzyme Cpl1 was also demonstrated to be an efficient enzybiotic (Loeffler *et al.*, 2003). The Cp-1 genome is a linear, 20-kbp dsDNA predicted to encode 28 proteins and a packaging RNA (pRNA). Like ϕ29-like viruses, Cp-1 uses protein priming for the initiation of DNA replication (Martin *et al.*, 1996). The biology of Dp-1 and Cp-1 is otherwise only poorly understood.

The 56.5-kbp genome of Dp-1 is predicted to encode 72 proteins (Fig. 10A) (Sabri *et al.*, 2011). Approximately half of the gene products could be functionally annotated by homology predictions. However, in this and hundreds of other completely sequenced phage genomes, more than half of phage gene products could not be annotated. Proteome-wide Y2H screens, coupled with mass spectrometry analysis (MS) of mature Dp-1 virions, identified 156 unique PPIs among 57 Dp-1 proteins [a detailed list can be found in Sabri *et al.* (2011)], and MS revealed that the mature virion is composed of eight structural proteins. A Dp-1 virion model (Figs. 10B and 10C) physically links many proteins with unknown function to the virion. Because they bind structural proteins but are absent from the mature virion, these Y2H PPIs either indicate novel structural components (when found by MS of the virion particles) or virion assembly facilitators. For instance, homology comparisons of gp40, gp41, and gp53 predict that these proteins are structural (Fig. 10B). However, MS analysis did not detect them as components of the virion. Even though functional predictions by homology comparisons are extremely helpful in proteome annotation, a certain fraction of proteins may be wrongly annotated in the absence of other experimental data (i.e., whether a protein is annotated as a structural component or an assembly facilitator can have an important impact on future experiments).

Such a comprehensive analysis also reveals unexpected interactions that normally would not be tested in hypothesis-driven experiments (Fig. 10E). For example, Dp-1 proteins believed to be involved in DNA replication and recombination, transcriptional regulation, and other pathways exhibit interactions with structural components. This indicates that DNA packaging and DNA replication/repair might be coupled (as in phage T4), for example, by resolving intermediate DNA structures in parallel with packaging. Although the identified PPIs were helpful in obtaining the first hints about the function of the proteins, not all expected PPIs between the structural proteins were detected (Fig. 10D). Nevertheless, this study demonstrated that homology-based genome annotation complemented by proteomic approaches is a useful strategy to gain novel insights into the biology of poorly understood bacteriophages.

The same combination of genome annotation and proteomics was repeated for the 28 putative Cp-1 proteins (Häuser *et al.*, 2011). They detected a total of 12 structural proteins by MS analysis. More than half the proteins showed at least one protein–protein interaction with 17 binary interactions in total. Notably, nearly all were detected between proteins encoded in the structural gene cluster, reflecting a highly modular organization of its interactome. In contrast, Dp-1, with its larger proteome/interactome, shows more cross-communication between proteins belonging to different pathways, although a functional enrichment of interactions between proteins belonging to related cellular processes was still detected (Sabri *et al.*, 2011). It is likely that larger phage proteomes/interaction networks routinely exhibit a higher frequency of protein cross-communication at the protein interaction level due to regulation between various pathways (i.e., the larger the proteome, the more promiscuous the interaction network).

F. *Bacillus subtilis* phage φ29-like viruses

ϕ29-like phages belong to the *Picovirinae* subfamily of the *Podoviridae*. Members include ϕ29, ϕ15, PZA, BS32, B103, M2Y (M2), Nf, and GA-1. All are lytic; most infect *B. subtilis*, but some grow in *B. pumilus, B. amyloliquefaciens*, and *B. licheniformis* (Meijer *et al.*, 2001a). The characteristics of their virions are a prolate capsid (e.g., ϕ29 is 41.5 by 31.5 nm) with attached head fibers, a connector, a short noncontractile tail (e.g., ϕ29 with 32.5 nm in length), and the presence of tail appendages (Anderson *et al.*, 1966) (Fig. 11). GA-1 and M2Y lack the gene for head fibers (Yoshikawa *et al.*, 1986), which may stabilize the capsid (Tao *et al.*, 1998). The approximate 20-kbp genome of ϕ29-like phages is linear and encodes about 25 proteins. The 5′ ends of the genome are attached covalently to a terminal protein (TP). ϕ29-like viruses are among the smallest dsDNA phages isolated so far and thus represent minimal model systems (Meijer *et al.*, 2001a).

1. Protein–protein interactions—A literature and database search on ϕ29-like viruses retrieved 30 PPIs (Tables X and XI) with evidence mainly from directed experiments and structure determination studies. Twenty-three are attributed to phage ϕ29 itself, five to GA-1, and two to Nf, emphasizing the role of ϕ29 as a model for the whole group. The biology of other ϕ29-like phages is poorly understood, and only a few proteins have been characterized experimentally. In some cases, ϕ29 PPIs are conserved among other ϕ29-like homologues, supporting a close relationship of these phages. However, there are also differences that reveal interesting insights into their evolution. Known ϕ29 protein–protein interactions include proteins involved in transcriptional regulation, DNA replication, and virion structure. Only three PPIs between ϕ29 and *B. subtilis* proteins have been identified so far.

2. Protein-primed DNA replication—Phage ϕ29 DNA polymerase (DNAP, gp2) interacts with terminal protein (TP, gp3) to initiate genome replication. Interactions have

also been shown between the corresponding GA-1 and Nf orthologs (Table XI). The structure of the ϕ29 TP–DNAP complex has been determined and suggests that the priming domain of TP occupies the dsDNA-binding tunnel, allowing the DNAP to bind negatively charged amino acid residues of TP (Kamtekar *et al.*, 2006).

Phage ϕ29 replication depends on the presence of a single dAMP residue linked covalently via its 5′-phosphoryl group to the hydroxyl group of Ser^{232} of TP. Formation of the phosphoester bond is catalyzed by the DNAP itself (Blanco and Salas, 1984; Hermoso *et al.*, 1985); thus formation of a stable DNAP–TP heterodimeric protein complex is required (Blanco *et al.*, 1987). The TP–dAMP is elongated by the same DNAP (Méndez *et al.*, 1992). After the synthesis of six to nine nucleotides, DNAP dissociates from TP and starts continuous, linear synthesis (Méndez *et al.*, 1997). This mechanism of protein-dependent DNA replication initiation was shown for Nf and GA-1 (Illana *et al.*, 1996; Longás *et al.*, 2008), *S. pneumoniae* phage Cp-1, *E. coli* phage PRD1, adenoviruses, and some plasmids and bacterial genomes (e.g., *Streptomyces*), although there may be differences in the various priming mechanisms (de Jong and van der Vliet, 1999; Martin *et al.*, 1996; Salas, 1991).

The TP–DNAP interaction plays a central role in ϕ29 DNA replication initiation. However, other PPIs with TP are known, and thus protein-primed DNA replication may be more complicated than is currently known (Figs. 11C and Fig. 12). Chemical cross-linking shows that TP forms homodimers (Serna-Rico *et al.*, 2003). Analysis of TP mutants suggests that the parental TP (TP bound to the parental genome) recruits the free TP–DNAP complex via a TP–TP interaction (Illana *et al.*, 1999), but an additional interaction between parental TP and DNAP might be important for the specificity of replication initiation (González-Huici *et al.*, 2000).

TP interacts with the replication organizer gp16.7 (Serna-Rico *et al.*, 2003) (Fig. 12). Gp16.7, which has the potential to bind to both ssDNA and dsDNA, is an integral membrane protein consisting of an N-terminal membrane anchor and a C-terminal cytoplasmic domain. It localizes ϕ29 DNA replication to the membrane (Meijer *et al.*, 2000, 2001b; Serna-Rico *et al.*, 2002, 2003). The C-terminal domain of gp16.7 dimerizes in solution but forms larger filaments in the presence of ssDNA (Asensio *et al.*, 2005; Serna-Rico *et al.*, 2003). Replication, which starts at both DNA ends, first produces a so-called type I replication intermediate consisting of dsDNA with ssDNA regions caused by displacement of the non-template DNA parental strand. Later, when the two replication forks have merged, the parental DNA strands become separated into two type II replication intermediates, still containing ssDNA regions in the parental template. A crystal structure of the gp16.7 DNA-binding C-terminal domain complexed with dsDNA reveals three gp16.7 dimers forming a deep, positively charged longitudinal cavity that interacts nonspecifically with the DNA phosphate backbone (Albert *et al.*, 2005). Rp16.7 localizes in peripheral helix-like structures in a bacterial MreB cytoskeleton-dependent manner (Muñoz-Espín *et al.*, 2010). In fact, protein gp16.7 interacts directly with MreB; this interaction is required for efficient ϕ29 DNA replication, allowing simultaneous replication of multiple templates at various peripheral sites.

Phage ϕ29 gp1 is another early protein that binds TP (Bravo *et al.*, 2000). Rp1, like gp16.7, is membrane associated and self-associates into long filamentous structures (Bravo and Salas, 1997, 1998). Its membrane association and polymerization are mediated through a C-terminal hydrophobic sequence, whereas binding to TP involves an N-terminal region. In contrast to gp16.7, gp1 does not bind DNA (Fig. 12) and is thought to be another component that directs ϕ29 DNA replication to the membrane (Bravo *et al.*, 2000). Any interplay between gp16.7 and gp1 in this process is unknown.

The ϕ29 histone-like, nonspecific dsDNA-binding protein gp6 forms a nucleoprotein complex with ϕ29 DNA that covers most of the genome, implicating it in genome organization (Serrano *et al.*, 1994). Rp6 either unwinds the genome termini or interacts with TP directly, thus making a TP complex competent to bind the genome ends (Blanco *et al.*, 1986; Serrano *et al.*, 1994). Rp6 forms long oligomeric protein filaments thought to function as a protein backbone for DNA binding (Abril *et al.*, 1999). GA-1 and Nf gp6 orthologues also self-associate (Freire *et al.*, 1996). Rp6 also binds gp17, an early protein that stimulates the first viral replication round *in vivo* when other replication proteins are present at low levels (Crucitti *et al.*, 1998, 2003). In contrast to gp6, gp17 does not bind DNA but its interaction with gp6 enhances gp6 binding to the replication origins, thereby stimulating early rounds of replication.

A homomeric interaction was demonstrated for the single-stranded DNA-binding protein of GA-1. GA-1 SSB was surprisingly found as a homohexamer in solution, whereas SSBs of Nf and ϕ29 (p5) appear to be stable monomers (Gascón *et al.*, 2000). The homohexamer binds to ssDNA with higher affinity than the monomer and exhibits a higher stimulatory effect on DNA replication.

Bacteriophages have evolved different mechanisms to protect their genomes from degradation by host nucleases in the cell. One protective strategy includes the incorporation of noncanonical nucleotides into their DNA. For instance, *B. subtilis* phage PBS2 uses uracil instead of thymine (Takahashi and Marmur, 1963). PBS2 achieves this unusual goal by increasing the dUTP pool, relative to dTTP, after infection. In addition, PBS2 encodes Ugi, a protein that specifically inhibits the host uracil–DNA glycosylase (UDG)(Cone *et al.*, 1980), which is involved in the first step of removing incorporated uracil residues via the base excision repair pathway. Normally, this takes place to avoid mutational effects in the host genome but it would impair the incorporation of uracil into the PBS2 genome. Cocrystallization of Ugi and UDG revealed that Ugi mimics uracil-containing duplex DNA, thereby blocking efficient DNA binding of UDG (Putnam *et al.*, 1999). ϕ29 blocks the host UDG by an interaction with the early protein gp56 (gp0.8) that competes with the DNA-binding ability of UDG (Serrano-Heras *et al.*, 2006, 2007, 2008). Although the ϕ29 genome does not contain uracil (Serrano-Heras *et al.*, 2006), ϕ29 DNAP is able to incorporate dUMP with a catalytic activity only twofold lower than for that of dTMP. Because ϕ29 DNAP does not discriminate stringently between dTMP and dUMP, UDG inhibition via gp56 minimizes uracil incorporation.

3. Interactions during transcriptional regulation—Transcriptional regulation of the ϕ29 genome has been studied extensively (Meijer *et al.*, 2001a; Rojo *et al.*, 1998). The transition from early to late gene expression is controlled by gp4 (Fig. 11). Gp4 is a homodimer in solution (Mencía *et al.*, 1996b); it forms a tetramer when bound to the intergenic region between gene *6* and gene *7*, which contains the A2b, A2c, and A3 promoters (Fig. 11A). One binding site is upstream of A3, the late promoter that lacks a -35 box (Barthelemy and Salas, 1989). Once gp4 is bound, it recruits, via a PPI, the host RNAP, leading both to its stabilization on the promoter and transcriptional activation (Nuez *et al.*, 1992). Although gp4 activates late gene expression, it represses early gene expression from the A2b and A2c promoters (Monsalve *et al.*, 1997; Rojo and Salas, 1991). Interestingly, repression of A2c and activation of A3 involve the same residues of gp4 with the C-terminal domain of the RNAP α subunit (Mencía *et al.*, 1996a; Monsalve *et al.*, 1996a,b). Rp6 also interacts with gp4 in regulating the transcription of promoters A2b, A2c, and A3. Gp6 binds gp4 cooperatively to form a repression complex at promoters A2b and A2c while stimulating A3 (Calles *et al.*, 2002; Elías-Arnanz and Salas, 1999).

4. Virion structure and morphogenesis—Cryo-EM analyses have revealed many details about the ϕ29 virion structure (Morais *et al.*, 2003, 2005; Tao *et al.*, 1998; Xiang *et al.*, 2008, 2009), and many structures of virion proteins and factors are known (Table X). Assembly starts from a connector core particle consisting of 12 subunits of gp10 on which the scaffolding protein gp7 binds, followed by recruitment of the major capsid protein gp8 (Guo *et al.*, 1991; Lee and Guo, 1995). The scaffolding protein is needed to create a lattice of concentric shells (Morais *et al.*, 2003) and helps to organize the single capsomers built up by gp8 except for the basal connector capsomer. ϕ29 proheads were shown to consist of 235 copies of gp8 arranged as hexameric and pentameric capsomeres, indicating that direct interactions between gp8 monomers occur (Morais *et al.*, 2005). The capsid fiber protein gp8.5, which is present in ϕ29 proheads, is presumably connected via gp8 to the prohead and is suggested to be organized as homotrimers via interactions of a C-terminal coiled-coil region (Morais *et al.*, 2005). In addition to gp8, gp8.5, and gp10, ϕ29 proheads contain a homopentameric packaging RNA (pRNA) that binds to the connector, forming a basket-like complex (Simpson *et al.*, 2000). pRNA is needed to translocate DNA into the prohead. Furthermore, the DNA translocation machinery needs the ATPase gp16 to drive the packaging reaction (see also chapter 9 of this volume). Rp16 was shown to bind to the connector protein (Ibarra *et al.*, 2001). While other phages use specific DNA sequences to recognize and recruit the genome to the procapsids, ϕ29 DNA packaging initiation is dependent on the TP gp3 present at the genome ends, indicating that an interaction between gp16 and DNA-bound gp3 recruits the DNA to proheads and initiates packaging (Guo *et al.*, 1987). Release of the scaffolding protein is associated with DNA packaging and pRNA and gp16 are released when there is no more DNA to package.

An interesting aspect of ϕ29 is that the virion contains several enzymes that are associated with structural proteins. For instance, gp12 is a homotrimer that participates in host cell recognition and entry. It also shows autocatalytic cleavage, although it remains unclear what the function of that reaction is. Similarly, gp13 is bound as a dimer at the distal end of the ϕ29 tail knob to gp9; gp13 cleaves both the polysaccharide backbone and peptide cross-links of the cell wall during infection.

IV. CONCLUSIONS

A. High-throughput data vs small-scale interactions

It took several decades to collect the interactions of phage λ, even though it has only a few dozen genes. These interactions have been studied in painstaking individual experiments. Since the mid-1990s, new strategies have been developed to identify and analyze PPIs on a larger scale, particularly two-hybrid-related methods and techniques involving protein complex purification and mass spectrometry. Despite the pioneering efforts of (Bartel *et al.*, 1997) to map the interactome of phage T7 in a “single” experiment, their results remain somewhat contentious. Why is that? Studies show that each two-hybrid system produces system-specific data, and each system may only be able to identify as few as 20–30% of all interactions (Chen *et al.*, 2010). It has been shown that the application of up to 10 different Y2H systems can identify up to 80% of all interactions, but there are still some that go undetected (Chen *et al.*, 2010). This limited sensitivity can be explained by differences between the individual Y2H systems, expression levels, the way fusion proteins are constructed (e.g., N-terminal fusions vs C-terminal fusions), or linkers between fusion proteins. Some interactions may be completely undetectable by Y2H assays as these experiments are typically done in yeast, which may not have the necessary chaperones for bacterial or phage proteins to fold properly or the proteins may localize differently than in their normal organism.

Similar limitations apply to strategies that involve protein complex purification and mass spectrometry. Because many purifications are sensitive to small changes in protocols, even when a complex is purified within the same laboratory different preparations often result in different protein compositions in subsequent MS analyses (Gavin *et al.*, 2006). If two different laboratories purify the same protein complexes using different methods, the results may differ even more dramatically (Hu *et al.*, 2009).

Even if large-scale screens identify the majority of interactions, they will always also identify false positives. For instance, a screen of λPPIs yielded 97 interactions among λ proteins (Rajagopala *et al.*, 2011). While the authors detected about half of the 33 published interactions listed in Table III, they also found many new interactions. Many do not seem plausible and are likely false positives. However, there is no way of knowing which ones are in fact false. We can only make educated guesses and rank all interactions by their plausibility, selecting only the best candidates for more detailed studies.

B. Phage of the same host has different interactomes

Where it is known, all bacteria are infected by numerous unrelated phages. While unrelated phages cannot have identical intraphage interactions, their proteins may interact with the same targets in their host cells. While interaction databases do not have enough information about phage–host interactions to draw general conclusions, several lines of evidence indicate that this is not generally true. For instance, the well-studied phages T7 and λ interact with different host proteins. They seem to share only one common interaction target, namely the RecBCD recombinase complex (see Tables II and IV). λ certainly has about twice as many host–phage interactions than T7, but this is certainly due to λ being temperate. T4 probably does interact somewhat more extensively with the host than T7, and one could argue that this is due to genome size. Similarly, in *Streptococcus* phage Dp-1 the authors found 38 interactions among the 72 phage proteins and its host, while the 28 (unrelated) proteins of phage Cp1 showed only 11 such interations (Häuser *et al.*, 2011). Together, Dp-1 and Cp-1 target a total of 36 host proteins, of which only 2 are shared. More host–phage interactomes are needed to draw more general conclusions though.

C. Evolution of interactions [λ, P22]

We expect that related phage have similar interaction patterns, both among phage proteins and between phage and host proteins. This is certainly true for very closely related phages. However, phages evolve much faster than any other living system and thus may lose or gain interactions faster too. Unfortunately, there is not enough interaction data to make detailed comparisons, even among the well-studied lambdoid phages. However, many individual cases of proteins are not obviously homologous by sequence but which are believed to share a common ancestor, for example, the capsid proteins of λ and HK97. These proteins also have similar structures and make similar contacts in the capsid (Hendrix, 2005). Evolutionary relationships are also supported by the extensive similarities in parts of their genomes, that is, genome mosaicism (Casjens, 2011; Casjens and Thuman-Commike, 2011; Hendrix and Casjens, 2006). It remains to be seen how many interactions are conserved and how successful phages are in inventing new interactions (or discarding them). More systematic studies of multiple phages in parallel will be required to obtain comparable data sets in which differences in interaction patterns are not based on the use of noncomparable methods.

Acknowledgments

Work on this chapter was partially funded by NIH Grant R01GM79710 to P.U., the European Union (Grant HEALTH-F3-2009-223101)(P.U., R.H., and S.B.), NIH Grant RO1 AI074825 (S.R.C), and the Spanish Ministry of Science and Innovation (Grant BFU2008-00215) to M.S.

References

Abbani MA, Papagiannis CV, Sam MD, Cascio D, Johnson RC, Clubb RT. Structure of the cooperative Xis-DNA complex reveals a micronucleoprotein filament that regulates phage lambda intasome assembly. Proc Natl Acad Sci USA. 2007; 104:2109–2114. [PubMed: 17287355]

Abril AM, Marco S, Carrascosa JL, Salas M, Hermoso JM. Oligomeric structures of the phage phi29 histone-like protein p6. J Mol Biol. 1999; 292:581–588. [PubMed: 10497023]

Agarwal M, Arthur M, Arbeit RD, Goldstein R. Regulation of icosahedral virion capsid size by the *in vivo* activity of a cloned gene product. Proc Natl Acad Sci USA. 1990; 87:2428–2432. [PubMed: 2181437]

Agirrezabala X, Martin-Benito J, Caston JR, Miranda R, Valpuesta JM, Carrascosa JL. Maturation of phage T7 involves structural modification of both shell and inner core components. EMBO J. 2005a; 24:3820–3829. [PubMed: 16211007]

Agirrezabala X, Martin-Benito J, Valle M, Gonzalez JM, Valencia A, Valpuesta JM, Carrascosa JL. Structure of the connector of bacteriophage T7 at 8A resolution: Structural homologies of a basic component of a DNA translocating machinery. J Mol Biol. 2005b; 347:895–902. [PubMed: 15784250]

Agirrezabala X, Velazquez-Muriel JA, Gomez-Puertas P, Scheres SH, Carazo JM, Carrascosa JL. Quasi-atomic model of bacteriophage t7 procapsid shell: insights into the structure and evolution of a basic fold. Structure. 2007; 15:461–472. [PubMed: 17437718]

Albert A, Munoz-Espin D, Jimenez M, Asensio JL, Hermoso JA, Salas M, Meijer WJ. Structural basis for membrane anchorage of viral phi29 DNA during replication. J Biol Chem. 2005; 280:42486–42488. [PubMed: 16275651]

Alfano C, McMacken R. Ordered assembly of nucleoprotein structures at the bacteriophage lambda replication origin during the initiation of DNA replication. J Biol Chem. 1989; 264:10699–10708. [PubMed: 2525129]

Ali SS, Beckett E, Bae SJ, Navarre WW. The 5.5 protein of phage T7 inhibits H-NS through interactions with the central oligomerization domain. J Bacteriol. 2011; 193:4881–4892. [PubMed: 21764926]

Anderson DL, Hickman DD, Reilly BE. Structure of *Bacillus subtilis* bacteriophage phi 29 and the length of phi 29 deoxyribonucleic acid. J Bacteriol. 1966; 91:2081–2089. [PubMed: 4957028]

Anderson WF, Takeda Y, Echols H, Matthews BW. The structure of a repressor: Crystallographic data for the Cro regulatory protein of bacteriophage lambda. J Mol Biol. 1979; 130:507–510. [PubMed: 480362]

Ang D, Keppel F, Klein G, Richardson A, Georgopoulos C. Genetic analysis of bacteriophage-encoded cochaperonins. Annu Rev Genet. 2000; 34:439–456. [PubMed: 11092834]

Asensio JL, Albert A, Muñoz-Espín D, González C, Hermoso J, Villar L, Jiménez-Barbero J, Salas M, Meijer WJ. Structure of the functional domain of phi29 replication organizer: Insights into oligomerization and DNA binding. J Biol Chem. 2005; 280:20730–20739. [PubMed: 15772069]

Atanasiu C, Byron O, McMiken H, Sturrock SS, Dryden DT. Characterisation of the structure of ocr, the gene 0.3 protein of bacteriophage T7. Nucleic Acids Res. 2001; 29:3059–3068. [PubMed: 11452031]

Atanasiu C, Su TJ, Sturrock SS, Dryden DT. Interaction of the ocr gene 0.3 protein of bacteriophage T7 with EcoKI restriction/modification enzyme. Nucleic Acids Res. 2002; 30:3936–3944. [PubMed: 12235377]

Ayers DJ, Sunshine MG, Six EW, Christie GE. Mutations affecting two adjacent amino acid residues in the alpha subunit of RNA polymerase block transcriptional activation by the bacteriophage P2 Ogr protein. J Bacteriol. 1994; 176:7430–7438. [PubMed: 8002564]

Backhaus H, Petri JB. Sequence analysis of a region from the early right operon in phage P22 including the replication genes 18 and 12. Gene. 1984; 32:289–303. [PubMed: 6241581]

Badia D, Camacho A, Pérez-Lago L, Escandón C, Salas M, Coll M. The structure of phage phi29 transcription regulator p4-DNA complex reveals an N-hook motif for DNA. Mol Cell. 2006; 22:73–81. [PubMed: 16600871]

Ball CA, Johnson RC. Efficient excision of phage lambda from the *Escherichia coli* chromosome requires the Fis protein. J Bacteriol. 1991; 173:4027–4031. [PubMed: 1829453]

Barrett KJ, Marsh ML, Calendar R. Interactions between a satellite bacteriophage and its helper. J Mol Biol. 1976; 106:683–707. [PubMed: 789896]

Bartel PL, Roecklein JA, SenGupta D, Fields S. A protein linkage map of Escherichia coli bacteriophage T7. Nat Genet. 1996; 12:72–77. [PubMed: 8528255]

Barthelemy I, Salas M. Characterization of a new prokaryotic transcriptional activator and its DNA recognition site. J Mol Biol. 1989; 208:225–232. [PubMed: 2504924]

Bazinet C, Benbasat J, King J, Carazo JM, Carrascosa JL. Purification and organization of the gene 1 portal protein required for phage P22 DNA packaging. Biochemistry. 1988; 27:1849–1856. [PubMed: 3288279]

Bell CE, Lewis M. Crystal structure of the lambda repressor C-terminal domain octamer. J Mol Biol. 2001; 314:1127–1136. [PubMed: 11743728]

Bertani G. Studies on lysogenesis. I. The mode of phage liberation by lysogenic *Escherichia coli*. J Bacteriol. 1951; 62:293–300. [PubMed: 14888646]

Bertani, LE.; Six, E. The P2-like phages and their parasite, P4. Calendar, R., editor. Plenum Press; New York: 1988. p. 73-143.

Bienkowska-Szewczyk K, Lipinska B, Taylor A. The R gene product of bacteriophage lambda is the murein transglycosylase. Mol Gen Genet. 1981; 184:111–114. [PubMed: 6460914]

Blanco L, Gutierrez J, Lazaro JM, Bernad A, Salas M. Replication of phage phi 29 DNA *in vitro*: Role of the viral protein p6 in initiation and elongation. Nucleic Acids Res. 1986; 14:4923–4937. [PubMed: 3088545]

Blanco L, Prieto I, Gutierrez J, Bernad A, Lazaro JM, Hermoso JM, Salas M. Effect of NH4+ ions on phi 29 DNA-protein p3 replication: Formation of a complex between the terminal protein and the DNA polymerase. J Virol. 1987; 61:3983–3991. [PubMed: 3682063]

Blanco L, Salas M. Characterization and purification of a phage phi 29-encoded DNA polymerase required for the initiation of replication. Proc Natl Acad Sci USA. 1984; 81:5325–5329. [PubMed: 6433348]

Botstein D, Waddell CH, King J. Mechanism of head assembly and DNA encapsulation in *Salmonella* phage P22. I. Genes, proteins, structures and DNA maturation. J Mol Biol. 1973; 80:669–695. [PubMed: 4773026]

Bowden DW, Modrich P. *In vitro* maturation of circular bacteriophage P2 DNA: Purification of ter components and characterization of the reaction. J Biol Chem. 1985; 260:6999–7007. [PubMed: 2987239]

Bowie JU, Sauer RT. Equilibrium dissociation and unfolding of the Arc repressor dimer. Biochemistry. 1989; 28:7139–7143. [PubMed: 2819054]

Bravo A, Illana B, Salas M. Compartmentalization of phage phi29 DNA replication: Interaction between the primer terminal protein and the membrane-associated protein p1. EMBO J. 2000; 19:5575–5584. [PubMed: 11032825]

Bravo A, Salas M. Initiation of bacteriophage phi29 DNA replication *in vivo*: assembly of a membrane-associated multiprotein complex. J Mol Biol. 1997; 269:102–112. [PubMed: 9193003]

Bravo A, Salas M. Polymerization of bacteriophage phi 29 replication protein p1 into protofilament sheets. EMBO J. 1998; 17:6096–6105. [PubMed: 9774353]

Breg JN, van Opheusden JH, Burgering MJ, Boelens R, Kaptein R. Structure of Arc repressor in solution: Evidence for a family of beta- sheet DNA-binding proteins. Nature. 1990; 346:586–589. [PubMed: 2377232]

Breitbart M, Salamon P, Andresen B, Mahaffy JM, Segall AM, Mead D, Azam F, Rohwer F. Genomic analysis of uncultured marine viral communities. Proc Natl Acad Sci USA. 2002; 99:14250–14255. [PubMed: 12384570]

Briani F, Deho G, Forti F, Ghisotti D. The plasmid status of satellite bacteriophage P4. Plasmid. 2001; 45:1–17. [PubMed: 11319927]

Broadbent SE, Davies MR, van der Woude MW. Phase variation controls expression of Salmonella lipopolysaccharide modification genes by a DNA methylation-dependent mechanism. Mol Microbiol. 2010; 77:337–353. [PubMed: 20487280]

Brown BM, Bowie JU, Sauer RT. Arc repressor is tetrameric when bound to operator DNA. Biochemistry. 1990; 29:11189–11195. [PubMed: 2271706]

Buchwald M, Murialdo H, Siminovitch L. The morphogenesis of bacteriophage lambda. II. Identification of the principal structural proteins. Virology. 1970a; 42:390–400. [PubMed: 4923012]

Buchwald M, Siminovitch L. Production of serum-blocking material by mutants of the left arm of the lambda chromosome. Virology. 1969; 38:1–7. [PubMed: 4891222]

Buchwald M, Steed-Glaister P, Siminovitch L. The morphogenesis of bacteriophage lambda. I. Purification and characterization of lambda heads and lambda tails. Virology. 1970b; 42:375–389. [PubMed: 4099070]

Calendar, R. The Bacteriophages. 2. Oxford University Press; Oxford: 2006.

Calendar R, Lindqvist B, Sironi G, Clark A. Characterization of REP- mutants and their interaction with P2 phage. Virology. 1970; 40:72–83. [PubMed: 4903860]

Calles B, Salas M, Rojo F. The phi29 transcriptional regulator contacts the nucleoid protein p6 to organize a repression complex. EMBO J. 2002; 21:6185–6194. [PubMed: 12426390]

Camacho A, Salas M. Mechanism for the switch of phi29 DNA early to late transcription by regulatory protein p4 and histone-like protein p6. EMBO J. 2001; 20:6060–6070. [PubMed: 11689446]

Camara B, Liu M, Reynolds J, Shadrin A, Liu B, Kwok K, Simpson P, Weinzierl R, Severinov K, Cota E, Matthews S, Wigneshweraraj SR. T7 phage protein Gp2 inhibits the *Escherichia coli* RNA polymerase by antagonizing stable DNA strand separation near the transcription start site. Proc Natl Acad Sci USA. 2010; 107:2247–2252. [PubMed: 20133868]

Campbell A, del-Campillo-Campbell A, Ginsberg ML. Specificity in DNA recognition by phage integrases. Gene. 2002; 300:13–18. [PubMed: 12468081]

Cardarelli L, Lam R, Tuite A, Baker LA, Sadowski PD, Radford DR, Rubinstein JL, Battaile KP, Chirgadze N, Maxwell KL, Davidson AR. The crystal structure of bacteriophage HK97 gp6: Defining a large family of head-tail connector proteins. J Mol Biol. 2010; 395:754–768. [PubMed: 19895817]

Casjens S. Bacteriophage lambda FII gene protein: Role in head assembly. J Mol Biol. 1974; 90:1–20. [PubMed: 4616093]

Casjens S. Molecular organization of the bacteriophage P22 coat protein shell. J Mol Biol. 1979; 131:1–14. [PubMed: 385887]

Casjens S. Evolution of mosaically related tailed bacteriophage genomes seen through the lens of phage P22 virion assembly. Virology. 2011 in press.

Casjens S, Eppler K, Parr R, Poteete AR. Nucleotide sequence of the bacteriophage P22 gene 19 to 3 region: Identification of a new gene required for lysis. Virology. 1989; 171:588–598. [PubMed: 2763468]

Casjens S, Hayden M. Analysis *in vivo* of the bacteriophage P22 headful nuclease. J Mol Biol. 1988; 199:467–474. [PubMed: 3280806]

Casjens S, Horn T, Kaiser AD. Head assembly steps controlled by genes F and W in bacteriophage lambda. J Mol Biol. 1972; 64:551–563. [PubMed: 5022189]

Casjens SR. Comparative genomics and evolution of the tailed-bacteriophages. Curr Opin Microbiol. 2005; 8:451–458. [PubMed: 16019256]

Casjens SR, Hendrix RW. Locations and amounts of major structural proteins in bacteriophage lambda. J Mol Biol. 1974; 88:535–545. [PubMed: 4476800]

Casjens SR, Thuman-Commike PA. Evolution of mosaically related tailed bacteriophage genomes seen through the lens of phage P22 virion assembly. Virology. 2011; 411:393–415. [PubMed: 21310457]

Catalano CE. The terminase enzyme from bacteriophage lambda: A DNA-packaging machine. Cell Mol Life Sci. 2000; 57:128–148. [PubMed: 10949585]

Catalano CE, Tomka MA. Role of gpFI protein in DNA packaging by bacteriophage lambda. Biochemistry. 1995; 34:10036–10042. [PubMed: 7632676]

Cerritelli ME, Conway JF, Cheng N, Trus BL, Steven AC. Molecular mechanisms in bacteriophage T7 procapsid assembly, maturation, and DNA containment. Adv Protein Chem. 2003a; 64:301–323. [PubMed: 13677051]

Cerritelli ME, Studier FW. Assembly of T7 capsids from independently expressed and purified head protein and scaffolding protein. J Mol Biol. 1996a; 258:286–298. [PubMed: 8627626]

Cerritelli ME, Studier FW. Purification and characterization of T7 head-tail connectors expressed from the cloned gene. J Mol Biol. 1996b; 258:299–307. [PubMed: 8627627]

Cerritelli ME, Trus BL, Smith CS, Cheng N, Conway JF, Steven AC. A second symmetry mismatch at the portal vertex of bacteriophage T7: 8-fold symmetry in the procapsid core. J Mol Biol. 2003b; 327:1–6. [PubMed: 12614603]

Chang CY, Kemp P, Molineux IJ. Gp15 and gp16 cooperate in translocating bacteriophage T7 DNA into the infected cell. Virology. 2010; 398:176–186. [PubMed: 20036409]

Chang JR, Poliakov A, Prevelige PE, Mobley JA, Dokland T. Incorporation of scaffolding protein gpO in bacteriophages P2 and P4. Virology. 2008; 370:352–361. [PubMed: 17931675]

Chang JR, Spilman MS, Rodenburg CM, Dokland T. Functional domains of the bacteriophage P2 scaffolding protein: Identification of residues involved in assembly and protease activity. Virology. 2009; 384:144–150. [PubMed: 19064277]

Cheetham GM, Jeruzalmi D, Steitz TA. Structural basis for initiation of transcription from an RNA polymerase-promoter complex. Nature. 1999; 399:80–83. [PubMed: 10331394]

Cheetham GM, Steitz TA. Structure of a transcribing T7 RNA polymerase initiation complex. Science. 1999; 286:2305–2309. [PubMed: 10600732]

Chen DH, Baker ML, Hryc CF, DiMaio F, Jakana J, Wu W, Dougherty M, Haase-Pettingell C, Schmid MF, Jiang W, Baker D, King JA, et al. Structural basis for scaffolding-mediated assembly and maturation of a dsDNA virus. Proc Natl Acad Sci USA. 2011; 108:1355–1360. [PubMed: 21220301]

Chen KC, Vannais DB, Jones C, Patterson D, Davidson JN. Mapping of the gene encoding the multifunctional protein carrying out the first three steps of pyrimidine biosynthesis to human chromosome 2. Hum Genet. 1989; 82:40–44. [PubMed: 2565865]

Chen YC, Rajagopala SV, Stellberger T, Uetz P. Exhaustive benchmarking of the yeast two-hybrid system. Nature Methods. 2010; 7:667–668. [PubMed: 20805792]

Cheng H, Shen N, Pei J, Grishin NV. Double-stranded DNA bacteriophage prohead protease is homologous to herpesvirus protease. Protein Sci. 2004; 13:2260–2269. [PubMed: 15273316]

Cheng X, Wang W, Molineux IJ. F exclusion of bacteriophage T7 occurs at the cell membrane. Virology. 2004; 326:340–352. [PubMed: 15302217]

Cho EH, Gumport RI, Gardner JF. Interactions between integrase and excisionase in the phage lambda excisive nucleoprotein complex. J Bacteriol. 2002; 184:5200–5203. [PubMed: 12193639]

Cho EH, Nam CE, Alcaraz R Jr, Gardner JF. Site-specific recombination of bacteriophage P22 does not require integration host factor. J Bacteriol. 1999; 181:4245–4249. [PubMed: 10400581]

Christie G, Anders D, McAlister V, Goodwin T, Julien B, Calendar R. Identification of upstream sequences essential for activation of a bacteriophage P2 late promoter. J Bacteriol. 2003; 185:4609–4614. [PubMed: 12867472]

Christie G, Temple L, Bartlett B, Goodwin T. Programmed translational frameshift in the bacteriophage P2 FETUD tail gene operon. J Bacteriol. 2002; 184:6522–6531. [PubMed: 12426340]

Christie GE, Calendar R. Interactions between satellite bacteriophage P4 and its helpers. Annu Rev Genet. 1990; 24:465–490. [PubMed: 2088176]

Clement JM, Lepouce E, Marchal C, Hofnung M. Genetic study of a membrane protein: DNA sequence alterations due to 17 lamB point mutations affecting adsorption of phage lambda. EMBO J. 1983; 2:77–80. [PubMed: 11894913]

Cone R, Bonura T, Friedberg EC. Inhibitor of uracil-DNA glycosylase induced by bacteriophage PBS2: Purification and preliminary characterization. J Biol Chem. 1980; 255:10354–10358. [PubMed: 6776115]

Cortines JR, Weigele PR, Gilcrease EB, Casjens SR, Teschke CM. Decoding bacteriophage P22 assembly: Identification of two charged residues in scaffolding protein responsible for coat protein interaction. Virology. 2011; 421:1–11. [PubMed: 21974803]

Court DL, Oppenheim AB, Adhya SL. A new look at bacteriophage lambda genetic networks. J Bacteriol. 2007; 189:298–304. [PubMed: 17085553]

Crisona NJ, Weinberg RL, Peter BJ, Sumners DW, Cozzarelli NR. The topological mechanism of phage lambda integrase. J Mol Biol. 1999; 289:747–775. [PubMed: 10369759]

Crucitti P, Abril AM, Salas M. Bacteriophage phi 29 early protein p17. Self-association and hetero-association with the viral histone-like protein p6. J Biol Chem. 2003; 278:4906–4911. [PubMed: 12480935]

Crucitti P, Lazaro JM, Benes V, Salas M. Bacteriophage phi29 early protein p17 is conditionally required for the first rounds of viral DNA replication. Gene. 1998; 223:135–142. [PubMed: 9858710]

d'Herelle, F. The Bacteriophage and Its Behavior. Williams & Wilkins; Baltimore, MD: 1926. p. 490-497.

Darling PJ, Holt JM, Ackers GK. Coupled energetics of lambda cro repressor self-assembly and site-specific DNA operator binding I: Analysis of cro dimerization from nanomolar to micromolar concentrations. Biochemistry. 2000; 39:11500–11507. [PubMed: 10985796]

Das A. How the phage lambda N gene product suppresses transcription termination: communication of RNA polymerase with regulatory proteins mediated by signals in nascent RNA. J Bacteriol. 1992; 174:6711–6716. [PubMed: 1400223]

Datta AB, Roy S, Parrack P. Role of C-terminal residues in oligomerization and stability of lambda CII: Implications for lysis-lysogeny decision of the phage. J Mol Biol. 2005a; 345:315–324. [PubMed: 15571724]

Datta I, Banik-Maiti S, Adhikari L, Sau S, Das N, Mandal NC. The mutation that makes *Escherichia coli* resistant to lambda P gene-mediated host lethality is located within the DNA initiator Gene dnaA of the bacterium. J Biochem Mol Biol. 2005b; 38:89–96. [PubMed: 15715952]

Datta I, Sau S, Sil AK, Mandal NC. The bacteriophage lambda DNA replication protein P inhibits the oriC DNA- and ATP-binding functions of the DNA replication initiator protein DnaA of *Escherichia coli*. J Biochem Mol Biol. 2005c; 38:97–103. [PubMed: 15715953]

De Anda J, Poteete AR, Sauer RT. P22 c2 repressor. Domain structure and function. J Biol Chem. 1983; 258:10536–10542. [PubMed: 6554278]

de Beer T, Fang J, Ortega M, Yang Q, Maes L, Duffy C, Berton N, Sippy J, Overduin M, Feiss M, Catalano CE. Insights into specific DNA recognition during the assembly of a viral genome packaging machine. Mol Cell. 2002; 9:981–991. [PubMed: 12049735]

de Beus MD, Doyle SM, Teschke CM. GroEL binds a late folding intermediate of phage P22 coat protein. Cell Stress Chaperones. 2000; 5:163–172. [PubMed: 11005374]

de Jong RN, van der Vliet PC. Mechanism of DNA replication in eukaryotic cells: Cellular host factors stimulating adenovirus DNA replication. Gene. 1999; 236:1–12. [PubMed: 10433960]

Deho, G.; Ghisotti, D. The satellite phage P4. Calendar, R., editor. Oxford University Press; New York: 2006. p. 391-408.

Deighan P, Diez CM, Leibman M, Hochschild A, Nickels BE. The bacteriophage lambda Q antiterminator protein contacts the beta-flap domain of RNA polymerase. Proc Natl Acad Sci USA. 2008; 105:15305–15310. [PubMed: 18832144]

Demerec M, Fano U. Bacteriophage-resistant mutants in *Escherichia coli*. Genetics. 1945; 30:119–136. [PubMed: 17247150]

Doan DNP, Dokland T. The gpQ portal protein of bacteriophage P2 forms dodecameric connctors in crystals. J Struct Biol. 2007; 157:432–436. [PubMed: 17049269]

Dodd IB, Perkins AJ, Tsemitsidis D, Egan JB. Octamerization of lambda CI repressor is needed for effective repression of P(RM) and efficient switching from lysogeny. Genes Dev. 2001; 15:3013–3022. [PubMed: 11711436]

Dodson M, Echols H, Wickner S, Alfano C, Mensa-Wilmot K, Gomes B, LeBowitz J, Roberts JD, McMacken R. Specialized nucleoprotein structures at the origin of replication of bacteriophage

lambda: Localized unwinding of duplex DNA by a six-protein reaction. Proc Natl Acad Sci USA. 1986; 83:7638–7642. [PubMed: 3020552]

Dokland, T. gpO peptidase (Enterobacteria phage P2). In: Rawlings, ND.; Salvesen, G., editors. Handbook of proteolytic enzymes. Elsevier; Oxford: 2011.

Dokland T, Isaksen ML, Fuller SD, Lindqvist BH. Capsid localization of the bacteriophage P4 Psu protein. Virology. 1993; 194:682–687. [PubMed: 8503181]

Dokland T, Lindqvist BH, Fuller SD. Image reconstruction from cryoelectron micrographs reveals the morphopoietic mechanism in the P2-P4 bacteriophage system. EMBO J Eur Mol Biol Organ J. 1992; 11:839–846.

Dokland T, Murialdo H. Structural transitions during maturation of bacteriophage lambda capsids. J Mol Biol. 1993; 233:682–694. [PubMed: 8411174]

Dokland T, Wang S, Lindqvist BH. The structure of P4 procapsids produced by coexpression of capsid and external scaffolding proteins. Virology. 2002; 298:224–231. [PubMed: 12127785]

Duffy C, Feiss M. The large subunit of bacteriophage lambda's terminase plays a role in DNA translocation and packaging termination. J Mol Biol. 2002; 316:547–561. [PubMed: 11866517]

Dufour E, Méndez J, Lázaro JM, de Vega M, Blanco L, Salas M. An aspartic acid residue in TPR-1, a specific region of protein-priming DNA polymerases, is required for the functional interaction with primer terminal protein. J Mol Biol. 2000; 304:289–300. [PubMed: 11090274]

Dunn JJ, Studier FW. Complete nucleotide sequence of bacteriophage T7 DNA and the locations of T7 genetic elements. J Mol Biol. 1983; 166:477–535. [PubMed: 6864790]

Echols H. Multiple DNA-protein interactions governing high-precision DNA transactions. Science. 1986; 233:1050–1056. [PubMed: 2943018]

Elías-Arnanz M, Salas M. Functional interactions between a phage histone-like protein and a transcriptional factor in regulation of phi29 early-late transcriptional switch. Genes Dev. 1999; 13:2502–2513. [PubMed: 10521395]

Eppler K, Wyckoff E, Goates J, Parr R, Casjens S. Nucleotide sequence of the bacteriophage P22 genes required for DNA packaging. Virology. 1991; 183:519–538. [PubMed: 1853558]

Eriksson JM, Haggard-Ljungquist E. The multifunctional bacteriophage P2 cox protein requires oligomerization for biological activity. J Bacteriol. 2000; 182:6714–6723. [PubMed: 11073917]

Eriksson SK, Liu T, Haggard-Ljungquist E. Interacting interfaces of the P4 antirepressor E and the P2 immunity repressor C. Mol Microbiol. 2000; 36:1148–1155. [PubMed: 10844698]

Esposito D, Gerard GF. The *Escherichia coli* Fis protein stimulates bacteriophage lambda integrative recombination *in vitro*. J Bacteriol. 2003; 185:3076–3080. [PubMed: 12730167]

Frackman S, Siegele DA, Feiss M. The terminase of bacteriophage lambda: Functional domains for cosB binding and multimer assembly. J Mol Biol. 1985; 183:225–238. [PubMed: 2989542]

Franklin NC. Conservation of genome form but not sequence in the transcription antitermination determinants of bacteriophages lambda, phi 21 and P22. J Mol Biol. 1985; 181:75–84. [PubMed: 3157001]

Freire R, Serrano M, Salas M, Hermoso JM. Activation of replication origins in phi29-related phages requires the recognition of initiation proteins to specific nucleoprotein complexes. J Biol Chem. 1996; 271:31000–31007. [PubMed: 8940089]

Friedman DI, Court DL. Bacteriophage lambda: Alive and well and still doing its thing. Curr Opin Microbiol. 2001; 4:201–207. [PubMed: 11282477]

Frumerie CM, Eriksson J, Dugast M, Haggard-Ljungquist E. Dimerization of bacteriophage P2 integrase is not required for binding to its DNA target but for its biological activity. Gene. 2005; 344:221–231. [PubMed: 15656988]

Fujiki H, Palm P, Zillig W, Calendar R, Sunshine M. Identification of a mutation within the structural gene for the a subunit of DNA-dependent RNA polymerase of *E. coli*. Mol Gen Genet. 1976; 145:19–22. [PubMed: 775306]

Fujisawa H, Shibata H, Kato H. Analysis of interactions among factors involved in the bacteriophage T3 DNA packaging reaction in a defined *in vitro* system. Virology. 1991; 185:788–794. [PubMed: 1962450]

Fujiyama A, Kohara Y, Okazaki T. Initiation sites for discontinuous DNA synthesis of bacteriophage T7. Proc Natl Acad Sci USA. 1981; 78:903–907. [PubMed: 6262782]

Fuller MT, King J. Assembly *in vitro* of bacteriophage P22 procapsids from purified coat and scaffolding subunits. J Mol Biol. 1982; 156:633–665. [PubMed: 6750133]

Funnell BE, Inman RB. Bacteriophage P2 DNA replication: Characterization of the requirement of the gene B protein *in vivo*. J Mol Biol. 1983; 167:311–334. [PubMed: 6602891]

García JA, Carrascosa JL, Salas M. Assembly of the tail protein of the *Bacillus subtilis* phage phi 29. Virology. 1983; 125:18–30. [PubMed: 6402855]

Garcia LR, Molineux IJ. Rate of translocation of bacteriophage T7 DNA across the membranes of *Escherichia coli*. J Bacteriol. 1995; 177:4066–4076. [PubMed: 7608081]

Garcia LR, Molineux IJ. Transcription-independent DNA translocation of bacteriophage T7 DNA into *Escherichia coli*. J Bacteriol. 1996; 178:6921–6929. [PubMed: 8955315]

Gascón I, Gutiérrez C, Salas M. Structural and functional comparative study of the complexes formed by viral o29, Nf and GA-1 SSB proteins with DNA. J Mol Biol. 2000; 296:989–999. [PubMed: 10686098]

Gavin AC, Aloy P, Grandi P, Krause R, Boesche M, Marzioch M, Rau C, Jensen LJ, Bastuck S, Dumpelfeld B, Edelmann A, Heurtier MA, et al. Proteome survey reveals modularity of the yeast cell machinery. Nature. 2006; 440:631–636. [PubMed: 16429126]

Geisselsoder J, Youdarian P, Deho G, Chidambaram M, Goldstein R, Ljungquist E. Mutants of satellite virus P4 that cannot derepress their bacteriophage P2 helper. J Mol Biol. 1981; 148:1–19. [PubMed: 7310867]

Georgopoulos, C.; Tilly, K.; Casjens, S. Lambdoid phage head assembly. In: Hendrix, R.; Roberts, J.; Stahl, FW.; Weisberg, R., editors. Lambda II. Cold Spring Harbor Laboratory; Cold Spring Harbor, NY: 1983. p. 279-304.

Georgopoulos CP, Hendrix RW, Casjens SR, Kaiser AD. Host participation in bacteriophage lambda head assembly. J Mol Biol. 1973; 76:45–60. [PubMed: 4578100]

Ghosh S, Hamdan SM, Cook TE, Richardson CC. Interactions of *Escherichia coli* thioredoxin, the processivity factor, with bacteriophage T7 DNA polymerase and helicase. J Biol Chem. 2008; 283:32077–32084. [PubMed: 18757858]

Ghosh S, Hamdan SM, Richardson CC. Two modes of interaction of the single-stranded DNA-binding protein of bacteriophage T7 with the DNA polymerase-thioredoxin complex. J Biol Chem. 2010; 285:18103–18112. [PubMed: 20375019]

Gilcrease EB, Winn-Stapley DA, Hewitt FC, Joss L, Casjens SR. Nucleotide sequence of the head assembly gene cluster of bacteriophage L and decoration protein characterization. J Bacteriol. 2005; 187:2050–2057. [PubMed: 15743953]

González-Huici V, Lázaro JM, Salas M, Hermoso JM. Specific recognition of parental terminal protein by DNA polymerase for initiation of protein-primed DNA replication. J Biol Chem. 2000; 275:14678–14683. [PubMed: 10799555]

Gottesman ME, Weisberg RA. Little lambda, who made thee? Microbiol Mol Biol Rev. 2004; 68:796–813. [PubMed: 15590784]

Gottesman S, Gottesman M, Shaw JE, Pearson ML. Protein degradation in *E. coli*: The lon mutation and bacteriophage lambda N and cII protein stability. Cell. 1981; 24:225–233. [PubMed: 6453650]

Greene B, King J. Binding of scaffolding subunits within the P22 procapsid lattice. Virology. 1994; 205:188–197. [PubMed: 7975215]

Greene B, King J. Scaffolding mutants identifying domains required for P22 procapsid assembly and maturation. Virology. 1996; 225:82–96. [PubMed: 8918536]

Grimes S, Anderson D. The bacteriophage phi29 packaging proteins supercoil the DNA ends. J Mol Biol. 1997; 266:901–914. [PubMed: 9086269]

Grundling A, Smith DL, Blasi U, Young R. Dimerization between the holin and holin inhibitor of phage lambda. J Bacteriol. 2000; 182:6075–6081. [PubMed: 11029427]

Guasch A, Pous J, Ibarra B, Gomis-Ruth FX, Valpuesta JM, Sousa N, Carrascosa JL, Coll M. Detailed architecture of a DNA translocating machine: The high-resolution structure of the bacteriophage phi29 connector particle. J Mol Biol. 2002; 315:663–676. [PubMed: 11812138]

Guo P, Peterson C, Anderson D. Initiation events in *in vitro* packaging of bacteriophage phi 29 DNA-gp3. J Mol Biol. 1987; 197:219–228. [PubMed: 3119862]

Guo PX, Erickson S, Xu W, Olson N, Baker TS, Anderson D. Regulation of the phage phi 29 prohead shape and size by the portal vertex. Virology. 1991; 183:366–373. [PubMed: 1905079]

Hadden JM, Declais AC, Carr SB, Lilley DM, Phillips SE. The structural basis of Holliday junction resolution by T7 endonuclease I. Nature. 2007; 449:621–624. [PubMed: 17873858]

Haggard-Ljungquist E, Halling C, Calendar R. DNA sequences of the tail fiber genes of bacteriophage P2: evidence for horizontal transfer of tail fiber genes among unrelated bacteriophages. J Bacteriol. 1992; 174:1462–1477. [PubMed: 1531648]

Haggard-Ljungquist E, Jacobsen E, Rishovd S, Six EW, Nilssen O, Sunshine MG, Lindqvist BH, Kim KJ, Barreiro V, Koonin EV, et al. Bacteriophage P2: Genes involved in baseplate assembly. Virology. 1995; 213:109–121. [PubMed: 7483254]

Halder S, Datta AB, Parrack P. Probing the antiprotease activity of lambda-CIII, an inhibitor of the *Escherichia coli* metalloprotease HflB (FtsH). J Bacteriol. 2007; 189:8130–8138. [PubMed: 17890311]

Hamada K, Fujisawa H, Minagawa T. Overproduction and purification of the products of bacteriophage T3 genes 18 and 19, two genes involved in DNA packaging. Virology. 1986; 151:110–118. [PubMed: 3962187]

Hamdan SM, Marintcheva B, Cook T, Lee SJ, Tabor S, Richardson CC. A unique loop in T7 DNA polymerase mediates the binding of helicase-primase, DNA binding protein, and processivity factor. Proc Natl Acad Sci USA. 2005; 102:5096–5101. [PubMed: 15795374]

Hamdan SM, Richardson CC. Motors, switches, and contacts in the replisome. Annu Rev Biochem. 2009; 78:205–243. [PubMed: 19298182]

Hang Q, Woods L, Feiss M, Catalano CE. Cloning, expression, and biochemical characterization of hexahistidine-tagged terminase proteins. J Biol Chem. 1999; 274:15305–15314. [PubMed: 10336415]

Häuser R, Sabri M, Moineau S, Uetz P. The proteome and interactome of Streptococcus pneumoniae phage Cp-1. J Bacteriol. 2011; 193:3135–3138. [PubMed: 21515781]

He ZG, Rezende LF, Willcox S, Griffith JD, Richardson CC. The carboxyl-terminal domain of bacteriophage T7 single-stranded DNA-binding protein modulates DNA binding and interaction with T7 DNA polymerase. J Biol Chem. 2003; 278:29538–29545. [PubMed: 12766155]

He ZG, Richardson CC. Effect of single-stranded DNA-binding proteins on the helicase and primase activities of the bacteriophage T7 gene 4 protein. J Biol Chem. 2004; 279:22190–22197. [PubMed: 15044449]

Heineman RH, Bull JJ. Testing optimality with experimental evolution: Lysis time in a bacteriophage. Evolution. 2007; 61:1695–1709. [PubMed: 17598749]

Hendrix, R.; Casjens, S. Bacteriophage lambda and its genetic neighborhood. In: Calendar, R., editor. The Bacteriophages. Vol. Chapter 27. Oxford University Press; Oxford: 2006. p. 409-445.

Hendrix, R.; Roberts, J.; Stahl, FW.; Weisberg, R. Lambda II. CSHL Press; Cold Spring Harbor, NY: 1983. p. 694

Hendrix RW. Bacteriophages: Evolution of the majority. Theor Popul Biol. 2002; 61:471–480. [PubMed: 12167366]

Hendrix RW. Bacteriophage HK97: Assembly of the capsid and evolutionary connections. Adv Virus Res. 2005; 64:1–14. [PubMed: 16139590]

Hendrix RW, Casjens SR. Protein fusion: A novel reaction in bacteriophage lambda head assembly. Proc Natl Acad Sci USA. 1974; 71:1451–1455. [PubMed: 4524648]

Hendrix RW, Casjens SR. Assembly of bacteriophage lambda heads: Protein processing and its genetic control in petit lambda assembly. J Mol Biol. 1975; 91:187–199. [PubMed: 1102701]

Hendrix RW, Duda RL. Bacteriophage lambda PaPa: Not the mother of all lambda phages. Science. 1992; 258:1145–1148. [PubMed: 1439823]

Hendrix RW, Duda RL. Bacteriophage HK97 head assembly: A protein ballet. Adv Virus Res. 1998; 50:235–288. [PubMed: 9521001]

Herman C, Thevenet D, D'Ari R, Bouloc P. The HflB protease of *Escherichia coli* degrades its inhibitor lambda cIII. J Bacteriol. 1997; 179:358–363. [PubMed: 8990286]

Hermoso JM, Méndez E, Soriano F, Salas M. Location of the serine residue involved in the linkage between the terminal protein and the DNA of phage phi 29. Nucleic Acids Res. 1985; 13:7715–7728. [PubMed: 3934646]

Hershey AD. Inheritance in bacteriophage. Ann N Y Acad Sci. 1952; 54:960–962. [PubMed: 12976998]

Ho Y, Rosenberg M. Characterization of the phage lambda regulatory protein cII. Ann Microbiol. 1982; 133:215–218.

Ho YS, Pfarr D, Strickler J, Rosenberg M. Characterization of the transcription activator protein C1 of bacteriophage P22. J Biol Chem. 1992; 267:14388–14397. [PubMed: 1385814]

Hohn T, Flick H, Hohn B. Petit lambda, a family of particles from coliphage lambda infected cells. J Mol Biol. 1975; 98:107–120. [PubMed: 1104865]

Horcajadas JA, Monsalve M, Rojo F, Salas M. The switch from early to late transcription in phage GA-1: Characterization of the regulatory protein p4G. J Mol Biol. 1999; 290:917–928. [PubMed: 10438592]

Hu P, Janga SC, Babu M, Diaz-Mejia JJ, Butland G, Yang W, Pogoutse O, Guo X, Phanse S, Wong P, Chandran S, Christopoulos C, et al. Global functional atlas of *Escherichia coli* encompassing previously uncharacterized proteins. PLoS Biol. 2009; 7:e96. [PubMed: 19402753]

Huang J, Villemain J, Padilla R, Sousa R. Mechanisms by which T7 lysozyme specifically regulates T7 RNA polymerase during different phases of transcription. J Mol Biol. 1999; 293:457–475. [PubMed: 10543943]

Huber HE, Beauchamp BB, Richardson CC. *Escherichia coli* dGTP triphosphohydrolase is inhibited by gene 1.2 protein of bacteriophage T7. J Biol Chem. 1988; 263:13549–13556. [PubMed: 2843524]

Ibarra B, Valpuesta JM, Carrascosa JL. Purification and functional characterization of p16, the ATPase of the bacteriophage phi29 packaging machinery. Nucleic Acids Res. 2001; 29:4264–4273. [PubMed: 11691914]

Illana B, Blanco L, Salas M. Functional characterization of the genes coding for the terminal protein and DNA polymerase from bacteriophage GA-1: Evidence for a sliding-back mechanism during protein-primed GA-1 DNA replication. J Mol Biol. 1996; 264:453–464. [PubMed: 8969297]

Illana B, Lázaro JM, Gutierrez C, Meijer WJ, Blanco L, Salas M. Phage phi29 terminal protein residues Asn80 and Tyr82 are recognition elements of the replication origins. J Biol Chem. 1999; 274:15073–15079. [PubMed: 10329712]

Isaksen ML, Dokland T, Lindqvist BH. Characterization of the capsid associating activity of bacteriophage P4's Psu protein. Virology. 1993; 194:647–681. [PubMed: 8389077]

Iwashita S, Kanegasaki S. Enzymic and molecular properties of base-plate parts of bacteriophage P22. Eur J Biochem. 1976; 65:87–94. [PubMed: 6284]

Jackson EN, Jackson DA, Deans RJ. EcoRI analysis of bacteriophage P22 DNA packaging. J Mol Biol. 1978; 118:365–388. [PubMed: 344888]

Jeruzalmi D, Steitz TA. Structure of T7 RNA polymerase complexed to the transcriptional inhibitor T7 lysozyme. EMBO J. 1998; 17:4101–4113. [PubMed: 9670025]

Julien B, Lefevre P, Calendar R. The two P2 Ogr-like domains of the delta protein from bacteriophage P4 are required for activity. Virology. 1997; 230:292–299. [PubMed: 9143285]

Kageyama Y, Murayama M, Onodera T, Yamada S, Fukada H, Kudou M, Tsumoto K, Toyama Y, Kado S, Kubota K, Takeda S. Observation of the membrane binding activity and domain structure of gpV, which comprises the tail spike of bacteriophage P2. Biochemistry. 2009; 48:10129–10135. [PubMed: 19780551]

Kaiser AD, Jacob F. Recombination between related bacteriophages and the genetic control of immunity and prophage localization. Virology. 1957; 4:509–517. [PubMed: 13507311]

Kamtekar S, Berman AJ, Wang J, Lázaro JM, de Vega M, Blanco L, Salas M, Steitz TA. The phi29 DNA polymerase:protein-primer structure suggests a model for the initiation to elongation transition. EMBO J. 2006; 25:1335–1343. [PubMed: 16511564]

Katsura, I. Tail assembly and injection. In: Hendrix, R.; Roberts, J.; Stahl, FW.; Weisberg, R., editors. Lambda II. Cold Spring Harbor Laboratory; Cold Spring Harbor, NY: 1983. p. 331-346.

Katsura I. Mechanism of length determination in bacteriophage lambda tails. Adv Biophys. 1990; 26:1–18. [PubMed: 2150582]

Katsura I, Tsugita A. Purification and characterization of the major protein and the terminator protein of the bacteriophage lambda tail. Virology. 1977; 76:129–145. [PubMed: 835226]

Kędzierska B, Lee DJ, Węgrzyn G, Busby SJ, Thomas MS. Role of the RNA polymerase alpha subunits in CII-dependent activation of the bacteriophage lambda pE promoter: identification of important residues and positioning of the alpha C-terminal domains. Nucleic Acids Res. 2004; 32:834–841. [PubMed: 14762211]

Kędzierska B, Szambowska A, Herman-Antosiewicz A, Lee DJ, Busby SJ, Węgrzyn G, Thomas MS. The C-terminal domain of the *Escherichia coli* RNA polymerase alpha subunit plays a role in the CI-dependent activation of the bacteriophage lambda pM promoter. Nucleic Acids Res. 2007; 35:2311–2320. [PubMed: 17389649]

Kemp P, Garcia LR, Molineux IJ. Changes in bacteriophage T7 virion structure at the initiation of infection. Virology. 2005; 340:307–317. [PubMed: 16054667]

Kemp P, Gupta M, Molineux IJ. Bacteriophage T7 DNA ejection into cells is initiated by an enzyme-like mechanism. Mol Microbiol. 2004; 53:1251–1265. [PubMed: 15306026]

Kennaway CK, Obarska-Kosinska A, White JH, Tuszynska I, Cooper LP, Bujnicki JM, Trinick J, Dryden DT. The structure of M.EcoKI Type I DNA methyltransferase with a DNA mimic antirestriction protein. Nucleic Acids Res. 2009; 37:762–770. [PubMed: 19074193]

Kennedy WP, Momand JR, Yin YW. Mechanism for de novo RNA synthesis and initiating nucleotide specificity by t7 RNA polymerase. J Mol Biol. 2007; 370:256–268. [PubMed: 17512007]

Kihara A, Akiyama Y, Ito K. Revisiting the lysogenization control of bacteriophage lambda: Identification and characterization of a new host component. HflD J Biol Chem. 2001; 276:13695–13700.

Kim K-J, Sunshine MG, Lindqvist BH, Six EW. Capsid size determination in the P2–P4 bacteriophage system: suppression of sir mutations in P2's capsid gene N by supersid mutations in P4's external scaffold gene sid. Virology. 2001; 283:49–58. [PubMed: 11312661]

King J, Casjens S. Catalytic head assembling protein in virus morphogenesis. Nature. 1974; 251:112–119. [PubMed: 4421992]

King J, Lenk EV, Botstein D. Mechanism of head assembly and DNA encapsulation in Salmonella phage P22. *II. Morphogenetic pathway*. J Mol Biol. 1973; 80:697–731. [PubMed: 4773027]

King RA, Anders DL, Christie GE. Site-directed mutagenesis of an amino acid residue in the bacteriophage P2 ogr protein implicated in interaction with *Escherichia coli* RNA polymerase. Mol Microbiol. 1992; 6:3313–3320. [PubMed: 1484487]

Kobiler O, Koby S, Teff D, Court D, Oppenheim AB. The phage lambda CII transcriptional activator carries a C-terminal domain signaling for rapid proteolysis. Proc Natl Acad Sci USA. 2002; 99:14964–14969. [PubMed: 12397182]

Kobiler O, Oppenheim AB, Herman C. Recruitment of host ATP-dependent proteases by bacteriophage lambda. J Struct Biol. 2004; 146:72–78. [PubMed: 15037238]

Kobiler O, Rokney A, Oppenheim AB. Phage lambda CIII: A protease inhibitor regulating the lysis-lysogeny decision. PLoS One. 2007; 2:e363. [PubMed: 17426811]

Kochan J, Carrascosa JL, Murialdo H. Bacteriophage lambda preconnectors. *Purification and structure*. J Mol Biol. 1984; 174:433–447. [PubMed: 6232391]

Kornitzer D, Altuvia S, Oppenheim AB. The activity of the CIII regulator of lambdoid bacteriophages resides within a 24-amino acid protein domain. Proc Natl Acad Sci USA. 1991; 88:5217–5221. [PubMed: 1828895]

Lander GC, Evilevitch A, Jeembaeva M, Potter CS, Carragher B, Johnson JE. Bacteriophage lambda stabilization by auxiliary protein gpD: Timing, location, and mechanism of attachment determined by cryo-EM. Structure. 2008; 16:1399–1406. [PubMed: 18786402]

Lander GC, Tang L, Casjens SR, Gilcrease EB, Prevelige P, Poliakov A, Potter CS, Carragher B, Johnson JE. The structure of an infectious P22 virion shows the signal for headful DNA packaging. Science. 2006; 312:1791–1795. [PubMed: 16709746]

LeBowitz JH, McMacken R. The *Escherichia coli* dnaB replication protein is a DNA helicase. J Biol Chem. 1986; 261:4738–4748. [PubMed: 3007474]

Lee CS, Guo P. Sequential interactions of structural proteins in phage phi 29 procapsid assembly. J Virol. 1995; 69:5024–5032. [PubMed: 7609072]

Leffers GG Jr, Gottesman S. Lambda Xis degradation *in vivo* by Lon and FtsH. J Bacteriol. 1998; 180:1573–1577. [PubMed: 9515930]

Lehne B, Schlitt T. Protein-protein interaction databases: Keeping up with growing interactomes. Hum Genom. 2009; 3:291–297.

Lengyel JA, Goldstein RN, Marsh M, Calendar R. Structure of the bacteriophage P2 tail. Virology. 1974; 62:161–174. [PubMed: 4607804]

Lengyel JA, Goldstein RN, Marsh M, Sunshine MG, Calendar R. Bacteriophage P2 head morphogenesis: cleavage of the major capsid protein. Virology. 1973; 53:1–23. [PubMed: 4574872]

Li M, Moyle H, Susskind MM. Target of the transcriptional activation function of phage lambda cI protein. Science. 1994; 263:75–77. [PubMed: 8272867]

Lin, L. Study of Bacteriophage T7 Gene 5.9 and Gene 5.5. SUNY; Stonybrook, NY: 1992.

Linderoth NA, Julien B, Flick KE, Calendar R, Christie G. Molecular cloning and characterization of bacteriophage P2 genes R and S involved in tail completion. Virology. 1994; 200:347–359. [PubMed: 8178426]

Linderoth NA, Ziermann R, Haggård-Ljungquist E, Christie GE, Calendar R. Nucleotide sequence of the DNA packaging and capsid synthesis genes of bacteriophage P2. Nucl Acids Res. 1991; 19:7207–7214. [PubMed: 1837355]

Lindqvist BH, Deho G, Calendar R. Mechanisms of genome propagation and helper exploitation by satellite phage P4. Microbiol Rev. 1993; 57:683–702. [PubMed: 8246844]

Little JW. An exonuclease induced by bacteriophage lambda. II. Nature of the enzymatic reaction. J Biol Chem. 1967; 242:679–686. [PubMed: 6017737]

Liu Q, Richardson CC. Gene 5.5 protein of bacteriophage T7 inhibits the nucleoid protein H-NS of *Escherichia coli*. Proc Natl Acad Sci USA. 1993; 90:1761–1765. [PubMed: 7680479]

Liu T, Renberg SK, Haggard-Ljungquist E. The E protein of satellite phage P4 acts as an anti-repressor by binding to the C protein of helper phage P2. Mol Microbiol. 1998; 30:1041–1050. [PubMed: 9988480]

Liu X, Zhang Q, Murata K, Baker ML, Sullivan MB, Fu C, Dougherty MT, Schmid MF, Osburne MS, Chisholm SW, Chiu W. Structural changes in a marine podovirus associated with release of its genome into Prochlorococcus. Nat Struct Mol Biol. 2010; 17:830–836. [PubMed: 20543830]

Liu Y, Haggard-Ljungquist E. Studies of bacteriophage P2 DNA replication: localization of the cleavage site of the A protein. Nucleic Acids Res. 1994; 22:5204–5210. [PubMed: 7816607]

Loeffler JM, Djurkovic S, Fischetti VA. Phage lytic enzyme Cpl-1 as a novel antimicrobial for pneumococcal bacteremia. Infect Immun. 2003; 71:6199–6204. [PubMed: 14573637]

Loeffler JM, Nelson D, Fischetti VA. Rapid killing of *Streptococcus pneumoniae* with a bacteriophage cell wall hydrolase. Science. 2001; 294:2170–2172. [PubMed: 11739958]

Longás E, de Vega M, Lázaro JM, Salas M. Functional characterization of highly processive protein-primed DNA polymerases from phages Nf and GA-1, endowed with a potent strand displacement capacity. Nucleic Acids Res. 2006; 34:6051–6063. [PubMed: 17071961]

Longás E, Villar L, Lázaro JM, de Vega M, Salas M. Phage phi29 and Nf terminal protein-priming domain specifies the internal template nucleotide to initiate DNA replication. Proc Natl Acad Sci USA. 2008; 105:18290–18295. [PubMed: 19011105]

Lopez R, Ronda C, Tomasz A, Portoles A. Properties of “diplophage”: A lipid-containing bacteriophage. J Virol. 1977; 24:201–210. [PubMed: 20516]

Lyakhov DL, He B, Zhang X, Studier FW, Dunn JJ, McAllister WT. Mutant bacteriophage T7 RNA polymerases with altered termination properties. J Mol Biol. 1997; 269:28–40. [PubMed: 9192998]

Lyakhov DL, He B, Zhang X, Studier FW, Dunn JJ, McAllister WT. Pausing and termination by bacteriophage T7 RNA polymerase. J Mol Biol. 1998; 280:201–213. [PubMed: 9654445]

Makela PH. Glucosylation of lipopolysaccharide in Salmonella: Mutants negative for O antigen factor 1221. J Bacteriol. 1973; 116:847–856. [PubMed: 4583253]

Mallory JB, Alfano C, McMacken R. Host virus interactions in the initiation of bacteriophage lambda DNA replication: Recruitment of *Escherichia coli* DnaB helicase by lambda P replication protein. J Biol Chem. 1990; 265:13297–13307. [PubMed: 2165499]

Marchand I, Nicholson AW, Dreyfus M. Bacteriophage T7 protein kinase phosphorylates RNase E and stabilizes mRNAs synthesized by T7 RNA polymerase. Mol Microbiol. 2001; 42:767–776. [PubMed: 11722741]

Marintcheva B, Qimron U, Yu Y, Tabor S, Richardson CC. Mutations in the gene 5 DNA polymerase of bacteriophage T7 suppress the dominant lethal phenotype of gene 2.5 ssDNA binding protein lacking the C-terminal phenylalanine. Mol Microbiol. 2009; 72:869–880. [PubMed: 19400798]

Marr MT, Datwyler SA, Meares CF, Roberts JW. Restructuring of an RNA polymerase holoenzyme elongation complex by lambdoid phage Q proteins. Proc Natl Acad Sci USA. 2001; 98:8972–8978. [PubMed: 11481468]

Marr MT, Roberts JW, Brown SE, Klee M, Gussin GN. Interactions among CII protein, RNA polymerase and the lambda PRE promoter: Contacts between RNA polymerase and the -35 region of PRE are identical in the presence and absence of CII protein. Nucleic Acids Res. 2004; 32:1083–1090. [PubMed: 14872063]

Marsic N, Roje S, Stojiljkovic I, Salaj-Smic E, Trgovcevic Z. *In vivo* studies on the interaction of RecBCD enzyme and lambda Gam protein. J Bacteriol. 1993; 175:4738–4743. [PubMed: 8335632]

Martin AC, Blanco L, Garcia P, Salas M, Mendez J. *In vitro* protein-primed initiation of pneumococcal phage Cp-1 DNA replication occurs at the third 3′ nucleotide of the linear template: A stepwise sliding-back mechanism. J Mol Biol. 1996; 260:369–377. [PubMed: 8757800]

Marvik OJ, Dokland T, Nøkling RH, Jacobsen E, Larsen T, Lindqvist BH. The capsid size-determining protein Sid forms an external scaffold on phage P4 procapsids. J Mol Biol. 1995; 251:59–75. [PubMed: 7643390]

Marvik OJ, Jacobsen E, Dokland T, Lindqvist BH. Bacteriophage P2 and P4 morphogenesis: assembly precedes proteolytic processing of the capsid proteins. Virology. 1994; 205:51–65. [PubMed: 7975237]

Mason SW, Greenblatt J. Assembly of transcription elongation complexes containing the N protein of phage lambda and the *Escherichia coli* elongation factors NusA, NusB, NusG, and S10. Genes Dev. 1991; 5:1504–1512. [PubMed: 1831176]

Massad T, Skaar K, Nilsson H, Damberg P, Henriksson-Peltola P, Haggard-Ljungquist E, Hogbom M, Stenmark P. Crystal structure of the P2 C-repressor: A binder of non-palindromic direct DNA repeats. Nucleic Acids Res. 2010; 38:7778–7790. [PubMed: 20639540]

Mattis AN, Gumport RI, Gardner JF. Purification and characterization of bacteriophage P22 Xis protein. J Bacteriol. 2008; 190:5781–5796. [PubMed: 18502866]

Maxwell KL, Reed P, Zhang RG, Beasley S, Walmsley AR, Curtis FA, Joachimiak A, Edwards AM, Sharples GJ. Functional similarities between phage lambda Orf and *Escherichia coli* RecFOR in initiation of genetic exchange. Proc Natl Acad Sci USA. 2005; 102:11260–11265. [PubMed: 16076958]

Maxwell KL, Yee AA, Booth V, Arrowsmith CH, Gold M, Davidson AR. The solution structure of bacteriophage lambda protein W, a small morphogenetic protein possessing a novel fold. J Mol Biol. 2001; 308:9–14. [PubMed: 11302702]

Mayer JE, Schweiger M. RNase III is positively regulated by T7 protein kinase. J Biol Chem. 1983; 258:5340–5343. [PubMed: 6406499]

McDonnell M, Lain R, Tomasz A. “Diplophage”: A bacteriophage of Diplococcus pneumoniae. Virology. 1975; 63:577–582. [PubMed: 234654]

Medina E, Wieczorek D, Medina EM, Yang Q, Feiss M, Catalano CE. Assembly and maturation of the bacteriophage lambda procapsid: gpC is the viral protease. J Mol Biol. 2010; 401:813–830. [PubMed: 20620152]

Meijer WJ, Horcajadas JA, Salas M. Phi29 family of phages. Microbiol Mol Biol Rev. 2001a; 65:261–287. [PubMed: 11381102]

Meijer WJ, Lewis PJ, Errington J, Salas M. Dynamic relocalization of phage phi 29 DNA during replication and the role of the viral protein p16.7. EMBO J. 2000; 19:4182–4190. [PubMed: 10921898]

Meijer WJ, Serna-Rico A, Salas M. Characterization of the bacteriophage phi29-encoded protein p16.7: A membrane protein involved in phage DNA replication. Mol Microbiol. 2001b; 39:731–746. [PubMed: 11169113]

Mencía M, Monsalve M, Rojo F, Salas M. Transcription activation by phage phi29 protein p4 is mediated by interaction with the alpha subunit of *Bacillus subtilis* RNA polymerase. Proc Natl Acad Sci USA. 1996a; 93:6616–6620.

Mencía M, Monsalve M, Salas M, Rojo F. Transcriptional activator of phage phi 29 late promoter: mapping of residues involved in interaction with RNA polymerase and in DNA bending. Mol Microbiol. 1996b; 20:273–282.

Méndez J, Blanco L, Esteban JA, Bernad A, Salas M. Initiation of phi 29 DNA replication occurs at the second 3′ nucleotide of the linear template: A sliding-back mechanism for protein-primed DNA replication. Proc Natl Acad Sci USA. 1992; 89:9579–9583. [PubMed: 1409668]

Méndez J, Blanco L, Salas M. Protein-primed DNA replication: A transition between two modes of priming by a unique DNA polymerase. EMBO J. 1997; 16:2519–2527. [PubMed: 9171364]

Mikawa YG, Maruyama IN, Brenner S. Surface display of proteins on bacteriophage lambda heads. J Mol Biol. 1996; 262:21–30. [PubMed: 8809176]

Moak M, Molineux IJ. Role of the Gp16 lytic transglycosylase motif in bacteriophage T7 virions at the initiation of infection. Mol Microbiol. 2000; 37:345–355. [PubMed: 10931329]

Moak M, Molineux IJ. Peptidoglycan hydrolytic activities associated with bacteriophage virions. Mol Microbiol. 2004; 51:1169–1183. [PubMed: 14763988]

Molineux, IJ. The T7 group. In: Calendar, R., editor. The Bacteriophages. Vol. Chapter 20. Oxford University Press; Oxford: 2006a. p. 277-301.

Molineux IJ. Fifty-three years since Hershey and Chase; much ado about pressure but which pressure is it? Virology. 2006b; 344:221–229. [PubMed: 16364752]

Monsalve M, Calles B, Mencía M, Salas M, Rojo F. Transcription activation or repression by phage psi 29 protein p4 depends on the strength of the RNA polymerase-promoter interactions. Mol Cell. 1997; 1:99–107. [PubMed: 9659907]

Monsalve M, Mencía M, Rojo F, Salas M. Activation and repression of transcription at two different phage phi29 promoters are mediated by interaction of the same residues of regulatory protein p4 with RNA polymerase. EMBO J. 1996a; 15:383–391. [PubMed: 8617213]

Monsalve M, Mencía M, Salas M, Rojo F. Protein p4 represses phage phi 29 A2c promoter by interacting with the alpha subunit of *Bacillus subtilis* RNA polymerase. Proc Natl Acad Sci USA. 1996b; 93:8913–8918. [PubMed: 8799127]

Mooney PQ, North R, Molineux IJ. The role of bacteriophage T7 gene 2 protein in DNA replication. Nucleic Acids Res. 1980; 8:3043–3053. [PubMed: 7001361]

Morais MC, Choi KH, Koti JS, Chipman PR, Anderson DL, Rossmann MG. Conservation of the capsid structure in tailed dsDNA bacteriophages: The pseudoatomic structure of phi29. Mol Cell. 2005; 18:149–159. [PubMed: 15837419]

Morais MC, Kanamaru S, Badasso MO, Koti JS, Owen BA, McMurray CT, Anderson DL, Rossmann MG. Bacteriophage phi29 scaffolding protein gp7 before and after prohead assembly. Nat Struct Biol. 2003; 10:572–576. [PubMed: 12778115]

Morita M, Tasaka M, Fujisawa H. Analysis of functional domains of the packaging proteins of bacteriophage T3 by site-directed mutagenesis. J Mol Biol. 1994; 235:248–259. [PubMed: 8289246]

Morita M, Tasaka M, Fujisawa H. Structural and functional domains of the large subunit of the bacteriophage T3 DNA packaging enzyme: Importance of the C-terminal region in prohead binding. J Mol Biol. 1995; 245:635–644. [PubMed: 7844832]

Mosig G, Yu S, Myung H, Haggard-Ljungquist E, Davenport L, Carlson K, Calendar R. A novel mechanism of virus-virus interactions: Bacteriophage P2 Tin protein inhibits phage T4 DNA synthesis by poisoning the T4 single-stranded DNA binding protein, gp32. Virology. 1997; 230:72–81. [PubMed: 9126263]

Mount DW, Harris AW, Fuerst CR, Siminovitch L. Mutations in bacteriophage lambda affecting particle morphogenesis. Virology. 1968; 35:134–149. [PubMed: 5652675]

Muñoz-Espín D, Daniel R, Kawai Y, Carballido-Lopez R, Castilla-Llorente V, Errington J, Meijer WJ, Salas M. The actin-like MreB cytoskeleton organizes viral DNA replication in bacteria. Proc Natl Acad Sci USA. 2009

Muñoz-Espín D, Holguera I, Ballesteros-Plaza D, Carballido-Lopez R, Salas M. Viral terminal protein directs early organization of phage DNA replication at the bacterial nucleoid. Proc Natl Acad Sci USA. 2010; 107:16548–16553. [PubMed: 20823229]

Murialdo H. Early intermediates in bacteriophage lambda prohead assembly. Virology. 1979; 96:341–367. [PubMed: 380144]

Murialdo H, Becker A. Head morphogenesis of complex double-stranded deoxyribonucleic acid bacteriophages. Microbiol Rev. 1978; 42:529–576. [PubMed: 362149]

Murialdo H, Tzamtzis D. Mutations of the coat protein gene of bacteriophage lambda that overcome the necessity for the Fl gene; the EFi domain. Mol Microbiol. 1997; 24:341–353. [PubMed: 9159521]

Murphy KC. Bacteriophage P22 Abc2 protein binds to RecC increases the 5′ strand nicking activity of RecBCD and together with lambda bet, promotes Chi- independent recombination. J Mol Biol. 2000; 296:385–401. [PubMed: 10669596]

Murray NE. Type I restriction systems: Sophisticated molecular machines (a legacy of Bertani and Weigle). MMBR. 2000; 64:412–434. [PubMed: 10839821]

Nakai H, Richardson CC. The gene 1.2 protein of bacteriophage T7 interacts with the *Escherichia coli* dGTP triphosphohydrolase to form a GTP-binding protein. J Biol Chem. 1990; 265:4411–4419. [PubMed: 2155228]

Nechaev S, Severinov K. Inhibition of *Escherichia coli* RNA polymerase by bacteriophage T7 gene 2 protein. J Mol Biol. 1999; 289:815–826. [PubMed: 10369763]

Nemecek D, Gilcrease EB, Kang S, Prevelige PE Jr, Casjens S, Thomas GJ Jr. Subunit conformations and assembly states of a DNA-translocating motor: The terminase of bacteriophage P22. J Mol Biol. 2007; 374:817–836. [PubMed: 17945256]

Nemecek D, Lander GC, Johnson JE, Casjens SR, Thomas GJ Jr. Assembly architecture and DNA binding of the bacteriophage P22 terminase small subunit. J Mol Biol. 2008; 383:494–501. [PubMed: 18775728]

Newlove T, Konieczka JH, Cordes MH. Secondary structure switching in Cro protein evolution. Structure (Camb). 2004; 12:569–581. [PubMed: 15062080]

Nickels BE, Roberts CW, Sun H, Roberts JW, Hochschild A. The sigma (70) subunit of RNA polymerase is contacted by the (lambda)Q antiterminator during early elongation. Mol Cell. 2002; 10:611–622. [PubMed: 12408828]

Nilsson, AS.; Haggård-Ljungquist, E. The P2-like bacteriophages. Calendar, R., editor. Oxford University Press; New York: 2006. p. 365-390.

Nilsson AS, Karlsson JL, Haggård-Ljungquist E. Site-specific recombination links the evolution of P2-like coliphages and pathogenic enterobacteria. Mol Biol Evol. 2004; 21:1–13. [PubMed: 12949155]

Nooren IM, Kaptein R, Sauer RT, Boelens R. The tetramerization domain of the Mnt repressor consists of two right-handed coiled coils. Nat Struct Biol. 1999; 6:755–759. [PubMed: 10426954]

Nuez B, Rojo F, Salas M. Phage phi 29 regulatory protein p4 stabilizes the binding of the RNA polymerase to the late promoter in a process involving direct protein-protein contacts. Proc Natl Acad Sci USA. 1992; 89:11401–11405. [PubMed: 1454827]

Odegrip R, Haggard-Ljungquist E. The two active-site tyrosine residues of the a protein play non-equivalent roles during initiation of rolling circle replication of bacteriophage p2. J Mol Biol. 2001; 308:147–163. [PubMed: 11327759]

Odegrip R, Schoen S, Haggard-Ljungquist E, Park K, Chattoraj DK. The interaction of bacteriophage P2 B protein with *Escherichia coli* DnaB helicase. J Virol. 2000; 74:4057–4063. [PubMed: 10756017]

Olia A, Prevelige P Jr, Johnson J, Cingolani G. Three-dimensional structure of a viral genome-delivery portal vertex. Nat Struct Mol Biol. 2011 in press.

Olia AS, Al-Bassam J, Winn-Stapley DA, Joss L, Casjens SR, Cingolani G. Binding-induced stabilization and assembly of the phage P22 tail accessory factor gp4. J Mol Biol. 2006; 363:558–576. [PubMed: 16970964]

Olia AS, Bhardwaj A, Joss L, Casjens S, Cingolani G. Role of gene 10 protein in the hierarchical assembly of the bacteriophage P22 portal vertex structure. Biochemistry. 2007; 46:8776–8784. [PubMed: 17620013]

Oppenheim AB, Kobiler O, Stavans J, Court DL, Adhya S. Switches in bacteriophage lambda development. Annu Rev Genet. 2005; 39:409–429. [PubMed: 16285866]

Pani B, Ranjan A, Sen R. Interaction surface of bacteriophage P4 protein Psu required for complex formation with the transcription terminator Rho. J Mol Biol. 2009; 389:647–660. [PubMed: 19409394]

Parker MH, Casjens S, Prevelige PE Jr. Functional domains of bacteriophage P22 scaffolding protein. J Mol Biol. 1998; 281:69–79. [PubMed: 9680476]

Parker MH, Stafford WF 3rd, Prevelige PE Jr. Bacteriophage P22 scaffolding protein forms oligomers in solution. J Mol Biol. 1997; 268:655–665. [PubMed: 9171289]

Parkinson MJ, Lilley DM. The junction-resolving enzyme T7 endonuclease I: Quaternary structure and interaction with DNA. J Mol Biol. 1997; 270:169–178. [PubMed: 9236119]

Parua PK, Mondal A, Parrack P. HflD, an *Escherichia coli* protein involved in the lambda lysis-lysogeny switch, impairs transcription activation by lambdaCII. Arch Biochem Biophys. 2010; 493:175–183. [PubMed: 19853572]

Pastrana R, Lazaro JM, Blanco L, Garcia JA, Mendez E, Salas M. Overproduction and purification of protein P6 of *Bacillus subtilis* phage phi 29: Role in the initiation of DNA replication. Nucleic Acids Res. 1985; 13:3083–3100. [PubMed: 3158884]

Pedulla ML, Ford ME, Karthikeyan T, Houtz JM, Hendrix RW, Hatfull GF, Poteete AR, Gilcrease EB, Winn-Stapley DA, Casjens SR. Corrected sequence of the bacteriophage p22 genome. J Bacteriol. 2003; 185:1475–1477. [PubMed: 12562822]

Pell LG, Liu A, Edmonds L, Donaldson LW, Howell PL, Davidson AR. The X-ray crystal structure of the phage lambda tail terminator protein reveals the biologically relevant hexameric ring structure and demonstrates a conserved mechanism of tail termination among diverse long-tailed phages. J Mol Biol. 2009; 389:938–951. [PubMed: 19426744]

Poteete AR, Botstein D. Purification and properties of proteins essential to DNA encapsulation by phage P22. Virology. 1979; 95:565–573. [PubMed: 380140]

Poteete AR, Fenton AC. DNA-binding properties of the Erf protein of bacteriophage P22. J Mol Biol. 1983; 163:257–275. [PubMed: 6302269]

Poteete AR, King J. Functions of two new genes in Salmonella phage P22 assembly. Virology. 1977; 76:725–739. [PubMed: 320755]

Poteete AR, Sauer RT, Hendrix RW. Domain structure and quaternary organization of the bacteriophage P22 Erf protein. J Mol Biol. 1983; 171:401–418. [PubMed: 6607360]

Potrykus K, Baranska S, Wegrzyn A, Wegrzyn G. Composition of the lambda plasmid heritable replication complex. Biochem J. 2002; 364:857–862. [PubMed: 12049651]

Prell HH, Harvey AM. P22 antirepressor protein prevents *in vivo* recA-dependent proteolysis of P22 repressor. Mol Gen Genet. 1983; 190:427–431. [PubMed: 6348481]

Prevelige PE Jr, Thomas D, King J. Scaffolding protein regulates the polymerization of P22 coat subunits into icosahedral shells *in vitro*. J Mol Biol. 1988; 202:743–757. [PubMed: 3262767]

Pruss GJ, Wang JC, Calendar R. In vitro packaging of covalently-closed circular monomers of bacteriophage DNA. J Mol Biol. 1975; 98:465–478. [PubMed: 1104873]

Ptashne, M. A Genetic Switch: Phage Lambda Revisited. Third ed. Cold Spring Harbor Laboratory Press; Cold Spring Harbor, NY: 2004.

Ptashne, M. A Genetic Switch. Phage Lambda Revisited. Cold Spring Harbor Laboratory Press; Cold Spring Harbor, NY: 2006.

Putnam CD, Shroyer MJ, Lundquist AJ, Mol CD, Arvai AS, Mosbaugh DW, Tainer JA. Protein mimicry of DNA from crystal structures of the uracil-DNA glycosylase inhibitor protein and its complex with *Escherichia coli* uracil-DNA glycosylase. J Mol Biol. 1999; 287:331–346. [PubMed: 10080896]

Qimron U, Marintcheva B, Tabor S, Richardson CC. Genomewide screens for *Escherichia coli* genes affecting growth of T7 bacteriophage. Proc Natl Acad Sci USA. 2006; 103:19039–19044. [PubMed: 17135349]

Radding CM, Rosenzweig J, Richards J, Cassuto E. Appendix: Separation and characterization of exonuclease, β protein and a complex of both. J Biol Chem. 1971; 146:2510–2512.

Rahmsdorf HJ, Pai SH, Ponta H, Herrlich P, Roskoski R Jr, Schweiger M, Studier FW. Protein kinase induction in *Escherichia coli* by bacteriophage T7. Proc Natl Acad Sci USA. 1974; 71:586–589. [PubMed: 4592695]

Rajagopala SV, Casjens S, Uetz P. The protein interaction map of bacteriophage lambda. BMC Microbiol. 2011; 11:213. [PubMed: 21943085]

Ranade K, Poteete AR. Superinfection exclusion (sieB) genes of bacteriophages P22 and lambda. J Bacteriol. 1993a; 175:4712–4718. [PubMed: 8335629]

Ranade K, Poteete AR. A switch in translation mediated by an antisense RNA. Genes Dev. 1993b; 7:1498–1507. [PubMed: 8339929]

Ray P, Murialdo H. The role of gene Nu3 in bacteriophage lambda head morphogenesis. Virology. 1975; 64:247–263. [PubMed: 1090075]

Rennell D, Poteete AR. Phage P22 lysis genes: Nucleotide sequences and functional relationships with T4 and lambda genes. Virology. 1985; 143:280–289. [PubMed: 2998005]

Rennell D, Poteete AR. Genetic analysis of bacteriophage P22 lysozyme structure. Genetics. 1989; 123:431–440. [PubMed: 2599364]

Rezende LF, Hollis T, Ellenberger T, Richardson CC. Essential amino acid residues in the single-stranded DNA-binding protein of bacteriophage T7: Identification of the dimer interface. J Biol Chem. 2002; 277:50643–50653. [PubMed: 12379653]

Rishovd S, Lindqvist BH. Bacteriophage P2 and P4 morphogenesis: protein processing and capsid size determination. Virology. 1992; 187:548–554. [PubMed: 1546453]

Rishovd S, Marvik OJ, Jacobsen E, Lindqvist BH. Bacteriophage P2 and P4 morphogenesis: Identification and characterization of the portal protein. Virology. 1994; 200:744–751. [PubMed: 8178458]

Roberts CW, Roberts JW. Base-specific recognition of the nontemplate strand of promoter DNA by *E. coli* RNA polymerase. Cell. 1996; 86:495–501. [PubMed: 8756731]

Roberts JW. Termination factor for RNA synthesis. Nature. 1969; 224:1168–1174. [PubMed: 4902144]

Roberts JW, Yarnell W, Bartlett E, Guo J, Marr M, Ko DC, Sun H, Roberts CW. Antitermination by bacteriophage lambda Q protein. Cold Spring Harb Symp Quant Biol. 1998; 63:319–325. [PubMed: 10384296]

Robertson ES, Aggison LA, Nicholson AW. Phosphorylation of elongation factor G and ribosomal protein S6 in bacteriophage T7-infected *Escherichia coli*. Mol Microbiol. 1994; 11:1045–1057. [PubMed: 8022276]

Robertson ES, Nicholson AW. Protein kinase of bacteriophage T7 induces the phosphorylation of only a small number of proteins in the infected cell. Virology. 1990; 175:525–534. [PubMed: 2183469]

Robertson ES, Nicholson AW. Phosphorylation of *Escherichia coli* translation initiation factors by the bacteriophage T7 protein kinase. Biochemistry. 1992; 31:4822–4827. [PubMed: 1534259]

Rodriguez-Cerrato V, Garcia P, Del Prado G, Garcia E, Gracia M, Huelves L, Ponte C, Lopez R, Soriano F. *In vitro* interactions of LytA, the major pneumococcal autolysin, with two bacteriophage lytic enzymes (Cpl-1 and Pal), cefotaxime and moxi-floxacin against antibiotic-susceptible and -resistant *Streptococcus pneumoniae* strains. J Antimicrob Chemother. 2007; 60:1159–1162. [PubMed: 17827138]

Rojo F, Mencia M, Monsalve M, Salas M. Transcription activation and repression by interaction of a regulator with the alpha subunit of RNA polymerase: The model of phage phi 29 protein p4. Prog Nucleic Acid Res Mol Biol. 1998; 60:29–46. [PubMed: 9594570]

Rojo F, Salas M. A DNA curvature can substitute phage phi 29 regulatory protein p4 when acting as a transcriptional repressor. EMBO J. 1991; 10:3429–3438. [PubMed: 1655421]

Sabri M, Häuser R, Ouellette M, Liu J, Dehbi M, Moeck G, Garcia E, Titz B, Uetz P, Moineau S. Genome annotation and intraviral interactome for the Streptococcus pneumoniae virulent phage Dp-1. J Bacteriol. 2011; 193:551–562. [PubMed: 21097633]

Saito H, Richardson CC. Processing of mRNA by ribonuclease III regulates expression of gene 1.2 of bacteriophage T7. Cell. 1981; 27:533–542. [PubMed: 6101205]

Salas M. Protein-priming of DNA replication. Annu Rev Biochem. 1991; 60:39–71. [PubMed: 1883199]

Sam MD, Papagiannis CV, Connolly KM, Corselli L, Iwahara J, Lee J, Phillips M, Wojciak JM, Johnson RC, Clubb RT. Regulation of directionality in bacteriophage lambda site-specific recombination: structure of the Xis protein. J Mol Biol. 2002; 324:791–805. [PubMed: 12460578]

Sam MD, Cascio D, Johnson RC, Clubb RT. Crystal structure of the excisionase-DNA complex from bacteriophage lambda. J Mol Biol. 2004; 338:229–240. [PubMed: 15066428]

Sanger F, Air GM, Barrell BG, Brown NL, Coulson AR, Fiddes CA, Hutchison CA, Slocombe PM, Smith M. Nucleotide sequence of bacteriophage phi X174 DNA. Nature. 1977; 265:687–695. [PubMed: 870828]

Sauer B, Ow D, Ling L, Calendar R. Mutants of satellite bacteriophage P4 that are defective in the suppression of transcriptional polarity. J Mol Biol. 1981; 145:29–46. [PubMed: 7021852]

Savalia D, Robins W, Nechaev S, Molineux I, Severinov K. The role of the T7 Gp2 inhibitor of host RNA polymerase in phage development. J Mol Biol. 2010; 402:118–126. [PubMed: 20650282]

Savva CG, Dewey JS, Deaton J, White RL, Struck DK, Holzenburg A, Young R. The holin of bacteriophage lambda forms rings with large diameter. Mol Microbiol. 2008; 69:784–793. [PubMed: 18788120]

Schmitt CK, Molineux IJ. Expression of gene 1.2 and gene 10 of bacteriophage T7 is lethal to F plasmid-containing *Escherichia coli*. J Bacteriol. 1991; 173:1536–1543. [PubMed: 1995595]

Schulz EC, Dickmanns A, Urlaub H, Schmitt A, Muhlenhoff M, Stummeyer K, Schwarzer D, Gerardy-Schahn R, Ficner R. Crystal structure of an intramolecular chaperone mediating triple-beta-helix folding. Nat Struct Mol Biol. 2010; 17:210–215. [PubMed: 20118935]

Semerjian AV, Malloy DC, Poteete AR. Genetic structure of the bacteriophage P22 PL operon. J Mol Biol. 1989; 207:1–13. [PubMed: 2738922]

Serna-Rico A, Munoz-Espin D, Villar L, Salas M, Meijer WJ. The integral membrane protein p16.7 organizes *in vivo* phi29 DNA replication through interaction with both the terminal protein and ssDNA. EMBO J. 2003; 22:2297–2306. [PubMed: 12727895]

Serna-Rico A, Salas M, Meijer WJ. The *Bacillus subtilis* phage phi 29 protein p16.7, involved in phi 29 DNA replication, is a membrane-localized single-stranded DNA-binding protein. J Biol Chem. 2002; 277:6733–6742. [PubMed: 11741949]

Serrano M, Gutierrez C, Freire R, Bravo A, Salas M, Hermoso JM. Phage phi 29 protein p6: A viral histone-like protein. Biochimie. 1994; 76:981–991. [PubMed: 7748942]

Serrano-Heras G, Bravo A, Salas M. Phage phi29 protein p56 prevents viral DNA replication impairment caused by uracil excision activity of uracil-DNA glycosylase. Proc Natl Acad Sci USA. 2008; 105:19044–19049. [PubMed: 18845683]

Serrano-Heras G, Ruiz-Maso JA, del Solar G, Espinosa M, Bravo A, Salas M. Protein p56 from the *Bacillus subtilis* phage phi29 inhibits DNA-binding ability of uracil-DNA glycosylase. Nucleic Acids Res. 2007; 35:5393–5401. [PubMed: 17698500]

Serrano-Heras G, Salas M, Bravo A. A uracil-DNA glycosylase inhibitor encoded by a non-uracil containing viral DNA. J Biol Chem. 2006; 281:7068–7074. [PubMed: 16421108]

Severinova E, Severinov K. Localization of the *Escherichia coli* RNA polymerase beta' subunit residue phosphorylated by bacteriophage T7 kinase Gp0.7. J Bacteriol. 2006; 188:3470–3476. [PubMed: 16672600]

Sevilla-Sierra P, Otting G, Wuthrich K. Determination of the nuclear magnetic resonance structure of the DNA-binding domain of the P22 c2 repressor (1 to 76) in solution and comparison with the DNA-binding domain of the 434 repressor. J Mol Biol. 1994; 235:1003–1020. [PubMed: 8289306]

Shotland Y, Shifrin A, Ziv T, Teff D, Koby S, Kobiler O, Oppenheim AB. Proteolysis of bacteriophage lambda CII by Escherichia coli FtsH (HflB). J Bacteriol. 2000; 182:3111–3116. [PubMed: 10809689]

Simon MN, Studier FW. Physical mapping of the early region of bacteriophage T7 DNA. J Mol Biol. 1973; 79:249–265. [PubMed: 4586410]

Simpson AA, Leiman PG, Tao Y, He Y, Badasso MO, Jardine PJ, Anderson DL, Rossmann MG. Structure determination of the head-tail connector of bacteriophage phi29. Acta Crystallogr D Biol Crystallogr. 2001; 57:1260–1269. [PubMed: 11526317]

Simpson AA, Tao Y, Leiman PG, Badasso MO, He Y, Jardine PJ, Olson NH, Morais MC, Grimes S, Anderson DL, Baker TS, Rossmann MG. Structure of the bacteriophage phi29 DNA packaging motor. Nature. 2000; 408:745–750. [PubMed: 11130079]

Singleton MR, Sawaya MR, Ellenberger T, Wigley DB. Crystal structure of T7 gene 4 ring helicase indicates a mechanism for sequential hydrolysis of nucleotides. Cell. 2000; 101:589–600. [PubMed: 10892646]

Sippy J, Feiss M. Analysis of a mutation affecting the specificity domain for prohead binding of the bacteriophage lambda terminase. J Bacteriol. 1992; 174:850–856. [PubMed: 1531050]

Six EW. The helper dependence of satellite bacteriophage P4: which gene functions of bacteriophage P2 are needed by P4? Virology. 1975; 67:249–263. [PubMed: 1099784]

Six EW, Sunshine MG, Williams J, Haggård-Ljungquist E, Lindqvist BH. Morphopoietic switch mutations of bacteriophage P2. Virology. 1991; 182:34–46. [PubMed: 1840708]

Souza L, Calendar R, Six E, Lindqvist B. A transactivation mutant of satellite phage P4. Virology. 1977; 81:81–90. [PubMed: 329561]

Stano NM, Patel SS. T7 lysozyme represses T7 RNA polymerase transcription by destabilizing the open complex during initiation. J Biol Chem. 2004; 279:16136–16143. [PubMed: 14764584]

Steinbacher S, Miller S, Baxa U, Budisa N, Weintraub A, Seckler R, Huber R. Phage P22 tailspike protein: Crystal structure of the head-binding domain at 2.3 A, fully refined structure of the endorhamnosidase at 1.56 A resolution, and the molecular basis of O-antigen recognition and cleavage. J Mol Biol. 1997; 267:865–880. [PubMed: 9135118]

Steinbacher S, Seckler R, Miller S, Steipe B, Huber R, Reinemer P. Crystal structure of P22 tailspike protein: Interdigitated subunits in a thermostable trimer. Science. 1994; 265:383–386. [PubMed: 8023158]

Stellberger T, Häuser R, Baiker A, Pothineni VR, Haas J, Uetz P. Improving the yeast two-hybrid system with permutated fusions proteins: The Varicella Zoster Virus interactome. Proteome Sci. 2010; 8:8. [PubMed: 20205919]

Stephanou AS, Roberts GA, Cooper LP, Clarke DJ, Thomson AR, MacKay CL, Nutley M, Cooper A, Dryden DT. Dissection of the DNA mimicry of the bacteriophage T7 Ocr protein using chemical modification. J Mol Biol. 2009; 391:565–576. [PubMed: 19523474]

Sternberg N, Hoess RH. Display of peptides and proteins on the surface of bacteriophage lambda. Proc Natl Acad Sci USA. 1995; 92:1609–1613. [PubMed: 7878027]

Sternberg N, Weisberg R. Packaging of coliphage lambda DNA. II. The role of the gene D protein. J Mol Biol. 1977; 117:733–759. [PubMed: 609100]

Steven AC, Trus BL, Maizel JV, Unser M, Parry DA, Wall JS, Hainfeld JF, Studier FW. Molecular substructure of a viral receptor-recognition protein. The gp17 tail-fiber of bacteriophage T7. J Mol Biol. 1988; 200:351–365. [PubMed: 3259634]

Stone JC, Miller RC Jr. Spontaneous temperature-sensitive mutations in bacteriophage T7. J Virol. 1985; 54:886–888. [PubMed: 3999196]

Studier FW. Gene 0.3 of bacteriophage T7 acts to overcome the DNA restriction system of the host. J Mol Biol. 1975; 94:283–295. [PubMed: 1095770]

Studier FW, Movva NR. SAMase gene of bacteriophage T3 is responsible for overcoming host restriction. J Virol. 1976; 19:136–145. [PubMed: 781304]

Studier FW. Identification and mapping of five new genes in bacteriophage T7. J Mol Biol. 1981; 153:493–502. [PubMed: 6896075]

Summer EJ, Berry J, Tran TA, Niu L, Struck DK, Young R. Rz/Rz1 lysis gene equivalents in phages of Gram-negative hosts. J Mol Biol. 2007; 373:1098–1112. [PubMed: 17900620]

Sunshine M, Usher D, Calendar R. Interaction of P2 bacteriophage with the dnaB gene of *Escherichia coli*. J Virol. 1975; 16:284–289. [PubMed: 1097733]

Sunshine MG, Sauer B. A bacterial mutation blocking P2 phage late gene expression. Proc Natl Acad Sci USA. 1975; 72:2770–2774. [PubMed: 1101267]

Susskind MM, Botstein D. Mechanism of action of Salmonella phage P22 antirepressor. J Mol Biol. 1975; 98:413–424. [PubMed: 1104871]

Susskind MM, Botstein D. Molecular genetics of bacteriophage P22. Microbiol Rev. 1978; 42:385–413. [PubMed: 353481]

Szambowska A, Pierechod M, Węrzyn G, Glinkowska M. Coupling of transcription and replication machineries in λ DNA replication initiation: Evidence for direct interaction of *Escherichia coli* RNA polymerase and the λ O protein. Nucleic Acids Res. 2010; 39:168–177. [PubMed: 20833633]

Tahirov TH, Temiakov D, Anikin M, Patlan V, McAllister WT, Vassylyev DG, Yokoyama S. Structure of a T7 RNA polymerase elongation complex at 2.9 A resolution. Nature. 2002; 420:43–50. [PubMed: 12422209]

Takahashi I, Marmur J. Replacement of thymidylic acid by deoxyuridylic acid in the deoxyribonucleic acid of a transducing phage for *Bacillus subtilis*. Nature. 1963; 197:794–795. [PubMed: 13980287]

Tang J, Lander G, Olia A, Li R, Casjens S, Prevelige P, Cingolani G, Baker T, Johnson J. Peering down the barrel of a bacteriophage portal: The genome packaging and release valve in P22. Structure. 2011; 19:496–502. [PubMed: 21439834]

Tang L, Gilcrease EB, Casjens SR, Johnson JE. Highly discriminatory binding of capsid-cementing proteins in bacteriophage L. Structure. 2006; 14:837–845. [PubMed: 16698545]

Tao Y, Olson NH, Xu W, Anderson DL, Rossmann MG, Baker TS. Assembly of a tailed bacterial virus and its genome release studied in three dimensions. Cell. 1998; 95:431–437. [PubMed: 9814712]

Temple L, Forsburg S, Calendar R, Christie G. Nucleotide sequence of the genes encoding the major tail sheath and tail tube proteins of bacteriophage P2. Virology. 1991; 181:353–358. [PubMed: 1825255]

Tokuno SI, Gough M. UV sensitivity of a nonrepressor regulatory protein of bacteriophage P22. J Virol. 1976; 18:65–70. [PubMed: 768525]

Tran NQ, Lee SJ, Richardson CC, Tabor S. A novel nucleotide kinase encoded by gene 1.7 of bacteriophage T7. Mol Microbiol. 2010; 77:492–504. [PubMed: 20497505]

Tsui L, Hendrix RW. Head-tail connector of bacteriophage lambda. J Mol Biol. 1980; 142:419–438. [PubMed: 6450838]

Tsui LC, Hendrix RW. Proteolytic processing of phage lambda tail protein gpH: Timing of the cleavage. Virology. 1983; 125:257–264. [PubMed: 6220513]

Tye BK, Huberman JA, Botstein D. Non-random circular permutation of phage P22 DNA. J Mol Biol. 1974; 85:501–528. [PubMed: 4853363]

Uetz P, Rajagopala SV, Dong YA, Haas J. From ORFeomes to protein interaction maps in viruses. Genome Res. 2004; 14:2029–2033. [PubMed: 15489322]

Valpuesta JM, Fujisawa H, Marco S, Carazo JM, Carrascosa JL. Three-dimensional structure of T3 connector purified from overexpressing bacteria. J Mol Biol. 1992; 224:103–112. [PubMed: 1548694]

Valpuesta JM, Sousa N, Barthelemy I, Fernandez JJ, Fujisawa H, Ibarra B, Carrascosa JL. Structural analysis of the bacteriophage T3 head-to-tail connector. Journal of structural biology. 2000; 131:146–155. [PubMed: 11042085]

van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009; 374:1543–1556. [PubMed: 19880020]

Vander Byl C, Kropinski AM. Sequence of the genome of Salmonella bacteriophage P22. J Bacteriol. 2000; 182:6472–6481. [PubMed: 11053393]

Vershon AK, Liao SM, McClure WR, Sauer RT. Bacteriophage P22 Mnt repressor: DNA binding and effects on transcription *in vitro*. J Mol Biol. 1987a; 195:311–322. [PubMed: 3656414]

Vershon AK, Liao SM, McClure WR, Sauer RT. Interaction of the bacteriophage P22 Arc repressor with operator DNA. J Mol Biol. 1987b; 195:323–331. [PubMed: 3656415]

Villafane R, Zayas M, Gilcrease EB, Kropinski AM, Casjens SR. Genomic analysis of bacteriophage epsilon 34 of *Salmonella enterica* serovar Anatum (15+). BMC Microbiol. 2008; 8:227. [PubMed: 19091116]

Wang J, Hofnung M, Charbit A. The C-terminal portion of the tail fiber protein of bacteriophage lambda is responsible for binding to LamB, its receptor at the surface of *Escherichia coli* K-12. J Bacteriol. 2000a; 182:508–512. [PubMed: 10629200]

Wang S, Chang JR, Dokland T. Assembly of bacteriophage P2 and P4 procapsids with internal scaffolding protein. Virology. 2006; 348:133–140. [PubMed: 16457867]

Wang S, Palasingam P, Nøkling RH, Lindqvist BH, Dokland T. *In vitro* assembly of bacteriophage P4 procapsids from purified capsid and scaffolding proteins. Virology. 2000; 275:133–144. [PubMed: 11017795]

Wang WF, Cheng X, Molineux IJ. Isolation and identification of fxsA, an *Escherichia coli* gene that can suppress F exclusion of bacteriophage T7. J Mol Biol. 1999; 292:485–499. [PubMed: 10497016]

Warren D, Sam MD, Manley K, Sarkar D, Lee SY, Abbani M, Wojciak JM, Clubb RT, Landy A. Identification of the lambda integrase surface that interacts with Xis reveals a residue that is also critical for Int dimer formation. Proc Natl Acad Sci USA. 2003; 100:8176–8181. [PubMed: 12832614]

Węgrzyn A, Taylor K, Węrzyn G. The cbpA chaperone gene function compensates for dnaJ in lambda plasmid replication during amino acid starvation of Escherichia coli. J Bacteriol. 1996; 178:5847–5849. [PubMed: 8824642]

Węrzyn A, Węrzyn G. Inheritance of the replication complex: A unique or common phenomenon in the control of DNA replication? Arch Microbiol. 2001; 175:86–93. [PubMed: 11285745]

Węrzyn G, Węrzyn A. Stress responses and replication of plasmids in bacterial cells. Microb Cell Fact. 2002; 1:2. [PubMed: 12076355]

Weigele PR, Sampson L, Winn-Stapley D, Casjens SR. Molecular genetics of bacteriophage P22 scaffolding protein's functional domains. J Mol Biol. 2005; 348:831–844. [PubMed: 15843016]

Werts C, Michel V, Hofnung M, Charbit A. Adsorption of bacteriophage lambda on the LamB protein of *Escherichia coli* K-12: point mutations in gene J of lambda responsible for extended host range. J Bacteriol. 1994; 176:941–947. [PubMed: 8106335]

White JH, Richardson CC. Gene 18 protein of bacteriophage T7: Overproduction, purification, and characterization. J Biol Chem. 1987; 262:8845–8850. [PubMed: 3036832]

Wickner S. DNA-dependent ATPase activity associated with phage P22 gene 12 protein. J Biol Chem. 1984; 259:14038–14043. [PubMed: 6150040]

Wickner SH, Zahn K. Characterization of the DNA binding domain of bacteriophage lambda O protein. J Biol Chem. 1986; 261:7537–7543. [PubMed: 3011787]

Wood LF, Tszine NY, Christie GE. Activation of P2 late transcription by P2 Ogr protein requires a discrete contact site on the C terminus of the alpha subunit of *Escherichia coli* RNA polymerase. J Mol Biol. 1997; 274:1–7. [PubMed: 9398509]

Xiang Y, Leiman PG, Li L, Grimes S, Anderson DL, Rossmann MG. Crystallographic insights into the autocatalytic assembly mechanism of a bacteriophage tail spike. Mol Cell. 2009; 34:375–386. [PubMed: 19450535]

Xiang Y, Morais MC, Cohen DN, Bowman VD, Anderson DL, Rossmann MG. Crystal and cryoEM structural studies of a cell wall degrading enzyme in the bacteriophage phi29 tail. Proc Natl Acad Sci USA. 2008; 105:9552–9557. [PubMed: 18606992]

Xu J, Hendrix RW, Duda RL. Conserved translational frameshift in dsDNA bacteriophage tail assembly genes. Mol Cell. 2004; 16:11–21. [PubMed: 15469818]

Yang F, Forrer P, Dauter Z, Conway JF, Cheng N, Cerritelli ME, Steven AC, Pluckthun A, Wlodawer A. Novel fold and capsid-binding properties of the lambda-phage display platform protein gpD. Nat Struct Biol. 2000; 7:230–237. [PubMed: 10700283]

Yin YW, Steitz TA. Structural basis for the transition from initiation to elongation transcription in T7 RNA polymerase. Science. 2002; 298:1387–1395. [PubMed: 12242451]

Yin YW, Steitz TA. The structural mechanism of translocation and helicase activity in T7 RNA polymerase. Cell. 2004; 116:393–404. [PubMed: 15016374]

Yoshikawa H, Elder JH, Ito J. Comparative studies on the small *Bacillus* bacteriophages. J Gen Appl Microbiol. 1986; 155:392–401.

Youderian P, Susskind MM. Identification of the products of bacteriophage P22 genes, including a new late gene. Virology. 1980; 107:258–269. [PubMed: 7445430]

Yura K, Yamaguchi A, Go M. Coverage of whole proteome by structural genomics observed through protein homology modeling database. J Struct Funct Genom. 2006; 7:65–76.

Zahn K, Blattner FR. Binding and bending of the lambda replication origin by the phage O protein. EMBO J. 1985; 4:3605–3616. [PubMed: 2936603]

Zahn K, Blattner FR. Direct evidence for DNA bending at the lambda replication origin. Science. 1987; 236:416–422. [PubMed: 2951850]

Zahn K, Landy A. Modulation of lambda integrase synthesis by rare arginine tRNA. Mol Microbiol. 1996; 21:69–76. [PubMed: 8843435]

Zhang X, Studier FW. Isolation of transcriptionally active mutants of T7 RNA polymerase that do not support phage growth. J Mol Biol. 1995; 250:156–168. [PubMed: 7608967]

Zhang X, Studier FW. Mechanism of inhibition of bacteriophage T7 RNA polymerase by T7 lysozyme. J Mol Biol. 1997; 269:10–27. [PubMed: 9192997]

Zhang X, Studier FW. Multiple roles of T7 RNA polymerase and T7 lysozyme during bacteriophage T7 infection. J Mol Biol. 2004; 340:707–730. [PubMed: 15223315]

Ziermann R, Calendar R. Characterization of the cos sites of bacteriophages P2 and P4. Gene. 1990; 96:9–15. [PubMed: 2265763]

Zillig W, Fujiki H, Blum W, Janekovic D, Schweiger M, Rahmsdorf H, Ponta H, Hirsch-Kauffmann M. *In vivo* and *in vitro* phosphorylation of DNA-dependent RNA polymerase of *Escherichia coli* by bacteriophage-T7-induced protein kinase. Proc Natl Acad Sci USA. 1975; 72:2506–2510. [PubMed: 1101258]

Zinder ND, Lederberg J. Genetic exchange in Salmonella. J Bacteriol. 1952; 64:679–699. [PubMed: 12999698]

Żylicz M, Ang D, Liberek K, Georgopoulos C. Initiation of lambda DNA replication with purified host- and bacteriophage-encoded proteins: The role of the dnaK, dnaJ and grpE heat shock proteins. EMBO J. 1989; 8:1601–1608. [PubMed: 2527744]

ABBREVIATIONS

EM	electron microscopy
LC	liquid chromatography
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORF	open reading frame
PPI	protein–protein interaction
Y2H	yeast two-hybrid

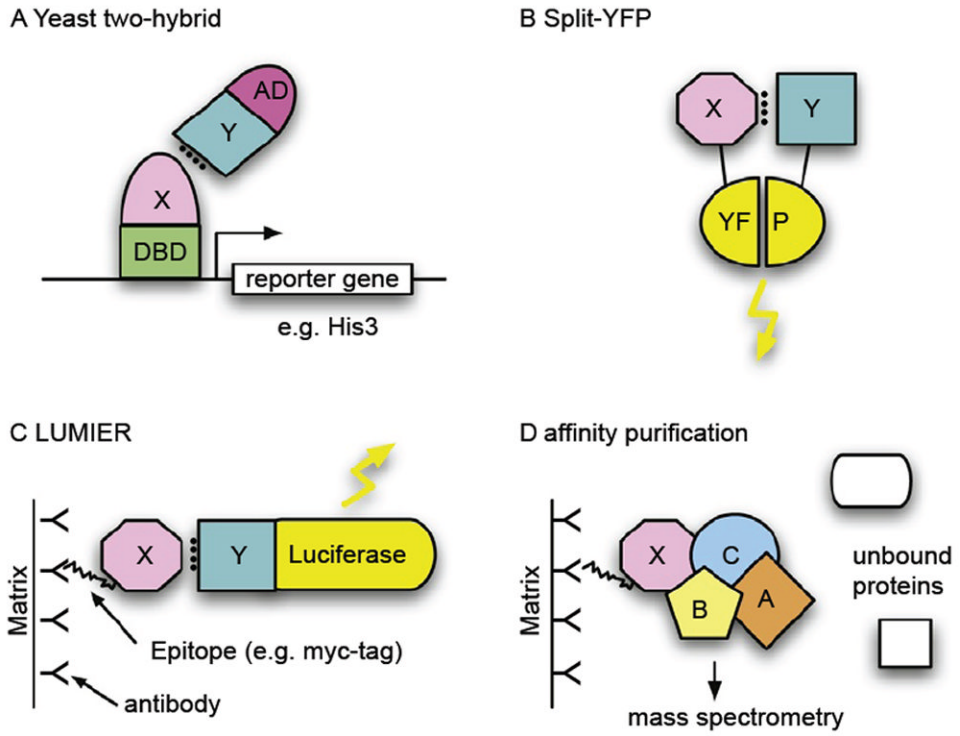

FIGURE 1.

Selected methods for the study of protein–protein interactions. (A) The yeast two-hybrid (Y2H) system is based on the levels of two fusion proteins (typically in yeast but any cell type can be used). One of the proteins contains a DNA-binding domain (DBD), which can bind to the promoter of a reporter gene (here: HIS3), and a second protein X, the bait. The second fusion protein consists of a transcription-activation domain (AD) and a second protein, Y. If proteins X and Y interact, a transcription factor is formed and the reporter gene is activated. In this case, that means that the cell can grow on histidine-free medium. A yeast colony growing on such medium thus indicates an interaction of the two inserted proteins. (B) Protein complementation assay (PCA), e.g., split-YFP. As in the Y2H assay, two interacting proteins bring together two protein fragments that are inactive when separate but active when in close proximity. Here, fragments of yellow-fluorescent protein (YFP) reassociate and fluoresce when reassembled. Other fluorescent proteins, such as the green fluorescent protein (GFP), have been used in a similar way. (C) LUMIER (LUMInescence-based mammalian intERactome). Two fusion proteins are purified by means of an epitope tag (here: FLAG tag), usually on an antibody-coated matrix. Interactions between X and Y can be detected using Luciferase, whose gene is fused to Y and which emits light when luciferin is added. (D) Affinity purification. Protein complexes can be purified from cellular lysates using an affinity epitope, as in (C) with a FLAG tag. Components of the complex can then be identified using mass spectrometry, using the unique mass of peptides when the protein is digested by trypsin.

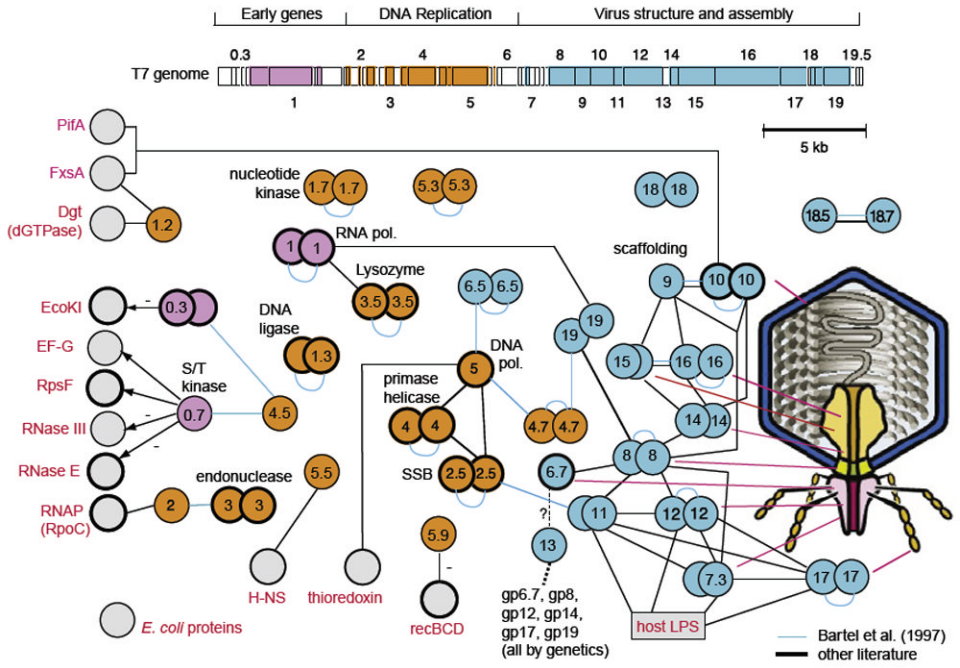

FIGURE 2.

Phage T7: genome, virion, and interactome. ORFeome and protein interaction map of bacteriophage T7. Cloned open reading frames (ORFs) and random fragments were used to generate a two-dimensional interaction map. ORFeomes can also be used by structural genomics projects to derive three-dimensional structures. A combination of interaction maps and crystal structures often allows reconstruction of protein complexes as in viral particles or their subunits. (Top) T7 genome with each ORF represented as a box. ORFs indicated by integral numbers were identified originally as essential by genetic screens. Other genes have decimal numbers; of these, only *2.5* and *7.3* are essential. Proteins found to interact with other proteins are indicated by colored boxes; colors indicate a simplified assignment to functional classes as shown. Interactions between proteins are shown as lines, with self-interactions shown as dimers. Hatched lines indicate expected interactions that have not been found by two-hybrid analysis. Gray proteins correspond to host proteins (*E. coli*). Blue proteins are involved in virus assembly and structure, and, where known, their location in the virus particle is shown on the right. Proteins with thick borders have been crystallized and their structure determined. Genetic map modified after Dunn and Studier (1983). Figure modified after Uetz *et al.* (2004). Interactions based primarily on data in Table II (see references therein).

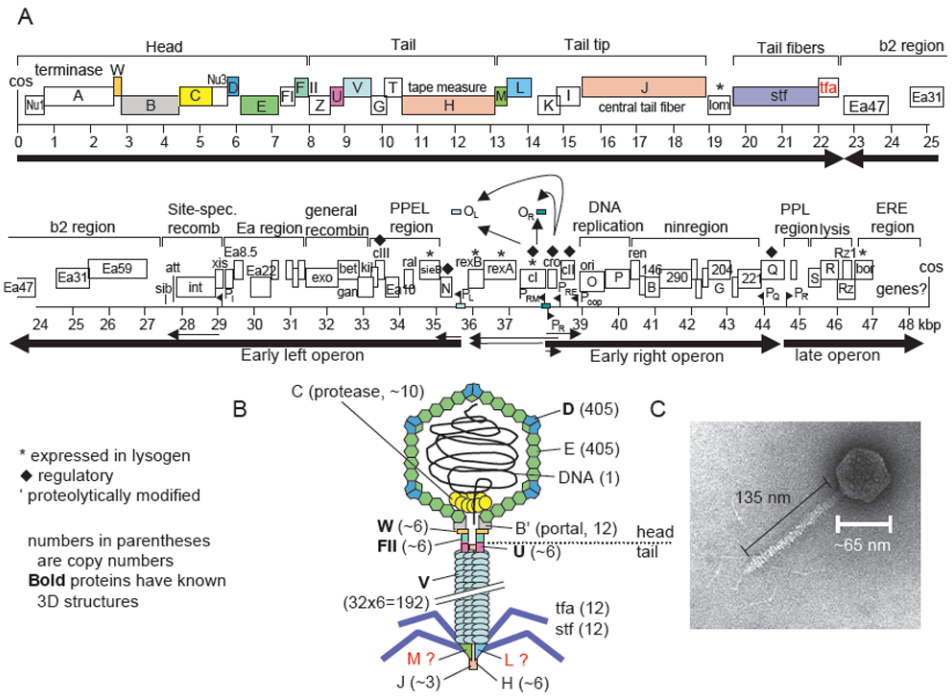

FIGURE 3.

Genome and virion of phage λ. (A) Genome of phage λ. Colored ORFs correspond to colored proteins in (B). Main transcripts are shown as arrows. After Hendrix and Casjens in Calendar (2006). (B) Schematic model of λ virion. Numbers indicate the number of protein copies in the particle. It is unclear whether gpM and gpL proteins are in the final particle or only required for assembly. (C) Electron micrograph of phage λ. Modified after Hendrix and Casjens (2006).

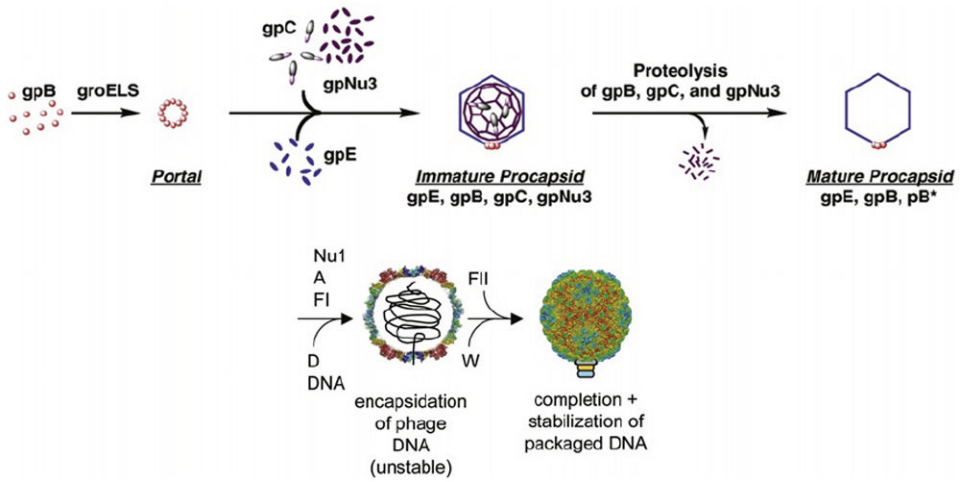

FIGURE 4.

Assembly of the phage λ head. Head assembly has been subdivided into five steps, although most steps are not very well understood in mechanistic terms. Note that the tail is assembled independently. GpC protease, scaffolding protein gpNu3, and portal protein gpB form an ill-defined initiator structure. Protein gpE joins this complex in a step requiring the chaperonins GroES and GroEL. Proteins gpNu1, gpA, and gpFI are required for DNA packaging. GpD joins and stabilizes the capsid as a structural protein; gpFII and gpW are connecting the head to the tail that joins once the head is completed. Modified after Georgopoulos *et al.* (1983) and Lander et al. (2008).

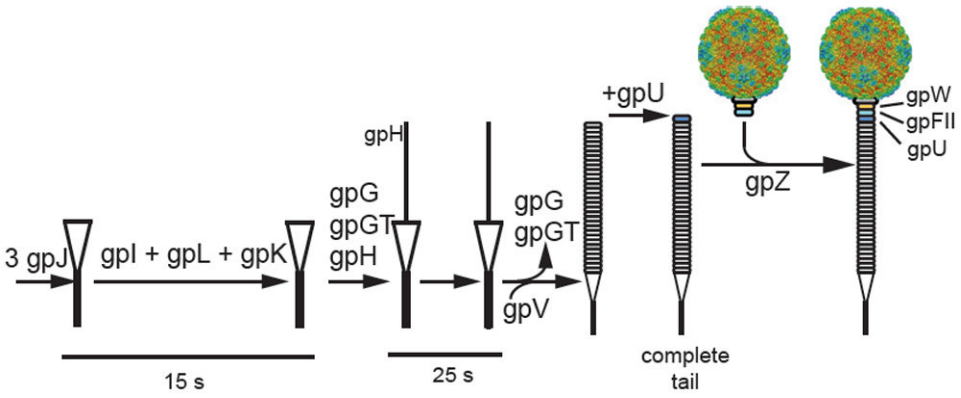

FIGURE 5.

Assembly of the phage λ tail. The λ tail is made of at least six proteins (gpU, V, J, H, tfa, stf) with another seven required for assembly (gpI, M, L, K, G/T, Z). Assembly starts with protein gpJ, which then, in a poorly characterized fashion, requires proteins gpI, gpL, gpK, and gpG/T to add the tape measure protein H. GpM joins and then gpG and gpG/T leave the complex so that the main tail protein gpV can assemble on the gpJ/H scaffold. Finally, gpU is added to the head-proximal end of the tail. GpZ is required to connect the tail to the preassembled head. Protein gpH is cleaved by the action of gpU and gpZ (Tsui and Hendrix, 1983). It remains unclear if proteins gpM and gpL are part of the final particle (Hendrix and Casjens, 2006). From http://www.pitt.edu/~duda/lambdatail.html.

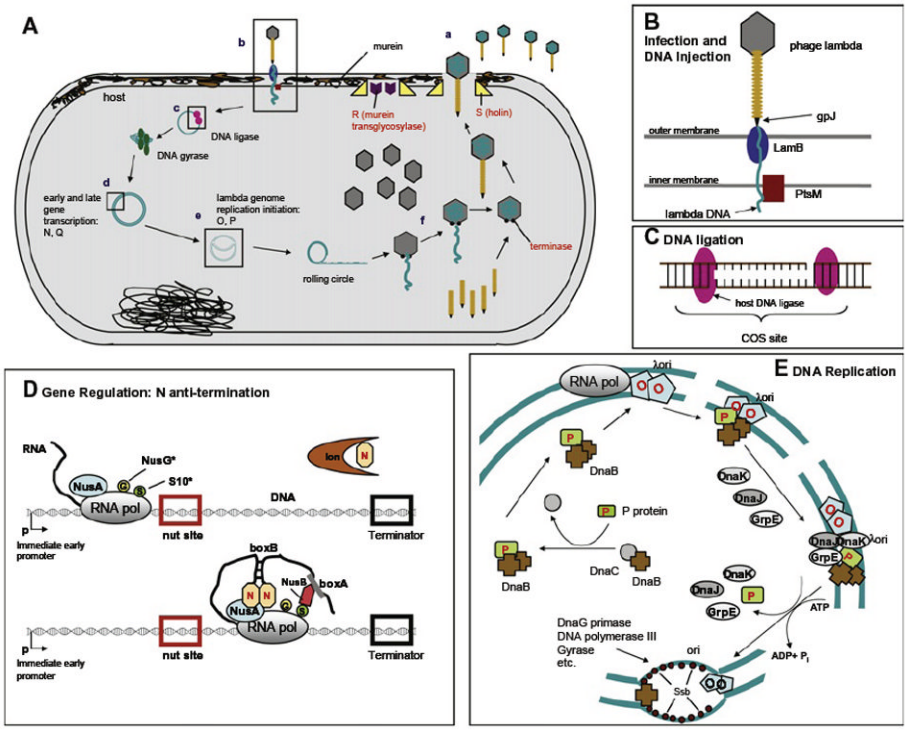

FIGURE 6.

Interactions of phage λ with its host, *E. coli*. (A) Overview of λ activities in *E. coli*: (a) free phage, (b) binding and entry, (c) DNA circularization and supercoiling, (d) transcription, (e), replication, and (f) virion assembly. Details are shown in B–E. (B) Infection and DNA ejection, (C) DNA ligation, (D) gene regulation. An asterisk means weakly bound to the RNA polymerase. (E) DNA replication. Phage proteins are labeled in red, host proteins in black. Modified after Das (1992) and Mason and Greenblatt (1991).

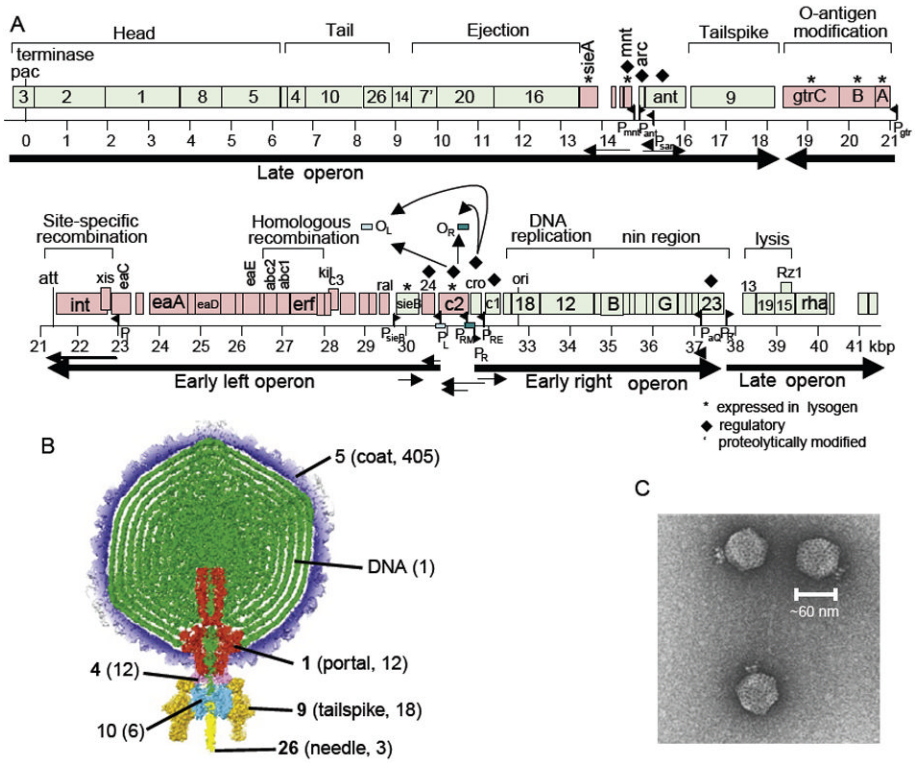

FIGURE 7.

Genome and virion of phage P22. (A) Genome of phage P22 with a scale in kbp below. Green open reading frames (ORFs; rectangles) are transcribed left to right; red ORFs are transcribed right to left. Known RNA polymerase promoters and transcripts are shown as black flags and arrows, respectively. (B) The asymmetric (not icosahedrally averaged) P22 virion three-dimensional cryo-EM reconstruction from Tang *et al.* (2011). Numbers in parentheses indicate molecules/virion, and bold numbers indicate proteins for which X-ray structures are known. (C). Negatively stained electron micrograph of P22 virions.

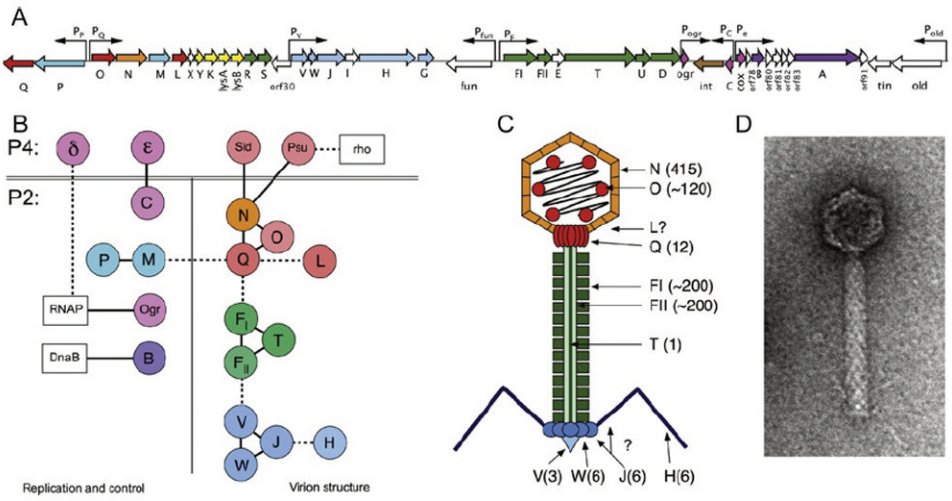

FIGURE 8.

(A) Schematic diagram of the 33.6-kb P2 genome. Open reading frames (ORFs) are indicated by arrows that reflect their direction and size and are color coded as follow: red/orange, capsid-associated proteins (gpQ, O, N, L); blue, terminase proteins (gpP, M); yellow, lysis proteins (gpY, K, lysA, lysB); green, tail-related proteins (gpR, S, FI, FII, T, U, D); blue, base plate and tail fiber-related proteins (gpV, W, J, H, G); pink, transcriptional control proteins (Ogr, C, Cox); brown, integrase (Int); and purple, replication-related proteins (gpA,B). Nonessential genes and ORFs of unknown function are white. Promoters are indicated by arrows above ORFs. (B) Diagram of protein–protein interactions listed in Table IX. Each P2 and P4 protein is shown as a circle, colored as given earlier. Host proteins are shown as white boxes. (C) Schematic diagram of the P2 virion, color coded as given earlier. Copy numbers of proteins, when known, are indicated in parentheses. (D) Electron micrograph of a P2 virion, stained negatively with uranyl acetate.

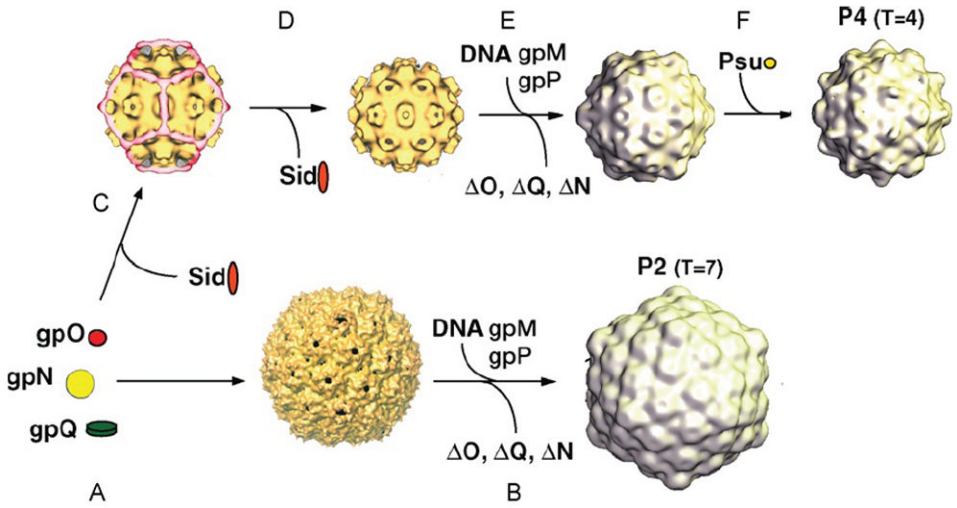

FIGURE 9.

P2 assembly. Schematic diagram of the P2/P4 capsid assembly pathway. (A) Capsid protein gpN, scaffolding protein gpO, and connector (portal) protein gpQ are assembled into the T=7 P2 procapsid. (B) GpN, gpO, and gpQ are then processed to their mature forms, N*, O*, and Q*. DNA is packaged into the procapsid by the P2 terminase complex (gpM and gpP), accompanied by expansion into the mature, angular capsid (B). (C) In the presence of the P4-encoded external scaffolding protein Sid, P2 structural proteins are assembled into a small, T=4 P4 procapsid. Loss of Sid (D), protein processing, and DNA packaging lead to the mature, expanded P4 capsid (E). The decoration protein Psu is added to the mature capsid (F).

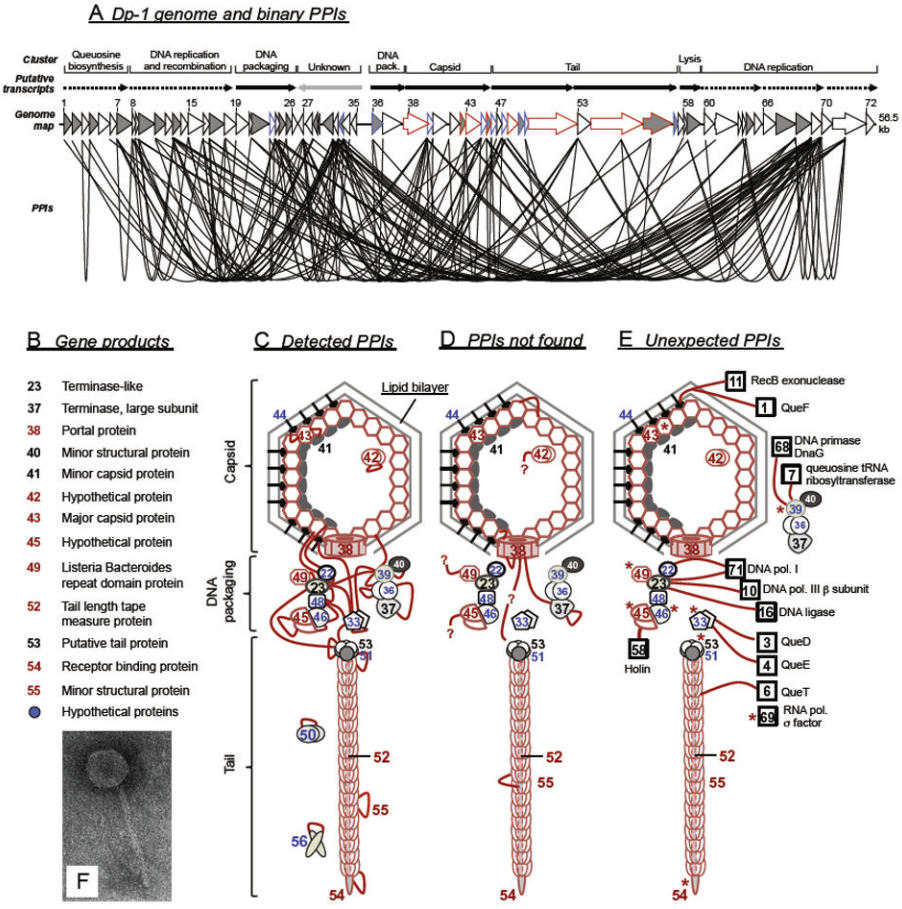

FIGURE 10.

The Dp-1 genome and interactome. (A) Dp-1 genome map. Open reading frames (ORFs) corresponding to their transcription direction are shown as arrows (genome map). Predicted transcripts and functional gene clusters are indicated. All protein–protein interactions (PPIs) identified by systematic Y2H screens among Dp-1 proteins are shown as lines that connect the corresponding ORF symbols. Proteins that bind themselves (homomers) are highlighted by gray ORF symbols. Other ORF colors: refer to Figure C-E. (B–E) A Dp-1 virion model based on identified binary PPIs, mass spectrometry analysis (MS) of mature Dp-1 virions, and homology predictions. (B) Dp-1 virion proteins, including structural proteins identified by MS analysis (in red), or proteins with a homology-based annotation that indicates a virion-related function (in black). (C) Core model of the Dp-1 virion: proteins highlighted in red were identified by MS analysis as structural components. Proteins highlighted in blue represent hypothetical gene products that interact with structural components, thus presumably playing a transient role in virion assembly as they were not identified by MS analysis of Dp-1 virions. Red edges that connect the proteins were shown to interact in Y2H tests. (D) Y2H screens do not identify all expected PPIs. Red lines represent PPIs that were expected to occur among the corresponding proteins known from homologues but were not identified in the systematic Y2H screens. (E) Systematic Y2H screens reveal unexpected PPIs. Proteins are included that were shown to bind with structural proteins and putative morphogenetic factors, e.g., DNA metabolism (DNA polymerase subunits, RecB, DNA ligase, DnaG), queuosine biosynthesis (Que proteins), lysis (Holin), and transcription (sigma factor). Interactions are symbolized by edges that connect the corresponding proteins (in the

case of sigma factor gp69, interaction partners are highlighted by an asterisk). (F) Electron micrograph of a mature Dp-1 virion. C–F from Sabri et al. (2010), with permission.

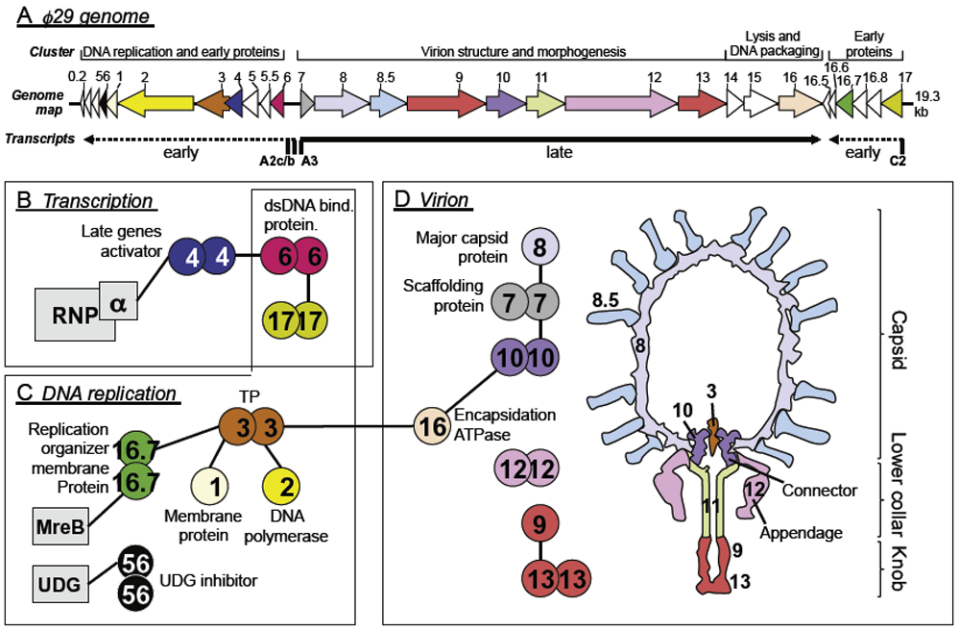

FIGURE 11.

Genome map and literature curated ϕ29 interactome. (A) Genome and simplified transcriptional map of ϕ29 (after Meijer *et al.*, 2001a). Major promoters are indicated by their names, and major transcripts are shown as dashed (early) and solid (late) arrows. Other promoters are not indicated for clarity. Open reading frame (ORF) arrows indicate transcription direction. The color of ORF symbols corresponds to the color used for protein symbols in B, C, and D. PPIs known for ϕ29, organized by their cellular function (transcription, DNA replication, or virion). *B. subtilis* proteins are shown as rectangles, phage proteins as circles. Equal protein symbols contacting each other indicate homomers. Heteromeric PPIs are highlighted by protein symbols that are connected by lines. (D) Schematic cross view of the mature ϕ29 virion (after Xiang et al., 2008). UDG, uracil–DNA glycosylase; RNAP, RNA polymerase; TP, terminal protein.

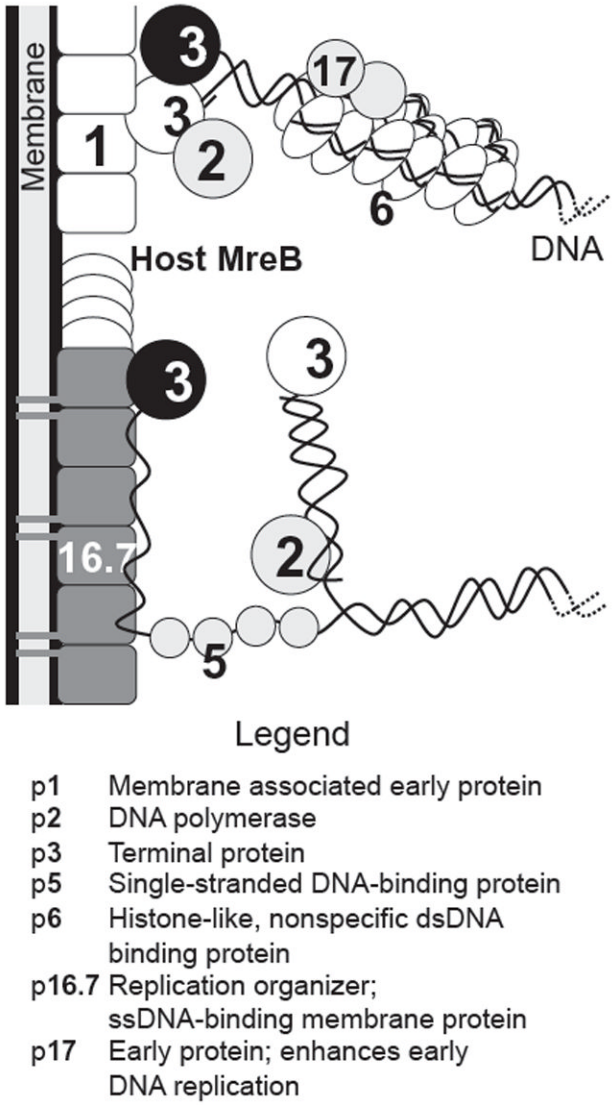

FIGURE 12.

Interactions in ϕ29 genome replication and membrane localization. Proteins that contact each other have been shown to interact. For clarity, only one genome end is shown. Parental TP is highlighted by a black symbol, whereas primer TP is in white. The upper part of the figure includes PPIs that preferentially play a role in replication initiation. The lower part of the figure indicates elongated DNA with the associated ssDNA regions. Because p16.7 and p5 (SSB) both bind ssDNA, they could either redirect the parental ssDNA strand to the membrane via TP-p16.7 and p16.7–ssDNA interactions or stabilize it in the cytoplasm via SSB alone (Meijer *et al.*, 2001b). After Bravo *et al.* (2000) and Serna-Rico *et al.* (2003).

TABLE I

Summary of phage interactomes described in this chapter[a]

Phage	Proteins	Phage–phage PPIs	Phage–host PPIs
T7	55	~43 (including 7 HTS[b])	15
λ	73	33 (+ 81 HTS)	26
P22	64	38	9
P2/P4	42/13	14	3
ϕ29	30	20	3
Dp-1	72	156 (HTS)	38 (HTS)
Cp-1	28	17 (HTS)	11 (HTS)

[a]Note that all interactions from this chapter are available as a downloadable supplement from http://www.uetz.us.

[b]High-throughput data (see text for details).

TABLE II

Protein–protein interactions of phage T7

Protein	Function	Interacts with	References
Class I			
gp0.3	B-DNA mimic	Host HsdRMS	Atanasiu *et al.*, 2001, 2002; Kennaway *et al.*, 2009; Murray, 2000; Stephanou *et al.*, 2009
gp0.3		gp0.3 (dimer)	Atanasiu *et al.*, 2001
gp0.3		gp4.5	Bartel *et al.*, 1996
gp0.7	Protein kinase	Host RNAP (activity change)	Rahmsdorf *et al.*, 1974; Severinova and Severinov, 2006; Zillig *et al.*, 1975
gp0.7		RNase III (activity change)	Mayer and Schweiger, 1983
gp0.7		RNase E (activity change)	Marchand *et al.*, 2001
gp0.7		Translation components	Robertson *et al.*, 1994; Robertson and Nicholson, 1990, 1992
gp0.7		gp4.5	Bartel *et al.*, 1996
gp1	T7 RNA polymerase	gp3.5	Jeruzalmi and Steitz, 1998; Zhang and Studier, 2004
gp1		gp19 (genetic)	Zhang and Studier, 1995, 2004
gp1.2	*E. coli* dGTPase inhibitor;	Host Dgt (dGTPase)	Huber *et al.*, 1988; Nakai and Richardson, 1990; Saito and Richardson, 1981
gp1.2	F-exclusion	F plasmid PifA	Cheng *et al.*, 2004; Schmitt and Molineux, 1991; Wang *et al.*, 1999
gp1.2		Host FxsA	Cheng *et al.*, 2004; Wang *et al.*, 1999
Class II			
gp1.7	Nucleotide kinase	gp1.7 (oligomer)	Tran *et al.*, 2010; Bartel *et al.*, 1996
gp2	*E. coli* RNAP inhibitor	Host RNAP	Camara *et al.*, 2010; Nechaev and Severinov, 1999
gp2		gp3	Bartel *et al.*, 1996
gp2.5	SSB	gp5 (with thioredoxin)	Hamdan *et al.*, 2005; He *et al.*, 2003; Ghosh *et al.*, 2008, 2010; Marintcheva *et al.*, 2009
gp2.5		gp4	Ghosh *et al.*, 2008; Hamdan *et al.*, 2005; He and Richardson, 2004
gp2.5		gp2.5 (dimer)	Rezende *et al.*, 2002; Bartel *et al.*, 1996
gp3	Endonuclease I, HJ resolvase	gp3 (dimer)	Hadden *et al.*, 2007; Parkinson and Lilley, 1997
gp3.5	Amidase (lysozyme)	gp1	Jeruzalmi and Steitz, 1998; Zhang and Studier, 2004
gp4	gp4A primase-helicase; gp4B	gp5 (with thioredoxin)	Hamdan *et al.*, 2005; He and Richardson, 2004
gp4	helicase	gp2.5	Hamdan *et al.*, 2005; He and Richardson, 2004
gp4		gp4 (hexamer)	Singleton *et al.*, 2000; Bartel *et al.*, 1996
gp4.5		gp0.7	Bartel *et al.*, 1996
gp5	DNA polymerase	gp4 (with thioredoxin)	Ghosh *et al.*, 2008; Hamdan *et al.*, 2005; Bartel *et al.*, 1996
gp5		gp2.5 (with thioredoxin)	Ghosh *et al.*, 2008, 2010; He *et al.*, 2003; Marintcheva *et al.*, 2009; Hamdan*et al.*, 2005

Protein	Function	Interacts with	References
gp5		gp4.7	Bartel *et al.*, 1996
gp5		gp6.5	Bartel *et al.*, 1996
gp5		Host thioredoxin	Ghosh *et al.*, 2008
gp5.3		gp5.3	Bartel *et al.*, 1996
gp5.5		Host H-NS	Lin, 1992; Liu and Richardson, 1993
gp5.9	Inhibits RecBCD nuclease	Host RecBCD	Lin, 1992
Class III			
gp6.7	Head completion; ejected virion protein	Other head proteins likely. gp13?	Kemp *et al.*, 2005
gp7.3	Tail chaperone; ejected structural virion protein	gp7.3, gp11, gp12	Kemp *et al.*, 2005
gp7.3		Host LPS	Kemp *et al.*, 2005
gp8	Head–tail connector (portal)	gp19	Fujisawa *et al.*, 1991; Morita *et al.*, 1995
gp8	protein	gp9/10/gp6.7/7.3/11/12/14 (structure)	Agirrezabala *et al.*, 2005a, 2007; Cerritelli and Studier, 1996a; Liu *et al.*, 2010
gp8		gp8 (dodecamer) (structure)	Agirrezabala *et al.*, 2005b; Cerritelli and Studier, 1996b
gp9	Scaffolding protein	gp8, gp10 (structure)	Agirrezabala *et al.*, 2007; Cerritelli and Studier, 1996a,b
			Bartel *et al.*, 1996
gp9		gp14/15/16 (structure)	—
gp10	Major capsid protein (-1 frame-shift -> minor gp10B)	gp8, gp9, gp14 (structure)	Agirrezabala *et al.*, 2005a,b, 2007; Cerritelli and Studier, 1996a; Cerritelli and Studier, 1996b
		gp10 (pentamer/hexamer) (structure)	Cerritelli and Studier, 1996a; Bartel *et al.*, 1996
gp10		Host FxsA; F plasmid PifA	Cheng *et al.*, 2004; Schmitt and Molineux, 1991; Wang *et al.*, 1999
gp11	Tail protein	gp7.3, gp8, gp11, gp12 (structure)	Kemp *et al.*, 2005; Agirrezabala *et al.*, 2007; Liu *et al.*, 2010
gp11		Host LPS	Kemp *et al.*, 2005
gp11		gp2.5	Bartel *et al.*, 1996
gp12	Tail protein	gp7.3, gp8, gp11, gp12 (structure)	Kemp *et al.*, 2005; Liu *et al.*, 2010
gp12		Host LPS	Kemp *et al.*, 2005; Qimron *et al.*, 2006
gp13	Virion chaperone	gp6.7, gp8, gp12, gp14, gp17, gp19 (genetics)	Kemp *et al.*, 2005, Stone and Miller, 1985
gp14	Ejected core protein	gp8, gp14, gp15, gp16 (structure)	Agirrezabala *et al.*, 2007; Liu *et al.*, 2010
gp15	Ejected core protein	gp14, gp15, gp16 (structure)	Agirrezabala *et al.*, 2007; Chang *et al.*, 2010; Liu *et al.*, 2010; Bartel *et al.*, 1996
gp16	Ejected core protein	gp14, gp15, gp16 (structure)	Agirrezabala *et al.*, 2007; Chang *et al.*, 2010; Liu *et al.*, 2010
gp16		Peptidoglycan	Moak and Molineux, 2000, 2004
gp17	Tail fiber protein	gp7.3/11/12 (structure)	Agirrezabala *et al.*, 2007; Chang *et al.*, 2010; Liu *et al.*, 2010
gp17		gp17 (trimer)	Steven *et al.*, 1988; Bartel *et al.*, 1996

Protein	Function	Interacts with	References
gp17		Host LPS	Steven *et al.*, 1988; Qimron *et al.*, 2006
gp18	Small terminase	gp18 (octamer)	White and Richardson, 1987; Hamada *et al.*, 1986
gp18.5-	gp18.7 Casjens *et al.*, 1989 Summer *et al.*, 2007; Bartel *et al.*, 1996	*Rz-Rz1* homologues; spanin	gp18.5–gp18.7
gp19	Large terminase	gp8	Fujisawa *et al.*, 1991; Hamada *et al.*, 1986; Morita *et al.*, 1994, 1995
gp19		gp19 (hexamer in the presence of prohead)	Fujisawa *et al.*, 1991
gp19		gp4.7	Bartel *et al.*, 1996

TABLE III

Published protein–protein interactions of phage λ

λ 1	λ 2	Notes	References
gpA	gpNu1	gpA (N-terminal) – gpNu1 (C-terminal)	Catalano, 2000; de Beer *et al.*, 2002; Hang *et al.*, 1999
gpA	gpB	gpA (C-terminal) – gpB (= portal)	Catalano, 2000; Duffy and Feiss, 2002
gpW	gpB	gpW (NMR, head–tail joining)	Casjens, 1974; Casjens *et al.*, 1972
gpW	gpFII	gpW required for gpFII binding	Casjens, 1974; Maxwell *et al.*, 2001
gpB	gpB	12-mer (22 amino acids removed from gpB N-terminal)	Kochan, Carrascosa and Murialdo, 1984; Tsui and Hendrix, 1980
gpC	gpE	Covalent PPI (in virion?)	Hendrix and Casjens, 1974;Hendrix and Duda, 1998
gpC′	gpB		Murialdo, 1979
gpC	gpNu3	gpC may degrade gpNu3 (before DNA packaging)	Hendrix and Casjens, 1975; Hohn *et al.*, 1975; Medina *et al.*, 2010; Murialdo and Becker, 1978
gpD	gpD	gpD forms trimers	Mikawa *et al.*, 1996; Sternberg and Hoess, 1995; Yang *et al.*, 2000
gpE	gpE	Major capsid protein	Casjens and Hendrix, 1974; Dokland and Murialdo, 1993; Lander *et al.*, 2008
gpU	gpU	“Probably a hexamer”	Katsura and Tsugita, 1977
gpD	gpE		Casjens and Hendrix, 1974; Dokland and Murialdo, 1993; Lander *et al.*, 2008
gpU	gpV	gpU is head-proximal tail protein	Pell *et al.*, 2009
gpV	gpV		Buchwald *et al.*, 1970a,b; Casjens and Hendrix, 1974; Katsura, 1983
gpO	gpP		Wickner and Zahn, 1986; Zahn and Blattner, 1985, 1987; Zahn and Landy, 1996)
gpO	gpO	gpO–gpO interactions when bound to ori DNA	Alfano and McMacken, 1989
gpB	gpA	Genetic evidence	Frackman *et al.*, 1985; Sippy and Feiss, 1992
gpFI	gpA	Genetic evidence	Catalano and Tomka, 1995
gpFI	gpE	Genetic evidence	Murialdo and Tzamtzis, 1997
gpH	gpG/gpGT	gpG/gpGT holds gpH in an extended fashion	Hendrix and Casjens, 2006
gpV	gpGT	T domain binds soluble gpV	Hendrix and Casjens, 2006
gpH	gpV	gpV probably assembles around gpH, displacing gpG/gpGT	Xu *et al.*, 2004
CI	CI	Forms octamer that links O_R to O_L	Bell and Lewis, 2001; Dodd *et al.*, 2001
Exo	Bet		Radding *et al.*, 1971
SieB	Esc	Esc is encoded in frame in SieB and inhbits SieB	Ranade and Poteete, 1993a,b
CII	CII	Homotetramers	Ho and Rosenberg, 1982
Xis	Int		Sam *et al.*, 2002
Xis	Xis	Xis-Xis binding mediates cooperative DNA binding	Sam *et al.*, 2004
Int	Int	Dimer	Warren *et al.*, 2003

λ 1	λ 2	Notes	References
Stf	Stf	Likely homotrimer by homology with T4 fibers	
gpS	gpS	Large ring in inner membrane	Savva *et al.*, 2008
gpS	gpS′	gpS′ inhibits gpS ring formation	Grundling *et al.*, 2000
gpB	gpE	Copurify in procapsid	Hendrix and Casjens, 1975
gpNu3	pNu3	Monomer–dimer equilibrium	C. Catalano, personal communication
CIII	CIII	Dimer	Halder *et al.*, 2007
Cro	Cro	Dimer; X-ray str	Anderson *et al.*, 1979
gpRz	gpRz1	Heteromultimer supposed to span the periplasm	Summer *et al.*, 2007
gpNu3	gpB	gpNu3 required for gpB incorporation into procapsid	Ray and Murialdo, 1975

TABLE IV

Published phage λ–host interactions[a]

λ	Host	Description	References
Transcription			
CI	RecA	RecA degrades CI[b]	Kobiler *et al.*, 2004
CI	RpoA		Kędzierska *et al.*, 2007
CI	RpoD		Li *et al.*, 1994; Nickels *et al.*, 2002
CII	ClpYQ	ClpYQ degrades CII in vitro	Kobiler *et al.*, 2004
CII	ClpAP	ClpAP degrades CII *in vitro*	Kobiler *et al.*, 2004
CII	HflD	HflD makes CII more vulnerable to FtsH (*hfl*, high-frequency lysogenization)	Kihara *et al.*, 2001
CII	HflB[c]	HflB (= FtsH) protease degrades cII	Kobiler *et al.*, 2002; Shotland *et al.*, 2000
CII	RpoA		Kędzierska *et al.*, 2004; Marr *et al.*, 2004
CII	RpoD		Kędzierska *et al.*, 2004
CIII	HflB	CIII inhibits HflB; HflB degrades CIII	Herman *et al.*, 1997; Kornitzer *et al.*, 1991
gpN	NusA	Transcriptional regulation	Friedman and Court, 2001
gpN	Lon	Lon degrades gpN	Kobiler *et al.*, 2004; Gottesman *et al.*, 1981
gpQ	σ^{70}	gpQ makes RNAP insensitive to *cis* terminal	Marr *et al.*, 2001;Nickels *et al.*, 2002; Roberts and Roberts, 1996; Roberts *et al.*, 1998
Head			
gpB	GroE	genetic interaction; *E. coli* GroE	Ang *et al.*, 2000; Georgopoulos *et al.*, 1973; Murialdo, 1979
gpE	GroE	genetic interaction	Georgopoulos *et al.*, 1973
Tail			
gpJ	LamB	LamB is the *E. coli* receptor	Buchwald and Siminovitch, 1969; Clement *et al.*, 1983; Mount *et al.*, 1968; Wang *et al.*, 2000a; Werts *et al.*, 1994
Stf	OmpC	OmpC is a secondary *E. coli* receptor	Hendrix and Duda, 1992
Recombination			
Xis	Lon	Xis is degraded by *E. coli* Lon protease	Leffers and Gottesman, 1998
Xis	FtsH	Xis is degraded by *E. coli* FtsH protease	Leffers and Gottesman, 1998
Xis	Fis	both required for excision	Ball and Johnson, 1991; Cho *et al.*, 2002; Esposito and Gerard, 2003
Int	IHF	Both catalyze recombination at *attP/attB*	Campbell *et al.*, 2002; Crisona *et al.*, 1999
Gam	RecB	Gam inhibits RecBCD	Marsic *et al.*, 1993
NinB	SSB	NinB also binds ssDNA	Maxwell *et al.*, 2005

Adv Virus Res. Author manuscript; available in PMC 2012 September 30.

λ	Host	Description	References
Replication			
gpO	ClpXP	ClpXP degrades gpO	Kobiler *et al.*, 2004
gpP	DnaA		Datta *et al.*, 2005b,c
gpP	DnaB		Mallory *et al.*, 1990

[a] CbpA (Wegrzyn *et al.*, 1996) perhaps interacts with DnaA and SeqA (Potrykus *et al.*, 2002; Wegrzyn and Wegrzyn, 2001, 2002).

[b] After DNA damage, RecA bound to single-stranded DNA stimulates autocleavage of the CI repressor (Kobiler *et al.*, 2004).

[c] HflB = FtsH.

TABLE V

P22 intraphage protein interactions

P22 1	P22 2	Description	References
gp3	gp3	Small terminase subunit; homononomer in solution	Nemecek *et al.*, 2007, 2008
gp3	gp2	Purify as complex; bind each other *in vitro*	Nemecek *et al.*, 2007; Poteete and Botstein, 1979
gp2	gp1	gp2 is large terminase subunit; assembles in packaging motor to gp1 by analogy with other phages (gp2 by itself is monomer in solution); evolutionary argument for P22 gp2–gp1 interaction	Casjens, 2011
gp1	gp1	Portal protein; homododecamer; EM of 12-mer; EM of virion; X-ray structure	Bazinet *et al.*, 1988; Lander *et al.*, 2006; Olia *et al.*, 2011
gp1	gp5	Purify as complex (procapsids); three-dimensional (3D) reconstructions of virion and procapsid	Botstein *et al.*, 1973; Chen *et al.*, 2011; Lander *et al.*, 2006
gp1	gp8	gp8 required for assembly of gp1 into procapsid; interaction seen in procapsid 3D reconstruction	Chen *et al.*, 1989; Greene and King, 1996; Weigele *et al.*, 2005
gp8	gp8	Scaffolding protein; forms homodimers and tetramers in solution	Parker *et al.*, 1997
gp8	gp5	Purify as complex (procapsid); bind *in vitro*	Fuller and King, 1982; Greene and King, 1994; Parker *et al.*, 1998
gp5	gp5	Coat (major capsid) protein; forms T=7 *l* icosahedral shell of virion	Botstein *et al.*, 1973; Casjens, 1979; Lander *et al.*, 2006
gp5	gp1	Purify as complex (procapsids); interaction seen in 3D reconstruction	Chen *et al.*, 2011; Lander *et al.*, 2006
gp4	gp4	Tail protein; monomer in solution (naturally unfolded?); gp4s barely touching each other in dodecamer ring in virion (i.e., contacts not large); EM, X-ray structure	Olia *et al.*, 2011; Tang *et al.*, 2011
gp4	gp5	Contact in high-resolution 3D reconstruction of virion	Olia *et al.*, 2006, 2011; Tang *et al.*, 2011
gp4	gp1	Order of assembly, EM, 3D reconstruction; X-ray cocrystal structure	Olia *et al.*, 2006, 2011; Tang *et al.*, 2011
gp4	gp10	12 gp4s contact 6 gp10s; order of assembly, EM, 3D reconstruction	Lander *et al.*, 2006; Olia *et al.*, 2007
gp4	gp9	gp4 ring contacts 6 gp9 trimers; 3D reconstruction	Lander *et al.*, 2006
gp10	gp10	Tail protein; probably hexamer in solution; 3D reconstruction	Lander *et al.*, 2006; Olia *et al.*, 2007
gp10	gp9	6 gp4s contact 6 gp9 trimers; 3D reconstruction	Lander *et al.*, 2006
gp10	gp26	6 gp10s contact one gp26 trimer	Lander*et al.*, 2006
gp26	gp26	Tail needle protein; trimer in solution - crystal structure; one trimer in virion	Olia *et al.*, 2007
gp16	gp8	Mutants of gp8 do not incorporate gp16 into virion	Chen *et al.*, 1989; Greene and King, 1996; Weigele *et al.*, 2005
C1	C1	C1 is homologue of λ CII; homotetramer	Ho *et al.*, 1992
Mnt	Mnt	Repressor of antirepressor gene; tetramer	Nooren *et al.*, 1999
Arc	Arc	Repressor of antirepressor gene; dimer in solution, tetramer on DNA	Bowie and Sauer, 1989; Breg *et al.*, 1990; Brown, Bowie and Sauer, 1990
Ant	C2	Antirepressor; binds to and inhibits C2 repressor	Susskind and Botstein, 1975
gp9	gp9	Tailspike protein; trimer in solution, 6 trimers in virion; crystal structure; binds to polysaccharide on cell surface	Lander *et al.*, 2006; Steinbacher *et al.*, 1994, 1997
Int	Xis	Form heteromultimer	Cho *et al.*, 2002

P22 1	P22 2	Description	References
Xis	Xis	Excisionase; homomultimers	Mattis *et al.*, 2008
Erf	Erf	Recombination protein; homomultimeric ring of 10–14 subunits	Poteete *et al.*, 1983
C3	C3	C3 is homologue of λ CIII; λ CIII is dimer by disulfide bond; P22 interaction by homology with λ CIII	Halder *et al.*, 2007
SieB	Esc	Similar to λ but not studied in detail	Ranade and Poteete, 1993a
C2	C2	Prophage repressor homologue of λ CI; homodimer	De Anda *et al.*, 1983
Cro	Cro	Dimer; solution studies and crystal structure	Darling *et al.*, 2000; Newlove *et al.*, 2004
gp18	gp12	Origin binding protein gp18 recruits DnaB-like gp12 to replication origin by analogy with λ (note that gp12 is not a homologue of λ P protein; gp18 is homologous to λ O protein only in N-terminal domain)	Backhaus and Petri, 1984
Rz	Rz1	Rz and Rz1 are supposed to bind to one another and form a bridge that spans the periplasm in phage λ; P22 gp15 and Rz1 should do the same by homology.	Summer *et al.*, 2007
gp13	gp13	Holin forms rings of large diameter in λ; by homology same should be true of P22 holin	Savva *et al.*, 2008
gp13	gp13′	Antiholin–holin interactions delay the formation of holin rings in λ; by homology same should be true in P22	Rennell and Poteete, 1985
Dec	Dec	Trimer; Note that P22 has no Dec, but its very close relative phage L does and L Dec binds to P22 capsids.	Tang *et al.*, 2006
Dec	gp5	Dec occupies a subset of the quasi-equivalent local threefold positions on the shell	Tang *et al.*, 2006

TABLE VI

P22–host protein interactions

P22	Host	Description	References
gp5	GroEL	Solution studies	de Beus *et al.*, 2000
gp24	NusA? etc?	Homologue/analogue of λ gpN; likely binds same host factors as λ gpN	Franklin, 1985; Hendrix and Casjens, 2006
C3	FtsH(HflB)	C3 is homologue of λ CIII; inhibition of FstH by homology with λ CIII	Semerjian *et al.*, 1989
C1	FtsH(HflB)	C1 is homologue of λ CII; CII is degraded by FtsH	Backhaus and Petri, 1984
C2	RecA	P22 repressor autocleavage stimulated by RecA binding like λ	Prell and Harvey, 1983; Tokuno and Gough, 1976
Xis, gp18, gp24, C1	Host protein degradation machinery	These may be degraded analogously to their λ homologues, but direct information is not available	Backhaus and Petri, 1984
gp23	RNA polymerase?	By homology to λ; gp23 is nearly identical to λ gpQ	Pedulla *et al.*, 2003
gp12	Host replication machinery	Possible interaction with host DnaG primase	Wickner, 1984
Abc2	RecC	Solution studies	Murphy, 2000

TABLE VII

Comparison of λ and P22 interactions

λ 1	λ 2	P22 1	P22 2	Description
gpA	gpB	gp2	gp1	Likely similar contacts—by evolutionary argument[a]
gpA	gpNu1	gp2	gp3	Likely similar contacts—by evolutionary argument [a]
gpNu1	gpNu1	gp3	gp3	gpNu1 N-terminal fragment is dimer; gp3 is nonomer; not known if they have the same fold (i.e., are ancient homologues)
gpW	gpB	gp4	gp1	gpW and gp4 have no known homology, but are analogous in that they are the first proteins to bind the underside of the the portal ring; gp4 has no structural homology to λ gpFII or gpW (Cardarelli *et al.*, 2010; Olia *et al.*, 2011)
gpW	gpFII			No clear gpFII homologue in P22 (gp4 and gp10 of P22 have no sequence similarity)
gpB	gpB	gp1	gp1	Both form dodeamer portal rings[a]
gpC	gpE			No gpC analogue in P22
gpC′	gpB			No gpC analogue in P22
gpC	gpNu3			No gpC analogue in P22
gpNu3	gpNu3	gp8	gp8	Monomer/dimer/tetramer for gp8; monomer/dimer for gpNu3
gpB	gpE	gp1	gp5	Seen in reconstructions[a]
gpNu3	gpB	gp8	gp1	Scaffolds required for portal assembly into procapsid
		gp8	gp5	Scaffold–coat interaction not studied for λ
gpD	gpD	Dec	Dec	Both trimers; bind slightly different sites.[a] Note that P22 has no Dec, but its very close relative phage L does and L Dec binds to P22 capsids
gpE	gpE	gp5	gp5	Both make icosahedral T=7 head shells[a]
gpU	gpU			No analogue in P22
gpD	gpE	Dec	gp5	Dec is more discriminatory than D, i.e., unlike D, Dec does not occupy all of the quasi-equivalent local threefold positions on the shell
		gp4	gp5	Unkown in λ
		gp4	gp10	No gp10 analogue in λ (but see gpFII above)
		gp4	gp9	No gp9 analogue in λ (but see Stf below?)
		gp10	gp9	No gp9 analogue in λ (but see Stf below?)
		gp10	gp10	No gp10 analogue in λ (but see gpFII above)
		gp10	gp26	No gp10 or gp26 (?) analogue in λ
		gp26	gp26	No gp26 analogue in λ (maybe gpJ?)
Stf	Stf	gp9	gp9	Both trimers (Stf by homology to T4 fibers); analogues, not homologues
gpU	gpV			No analogues in P22
gpV	gpV			No analogue in P22

Adv Virus Res. Author manuscript; available in PMC 2012 September 30.

λ 1	λ 2	P22 1	P22 2	Description
gpO	gpP	gp18	gp12	gpO and gp18 are homologous but gpP and gp12 are not; nonetheless, a good argument can be made that gp18 and gp12 must interact similarly to gpO and gpP to get replication started
gpW	gpW	gp4	gp4	Analogues—first proteins to bind below the portal ring (see gpW–gpB interaction above)
gpFI	gpA			No gpFI analogue in P22
gpFI	gpE			No gpFI analogue in P22
gpH	gpG/gpGT			No analogues in P22
gpV	gpGT			No analogues in P22
gpH	gpV			No analogues in P22
		Arc	Arc	No analogue in λ
		Ant	C2	No Ant in λ
		Mnt	Mnt	No analogue in λ
CI	CI	C2	C2	Homologues (Sevilla-Sierra *et al.*, 1994)
Exo	Bet	Erf	Erf	λ Exo and P22 Erf proteins are not homologues and function in basically different ways, but they are both essential for homologous recombination
SieB	Esc	SieB	Esc	Good homologues in P22 but they are unstudied
CII	CII	C1	C1	Homotetramers in both cases
Xis	Int	Xis	Int	Xis proteins are quite different
Xis?	Xis?	Xis	Xis	Monomer in λ, but binds cooperatively so could interact on DNA (Abbani *et al.*, 2007); multimer in P22
CIII	CIII	C3	C3	C3 is homologue of λ CIII; λ CIII is dimer (Halder *et al.*, 2007); P22 interaction by homology with λ CIII
Cro	Cro	Cro	Cro	Both homodimers
gpRz	gpRz1	gp15	gp15	Predicted for P22 by homology

[a]Not recognizably similar in amino acid sequence but *very* likely ancient homologues.

TABLE VIII

Comparison of phage λ–host and P22–host interactions

λ	Host	P22	Host	Notes
CII	HflB	C1	HflB	Should be true for P22 by homology
CIII	HflB	C3	HflB	Should be true for P22 by homology
gpJ	LamB			P22 tails recognize polysaccharide so no analogue in P22
Stf	OmpC			P22 tails recognize polysaccharide so no analogue in P22
Xis	Lon	Xis	Lon?	Might be true for P22 by homology
Xis	FtsH	Xis	FtsH?	Might be true for P22 by homology
gpN	RNAP	gp24	RNAP?	Likely true for P22 by similarity of function
Int	IHF			P22 does not interact with IHF (Cho *et al.*, 1999)
Xis	Fis			Unknown for P22
gpQ	σ^{70}	gp23	σ^{70}	Likely true for P22 by similarity of function
P	DnaB			No analogue of P in P22
		gp12	DnaG?	No analogue of 12 in λ
gpE	GroE	gp5	GroE	
gpB	GroE			Not known for P22
gpN	Lon	gp24	Lon	Not known for P22
CI	RecA	C2	RecA	Might be true for P22 by homology and induction by ultraviolet light
CII	ClpYQ	C1	ClpYQ	Might be true for P22 by homology
CII	ClpAP	C1	ClpAP	Might be true for P22 by homology
gpO	ClpXP	gp18	ClpXP	Might be true for P22 by homology
gpN	NusA	gp24	NusA	Likely true by similarity of function
CII	HflD	C1	HflD	Might be true for P22 by homology
Gam	RecB			No Gam in P22
		Abc2	RecC	No Abc2 in λ

TABLE IX

Protein–protein interaction of phages P2 and P4

Protein	Function	Interactions	Notes	References
P2–P2 proteins				
gpC	Immunity repressor	Dimer	Y2H 3D structure	Eriksson *et al.*, 2000; Massad *et al.*, 2010
Cox	Transcriptional repressor, excisionase	Tetramer that can self-associate to octamers	*In vitro*; cross-linking and gel filtration	Eriksson and Haggard-Ljungquist, 2000
Int	Integrase	Dimer	*In vitro*; cross-linking Y2H	Frumerie *et al.*, 2005
gpF_I	Tail sheath	Polymer, six molecules per sheath striation	Electron microscopy	Lengyel *et al.*, 1974
gpF_{II}	Tail tube	Polymer, six molecules per tube striation	Electron microscopy	Lengyel *et al.*, 1974
gpM	Small terminase subunit	Polymer, 8- to 10-fold ring	Biochemistry	Dokland, unpublished data
gpM	Small terminase subunit	gpP	Biochemistry	Bowden and Modrich, 1985
gpN	Major capsid protein	T=7 icosahedron (415 copies)	Cryo-EM and 3D reconstruction	Dokland *et al.*, 1992
		gpO	Biochemistry	Chang *et al.*, 2008, 2009
gpO	Internal scaffolding protein	Dimer	Biochemistry, chromatography	Chang *et al.*, 2008, 2009
		gpN		
gpP	Large terminase subunit	gpP	Biochemistry	Bowden and Modrich, 1985
gpQ	Connector, portal protein	Dodecameric ring	EM, crystallography	Doan and Dokland, 2007; Rishovd *et al.*, 1994
gpT	Tape measure	gpF_{II} (gpF_I ?)	Inside tail tube	
gpV	Tailspike	Tetramer	Sedimentation velocity and molecular mass determination	Haggard-Ljungquist *et al.*, 1995; Kageyama *et al.*, 2009
gpV	Tailspike	gpW, base plate component. Belongs to the T4 gene 25-like superfamily	Copurification	Haggard-Ljungquist *et al.*, 1995
P2–other phage proteins				
Tin	Block superinfection of T-even phages	T4 SSB protein (gp32)	Genetic evidence	Mosig *et al.*, 1997
gpC	Immunity repressor	P4 anti-repressor ε	Genetic evidence. Y2H	Geisselsoder *et al.*, 1981; Liu *et al.*, 1998; Eriksson *et al.*, 2000
gpN	Major capsid protein	P4 Sid; size determinator, external scaffold	Cryo-EM and 3D reconstruction	Marvik *et al.*, 1995; Wang *et al.*, 2000; Dokland *et al.*, 2002
gpN	Major capsid protein	P4 Psu; polarity suppressor; decoration protein	Cryo-EM and 3D reconstruction	Dokland *et al.*, 1993
P2–host proteins				

Protein	Function	Interactions	Notes	References
gpB	Helicase loader. Required for lagging strand synthesis	*E. coli* helicase DnaB	Genetic evidence. Electron microscopy. *In vitro* binding.	Sunshine *et al.*, 1975; Funnell and Inman, 1983; Odegrip *et al.*, 2000
Ogr	Transcriptional activator of late operons	*E. coli* RNA polymerase α C-terminal domain	Genetic evidence	Sunshine and Sauer, 1975; Fujiki *et al.*, 1976; King *et al.*, 1992; Ayers *et al.*, 1994; Wood *et al.*, 1997
P4–host proteins				
Psu	Polarity suppressor; anti-terminator	Rho	Genetics; chemical cross-linking	Sauer *et al.*, 1981; Pani *et al.*, 2009
Delta	Transcriptional activator, contains two Ogr domains	*E. coli* RNA polymerase	Genetics; homology to Ogr	Julien *et al.*, 1997

TABLE X

Protein–protein interactions of phage ϕ29 including phage–host interactions[a]

ϕ29 1	Function 1	ϕ29 2	Function 2	References
gp2	DNA polymerase	gp3	DNA terminal protein TP	Kamtekar *et al.*, 2006; Blanco *et al.*, 1987; Dufour *et al.*, 2000; González-Huici *et al.*, 2000
gp3	DNA terminal protein TP	gp1	Membrane-associated early protein	Bravo *et al.*, 2000
gp3	DNA terminal protein TP	gp3	DNA terminal protein TP	Serna-Rico *et al.*, 2003
gp3	DNA terminal protein	gp16	Packaging ATPase	Guo *et al.*, 1987 Grimes and Anderson, 1997
gp4	Late gene activator	gp4	Late gene activator	Badia *et al.*, 2006 Mencía *et al.*, 1996b
gp4	Late gene activator	gp6	Histone-like, nonspecific DNA-binding protein	Calles *et al.*, 2002; Camacho and Salas, 2001
gp6	Histone-like, nonspecific dsDNA-binding protein	gp6	Histone-like, nonspecific dsDNA-binding protein	Abril *et al.*, 1999; Pastrana *et al.*, 1985
gp7	Scaffolding protein	gp7	Scaffolding protein	Morais *et al.*, 2003
gp7	Scaffolding protein	gp8	Major head protein	Lee and Guo, 1995
gp7	Scaffolding protein	gp10	Upper collar/connector protein	Guo *et al.*, 1991; Lee and Guo, 1995
gp10	Upper collar/connector protein	gp10	Upper collar/connector protein	Guasch *et al.*, 2002; Simpson *et al.*, 2001
gp12	Preneck appendage protein (anti-receptor)	gp12	Preneck appendage protein (anti-receptor)	Xiang *et al.*, 2009
gp13	Tail-associated, peptidoglycan-degrading enzyme	gp9	Tail knob protein	García *et al.*, 1983
gp13	Tail-associated, peptidoglycan-degrading enzyme	gp13	Tail-associated, peptidoglycan-degrading enzyme	Xiang *et al.*, 2008
gp16.7	Replication organizer; DNA-binding membrane protein p16.7	gp16.7	Replication organizer; DNA-binding membrane protein p16.7	Asensio *et al.*, 2005; Albert *et al.*, 2005; Crucitti *et al.*, 1998; Serna-Rico *et al.*, 2003; Meijer *et al.*, 2001b
gp16.7	Replication organizer; DNA-binding membrane protein p16.7	gp3	DNA terminal protein TP	Serna-Rico *et al.*, 2003
gp17	Early protein involved in early DNA replication	gp6	Histone-like, nonspecific dsDNA-binding protein	Crucitti *et al.* 2003
gp17	Early protein involved in early DNA replication	gp17	Early protein involved in early DNA replication	Crucitti *et al.*, 2003
gp56 = gp0.8	Host uracil-DNA glycosylase inhibitor	gp56= gp0.8	Host uracil-DNA glycosylase inhibitor	Serrano-Heras *et al.*, 2007)
ϕ29–*Bacillus subtilis* interactions				
gp4	Late gene activator (3)	RpoA	RNA polymerase subunit α	Mencía *et al.*, 1996a; Monsalve *et al.*, 1996b
gp16.7	Replication organizer, DNA-binding membrane protein gp16.7 (2)	MreB	Actin-like cytoskeleton protein	Muñoz-Espín *et al.*, 2009

ϕ29 1	Function 1	ϕ29 2	Function 2	References
gp56 = gp0.8	UDG inhibitor (1)	UDG	Uracil-DNA glycosylase	Serrano-Heras *et al.*, 2006

[a]Data from BOND, IntACT, and PDB (ϕ29, Taxon id 186846). All proteins are termed "gp" (gene product), although they are also termed "p" (protein), e.g., gp4 = p4. In the phage–host interaction list, the first protein is from ϕ29, the second from *B. subtilis*. (1) Host RNAP binds via α subunit to p4 (i) bound at the late promoter PA3, thus activating late transcription and (ii) bound to the promoter PA2c, thus blocking transcription through promoter clearance inhibition. (2) PPI plays a role in the organization of ϕ29 DNA replication as peripheral helix-like structures. (3) Inhibition of host UDG; avoids removal of uracil from ϕ29 DNA via UDG-base excision repair.

TABLE XI

Protein–protein interactions of ϕ29-related phages[a]

	Protein *1*		Protein *2*		
Phage		**Function**		**Function**	**References**
GA-1	gp6	Histone-like, nonspecific dsDNA binding protein	gp6	Histone-like, nonspecific dsDNA-binding protein	Freire *et al.*, 1996
Nf	gp6	dsDNA binding protein	gp6	dsDNA-binding protein	Freire *et al.*, 1996
GA-1	gp2	DNA polymerase	gp3	DNA terminal protein	Illana *et al.*, 1996; Longás *et al.*, 2006
Nf	gp2	DNA polymerase	gp3	DNA terminal protein	Longás *et al.*, 2006; González-Huici *et al.*, 2000
GA-1	gp5	Single-stranded DNA-binding protein SSB (1)	gp5	Single-stranded DNA-binding protein SSB	Gascón *et al.*, 2000
GA-1	gp12	Neck appendage protein (2)	gp12	Neck appendage protein	Schulz *et al.*, 2010
GA-1	$gp4_G$	Transcriptional regulator (3)	$gp4_G$	Transcriptional regulator	Horcajadas *et al.*, 1999

[a]Data from BOND, IntACT, and PDB (searched for ϕ29, Taxon id 186846). (1) ϕ29 and Nf SSB were shown to be stable monomers in solution, whereas GA-1 SSB forms homohexamers. (2) Homotrimer; autocatalytic cleavage similar to ϕ29 gp12. PDB: 3GUD. (3) Homodimer; negative regulator of early transcription; was shown not to interact with RNAP α subunit as the homologue gp4 of ϕ29.