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(57) **Abstract:** A modified bacteriophage capable of infecting a plurality of different target bacteria, which bacteriophage includes a toxin gene encoding a toxin protein which is toxic to the target bacteria; wherein the bacteriophage is lytic; and wherein the bacteriophage expresses host range determinant proteins which have a plurality of bacterial host specificities.



WO 2017/174810 A1

## **MODIFIED BACTERIOPHAGE**

The present invention relates to a modified bacteriophage, uses thereof, and compositions containing the modified bacteriophage.

### **Background to the Invention**

The World Health Organisation's 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is a global problem that is jeopardising the ability to treat common infections in the community and hospitals. Without urgent action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill (WHO, 2014). Antibiotic resistance complicates patients' recovery from even minor operations and is increasingly causing treatment failures. In fact, there are now strains of some genera of bacteria circulating globally which are resistant to all available antibiotics. Such strains commonly fall within the scope of the so-called ESKAPE pathogens – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species (Boucher *et al.*, 2009). The term ESKAPE pathogens was coined by Boucher *et al.*, to emphasize that these bacteria currently cause a majority of hospital infections in the US and Europe and can effectively "escape" the majority, if not all, available antibiotics with panantibiotic-resistant infections now occurring. The death rate for patients with serious infections caused by common bacteria treated in hospitals is approximately twice that of patients with infections caused by the same non-resistant bacteria, e.g. people with methicillin-resistant *Staphylococcus aureus* (MRSA) infections are estimated to be 64% more likely to die than people with a non-resistant form of the infection (WHO, 2014). Of the Gram positive bacteria, methicillin resistant *S. aureus* continues to be a major cause of morbidity and mortality in hospitals in the US and Europe. However, in more recent years, several highly resistant Gram negative pathogens, including *Acinetobacter* species, multidrug resistant (MDR) *P. aeruginosa*, and carbapenem-resistant *Klebsiella* species and *Escherichia coli*, have emerged as major pathogens causing serious, and sometimes untreatable, infections. Advances in medicine mean that increasingly complex procedures take place: and these advances are leading to a growing number of elderly patients and patients undergoing surgery, transplantation, and chemotherapy all of which will produce an even greater number of

immunocompromised individuals at risk of these infections (Walker *et al.*, 2009). This phenomenon has led to a greater dependence on, and requirement for, effective antibiotics.

*P. aeruginosa* is one bacterium which is frequently multi-drug resistant (MDR) having intrinsic resistance due to low permeability of its outer membrane limiting drugs getting into the cell, and a multitude of efflux pumps to expel any drugs that successfully manage to enter the cell. *P. aeruginosa* is also acquiring additional resistance mechanisms, including resistance to the “antibiotics of last resort” for Gram negatives, the carbapenems. *P. aeruginosa* causes approximately 10% of all hospital acquired infections and is the second leading cause of hospital-acquired pneumonia, which accounts for 50 % of all hospital-acquired infection prescribing. *P. aeruginosa* infections in hospitals commonly require intravenous (IV) treatment with current standard of care for *P. aeruginosa* infections dictating that patients are treated with at least two antibiotics. Unfortunately, resistance frequently develops in patients during therapy. With so few new classes of antibiotic developed and approved for market within the last 30-40 years, there is a critical need for novel, safe and effective antibacterial agents.

As an alternative to conventional antibiotics, one family of proteins which demonstrate broad spectrum antibacterial activity inside bacteria comprises the  $\alpha/\beta$ -type small acid-soluble spore proteins (known henceforth as SASP). Inside bacteria, SASP bind to the bacterial DNA: visualisation of this process, using cryoelectron microscopy, has shown that SspC, the most studied SASP, coats the DNA and forms protruding domains and modifies the DNA structure (Francesconi *et al.*, 1988; Frenkiel-Krispin *et al.*, 2004) from B-like (pitch 3.4 nm) towards A-like (3.18 nm; A-like DNA has a pitch of 2.8 nm). The protruding SspC motifs interact with adjacent DNA-SspC filaments packing the filaments into a tight assembly of nucleo-protein helices. In 2008, Lee *et al.* reported the crystal structure at 2.1 Å resolution of an  $\alpha/\beta$ -type SASP bound to a 10-bp DNA duplex. In the complex, the  $\alpha/\beta$ -type SASP adopt a helix-turn-helix motif, interact with DNA through minor groove contacts, bind to approximately 6 bp of DNA as a dimer and the DNA is in an A-B type conformation. In this way DNA replication is halted and, where bound, SASP prevent DNA transcription. SASP bind to DNA in a non-sequence specific manner (Nicholson *et al.*, 1990) so that mutations in the bacterial DNA do not affect the binding of SASP. Sequences of  $\alpha/\beta$ -type SASP may be found in appendix 1 of WO02/40678, including SASP-C from *Bacillus megaterium* which is the preferred  $\alpha/\beta$ -type SASP.



WO02/40678 describes the use as an antimicrobial agent of bacteriophage modified to incorporate a SASP gene. In order to provide effective production of the modified bacteriophage in a bacterial host, WO02/40678 aims to avoid factors which may disrupt proliferation of the production host, such as expression of the SASP gene during production. To this end, the SASP gene was put under the control of an inducible promoter. In a preferred arrangement, at least one of the gene encoding products involved in the lytic process was inactivated.

WO2009019293 describes that effective production of bacteriophage may be achieved where the bacteriophage has been modified to delete a lysis gene and to carry a gene encoding a SASP under the control of a promoter which is controlled independently of the bacteriophage, and which is constitutive with no exogenous or *in trans* regulation necessary or provided. Such a modified bacteriophage is maintained as a prophage in a manufacturing host strain, and may be amplified by suitable induction methods to synthesise new phage within the manufacturing host strain. In this arrangement, the manufacturing host strain must be lysed by the addition of exogenous substances, e.g. lytic enzymes or chemicals, in order to release viable phage. An example of a suitable promoter is the *fbaA* promoter from *S. aureus* which is used to drive expression of the SASP-C gene from *Bacillus megaterium* and which, when present in multiple copies, for example following infection of target cells, drives toxic levels of SASP expression.

Bacteriophage vectors modified to contain a SASP gene have generally been named SASPject vectors. Once the SASP gene has been delivered to a target bacterium, SASP is produced inside those bacteria where it binds to bacterial DNA and changes the conformation of the DNA from B-like towards A-like. Production of sufficient SASP inside target bacterial cells causes a drop in viability of affected cells.

Bacteriophage have been used as medicines for the treatment of bacterial infections since the 1920s or 30s. Generally, bacteriophage are specific to their bacterial host. Some bacteriophage are temperate and others non-temperate. Temperate phage are able to infect the host cell and integrate into the host cell genome becoming a prophage which is generally harmless to the host cell in this state. Non-temperate or "lytic" phage are only able to replicate in a lytic lifestyle by making new bacteriophage progeny and ending in lysis of the host cell and release of mature phage particles. For useful medicines, the challenge is to provide bacteriophage

compositions which can be used to treat infection from a variety of different bacteria in an effective way. It is commonly thought that this is achieved using the most potent bacteriophage compositions available: those with a broadened host range, possibly as a mixture or "cocktail" of bacteriophage (Carlton, 1999; Kutateladze and Adamia, 2010). Cocktails of wild type phage have been used to ensure sufficient spectrum of activity against clinical strains of bacteria (Burrowes and Harper, 2012). Such cocktails can consist of up to 20 different and unrelated phage (Abedon 2008). As an alternative to the cocktail approach, *E. coli* bacteriophage K1-5 has been isolated. This is a naturally-occurring obligately lytic phage which carries more than one host range determinant (HRD) allowing it to infect and replicate on both K1 and K5 strains of *E. coli* (Scholl *et al*, 2001). These phage are considered to be extra potent.

There remains a need to provide improved bacteriophage for use in treating bacterial infections in medicine as well as inhibiting or preventing bacterial cell growth in medical and non-medical situations.

### **Summary of the Invention**

In a first aspect, the present invention provides a modified bacteriophage capable of infecting a plurality of different target bacteria, which bacteriophage includes a toxin gene encoding a toxin protein which is toxic to the target bacteria; wherein the bacteriophage is lytic; and wherein the bacteriophage expresses host range determinant (HRD) proteins which have a plurality of bacterial host specificities. The bacterial host specificity of the HRD is advantageously within the same bacterial species.

It has surprisingly been found that a modified bacteriophage may be produced which is capable of infecting a variety of different target bacteria, and which is effective for use in medicine when engineered to carry a gene for a toxic protein. The modified bacteriophage is lethal to bacterial cells, and, despite being lytic, and thus requiring completion of the phage lifecycle to be released from cells, can be manufactured in a host cell through several rounds of infection and replication.

In one aspect, the HRD proteins which have a plurality of bacterial host specificities are hybrid HRD proteins each comprising an amino acid sequence from a plurality of different bacteriophages. Because the modified bacteriophage expresses a hybrid HRD protein this

confers an enhanced host range on the phage. Bacteriophages according to the invention may be produced by genetic engineering, for example by selecting HRD from closely related phage. Having created such an extra-potent lytic phage, it can then be engineered to create a vector incorporating the toxin gene, which vector is capable of being manufactured in a host cell and effective as an antibacterial agent *in vivo*.

In another aspect, the HRD proteins expressed by the bacteriophage comprise a plurality of different HRDs, wherein each HRD has a different bacterial host specificity. In this aspect the HRDs can be homologous, heterologous, (hybrid) or a mixture of homologous and hybrid HRDs. The plurality of different HRDs confers upon the bacteriophage an enhanced host range. Such bacteriophage may be produced by genetic engineering, for example by selecting HRDs from phage which infect the same bacterial species. Having created such an extra-potent lytic phage, it can then be engineered to create a vector incorporating the toxin gene, which vector is capable of being manufactured in a host cell and effective as an antibacterial agent *in vivo*.

In a preferred arrangement, the toxin gene comprises an  $\alpha/\beta$  small acid-soluble spore protein (SASP) gene encoding a SASP. In one aspect, the term 'SASP' as used in the specification refers to a protein with  $\alpha/\beta$ -type SASP activity, that is, the ability to bind to DNA and modify its structure from its B-like form towards A-like form, and not only covers the proteins listed in appendix 1 of WO02/40678, but also any homologues thereof, as well as any other protein also having  $\alpha/\beta$ -type SASP activity. In an alternative aspect, the term 'SASP' as used in the specification refers to any protein listed in appendix 1 of WO02/40678, or any homologue having at least 70%, 75%, 80%, 85%, 90%, 92%, 94%, 95%, 96%, 98% or 99% sequence identity with any one of the proteins listed in appendix 1 of WO02/40678. In another alternative aspect, the term 'SASP' as used in the specification refers to any protein listed in appendix 1 of WO02/40678.

The SASP gene may be chosen from any one of the genes encoding the SASP disclosed in Appendix 1 of WO02/40678. In a preferred arrangement the SASP is SASP-C. The SASP-C may be from *Bacillus megaterium*.

It is preferred that the SASP gene is under the control of a constitutive promoter which is

advantageously sufficiently strong to drive production of toxic levels of SASP when the modified bacteria phage is present in multiple copies in the target bacterium. Useful constitutive promoters include *pdhA* for pyruvate dehydrogenase E1 component alpha sub units, *rpsB* for the 30S ribosomal protein S2, *pgi* for glucose-6-phosphate isomerase and the fructose bisphosphate aldolase gene promoter *fda*. Preferred regulated promoters, active during infection, are *lasB* for elastase. These promoters are typically from *P. aeruginosa*. Promoters having a sequence showing at least 90% sequence identity to these promoter sequences may also be used.

The present invention is generally applicable to bacteriophage infecting a variety of different target bacteria. In one arrangement at least one of the target bacteria is *Pseudomonas*. Advantageously, the plurality of different target of bacteria is a plurality of different *Pseudomonas* bacteria. An important target is *Pseudomonas aeruginosa*.

It was previously considered that an obligate lytic phage would be unsuitable for use as a SASPject vector, since a requirement of a SASPject vector is that it is specifically not lytic for optimal therapeutic use. A non-lytic vector allows an increased time window for SASP expression, thereby increasing the efficacy of the treatment. In addition, prevention of rapid lysis upon treatment *in vivo*, was considered advantageous because it would limit the potential release of antibiotic resistance genes and toxic cell wall components which can lead to a dangerous inflammatory response.

The approach described in the present invention is advantageous as compared to the phage cocktail approach described previously. Mixtures of modified bacteriophage, such as SASPject vectors, are identical in structure and genome sequence, other than carrying a different HRD or hybrid HRD. One advantage is that control of the manufacturing process for the mix of SASPjects will be straightforward, which is an important aspect of a pharmaceutical preparation: the process will be materially the same for phage modified to carry a heterologous HRD as they share identical or near-identical biophysical properties. Another advantage is that the *in vivo* characteristics of the SASPject vectors are likely to be similar, e.g. pharmacokinetics/pharmacodynamics, as each vector is structurally the same or similar.

In one aspect of the present invention it has been found that phage can be created which are extra-potent obligately-lytic bacteriophage carrying HRDs which have a plurality of bacterial

host specificities. Surprisingly, such phage can be used to make enhanced SASPject vectors which retain a lytic phenotype, and remain effective *in vivo*, and such phage can be manufactured to an adequate titre in a bacterial host. WO02/40678 and WO2009019293 have taught the creation of SASPject vectors from bacteriophage which have been modified to remove one or more lysis genes, and which reside as prophage in a host cell. Such SASPject vectors are manufactured by prophage induction and the cells are lysed by the exogenous addition of lysis agents, e.g. cell wall degrading enzymes or chemicals such as chloroform. As such, the cells do not need to remain viable until the end of the phage lifecycle, as the final lysis step is not reliant upon the synthesis and accumulation in the host cell of the modified phage's own lysis proteins. Given the toxic nature of the SASP protein, and the extra-potent nature of the modified phage described in the present invention, it was not anticipated that such phage would be suitable for modification to create SASPjects which could be manufactured via an obligate lytic lifecycle, requiring the phage to complete its lytic lifecycle in order to create viable SASPject vectors. However, it has been found that such SASPject vectors are capable of replication in host cells to an adequate titre. This allows the manufacture of SASPject vectors in a quantity suitable for effective *in vivo* use. Advantageously, SASPject vectors based upon such modified obligate lytic phage are capable of replication at the site of infection. This means that the dose required for a lytic SASPject can be lower than that required for a non-lytic SASPject when used *in vivo*. Lytic SASPject vectors according to the invention may be considered more potent than their non-lytic counterparts.

Phage suitable for such modification may be isolated by screening for phage capable of infecting a chosen bacterial species. For instance, phage may be isolated which infect *Pseudomonas aeruginosa*, by screening environmental sources for phage which are able to form plaques on representative *P. aeruginosa* strains (Gill and Hyman, 2010). Isolated phage may have their whole genomes sequenced and annotated. HRDs may be tail fibre proteins, which are commonly found to be proteins responsible for the initial recognition/binding to the host bacterium, for instance in phage T4, T5 and T7 (Rakhuba *et al.*, 2010). Alternatively other HRD may be baseplate proteins. Phage genomes may be searched for potential HRD sequences by assessing the homology of all proteins in the phage genome to known sequences, using BLAST searches.

According to the present invention it is preferred that each HRD has a broad host range. This may be defined as the ability to infect >50% of a diverse collection or clinical isolates, totalling

at least 35, preferably at least 40, more preferably at least 44, and most preferably >50 in number. Such isolates should be from a range of geographical locations, including Europe, the Americas, and Asia, should carry a diverse range of antibiotic resistance phenotypes, including multi-drug resistant (MDR) strains, and should be from a diverse range of infection sites, such as strains cultured from blood, lung and skin infections. Such isolates can be obtained from public strain collections such as the American Type Culture Collection (ATCC) and the National Collection of Type Cultures (NCTC). Generally, each tail fibre protein comprises a C-terminal receptor binding region for binding to the target bacteria and an N-terminal region linking the C-terminal receptor binding region to the body of the bacteriophage. Each of the C-terminal and N-terminal regions may be from different bacteriophage. In one arrangement, the N-terminal region comprises amino acids 1 to 628 of the tail fibre protein and the C-terminal region comprises the amino acids 629 to 964 of the tail fibre protein.

The C-terminal region may have no more than 96% amino acid sequence identity with the C-terminal region of bacteriophage Phi33 and may be from any one of the bacteriophage Phi33, LBL3, SPM-1, F8, PB1, KPP12, LMA2, SN, 14-1, JG024, NH-4, PTP47, C36, PTP92 and PTP93. Lower amino acid sequence identities in the C-terminal region are preferred. Advantageously the sequence identity is less than 90%, more advantageously less than 80%, preferably less than 70%, more preferably less than 60%, still more preferably less than 50%, particularly preferably less than 40%, more particularly preferably less than 30%. The N-terminal region may have at least 90% and advantageously at least 95% amino acid sequence identity with the N-terminal region of bacteriophage Phi33 and may be from any one of bacteriophage Phi33, LBL3, SPM-1, F8, PB1, KPP12, LMA2, SN, 14-1, JG024, NH-4, PTP47, C36, PTP92 and PTP93. The N-terminal region and the C-terminal region may be from the same bacteriophage to provide a homologous tail fibre protein. Alternatively, the N-terminal region and the C-terminal region may be from different bacteriophage tail fibre proteins to provide a heterologous tail fibre protein. In one arrangement where the phage tail fibre protein is homologous, each tail fibre protein is from a bacteriophage selected from Phi33, LBL3, SPM-1, F8, PB1, KPP12, LMA2, SN, 14-1, JG024, NH-4, PTP47, C36, PTP92 and PTP93.

It is advantageous to identify phage tail fibre proteins which share sequence identity of greater than 90% in the N-terminal region. For example several phage – Phi33, PTP47, PTP92 and C36 – with a broad host range for *P. aeruginosa* strains (all of these phage infect >60%, when analysed against 260 strains), have been isolated/identified and their genomes sequenced.

Analysis of the genome sequences of Phi33, PTP47, PTP92 and C36 reveals that they contain genes encoding putative tail fibre proteins with a high level of sequence identity in the N-terminal region (>95% amino acid sequence identity), following a 2 sequence BLAST alignment, compared to the Phi33 tail fibre amino acids 1-628 (amino acid identity in parentheses): C36 (96%), PTP47 (98%), PTP92 (97%). BLAST searches have shown that these 4 phages are related to 10 other deposited phage genome sequences which, together, form the family of PB1-like phage: PB1, SPM1, F8, LBL3, KPP12, LMA2, SN, JG024, NH-4, 14-1 (Ceyssens *et al.*, 2009). The homology of these putative tail fibre proteins was assessed. Following a 2 sequence BLAST alignment, compared to the Phi33 tail fibre protein (amino acid identity in parentheses): LBL3 (96%), SPM-1 (95%), F8 (95%), PB1 (95%), KPP12 (94%), LMA2 (94%), SN (87%), 14-1 (86%), JG024 (83%), NH-4 (83%), C36 (96%), PTP47 (86%), PTP92 (83%). An alignment of all 14 of the aforementioned phage tail fibre proteins is shown in Figure 13.

Analysis of the annotated tail fibre protein sequences from these 14 phages reveals that the N-terminal region of the proteins - equivalent to Phi33 tail fibre amino acids 1-628 – show an even higher level of sequence identity at the amino acid level than the sequence identity of these proteins over their entire length, in the range of 96-100% for all 14 proteins. Following a 2 sequence BLAST alignment, compared to the N-terminal amino acids 1-628 of the Phi33 tail fibre protein (amino acid identity in parentheses): LBL3 (96%), SPM-1 (96%), F8 (96%), PB1 (96%), KPP12 (98%), LMA2 (99%), SN (99%), 14-1 (97%), JG024 (97%), NH-4 (97%), PTP47 (98%), C36 (96%), PTP92 (97%). However, the C-terminal region of the protein – equivalent to Phi33 tail fibre amino acids 629-964 – is not as conserved as the N-terminal region in some of the proteins, the range of sequence identity being typically 57-96%. Following a 2 sequence BLAST alignment, compared to the C-terminal 629-964 amino acids of the Phi33 tail fibre protein (amino acid identity in parentheses): LBL3 (94%), SPM-1 (93%), F8 (93%), PB1 (94%), KPP12 (87%), LMA2 (85%), SN (65%), 14-1 (65%), JG024 (57%), NH-4 (57%), PTP47 (64%), C36 (96%), PTP92 (57%). Analysis of phage tail fibres from other, well characterised, phage has shown that they possess an N-terminal tail base plate binding region and a C-terminal receptor binding region (Veesler and Cambillau, 2011). In experimental analysis of their bacterial strain host range, using plaque assay or growth inhibition tests, the phage Phi33, PTP47, PTP92 and C36 have overlapping but non-identical host range (Table 1). Taken together with the established evidence for the role of the C-terminal region of phage tail fibres being involved in bacterial host receptor binding, and the

sequence variation in the C-terminal region of these 4 phage, and their similar but non-identical host range, it is postulated that the C-terminal variation is associated with host range in the phage assessed.

It is further provided, according to this invention, that the genes for a homologous tail fibre protein can be taken from one phage and added to another, replacing the resident tail fibre, based upon their high level of sequence identity in the N-terminal region. The N-terminal region is thought to be involved in the binding of the tail fibre to the phage tail (Veesler and Cambillau, 2011), allowing the formation of viable phage with the host range associated with donor phage's tail fibre. Hybrid tail fibre genes may be made, carrying the conserved N-terminal tail attachment region of the tail fibre from a recipient phage, together with the variable C-terminal receptor-binding region from a homologous donor phage tail fibre protein, using tail fibres genes such as those described herein. Such tail fibre hybrid genes could be used to replace the tail fibres of the phage. This provides an N-terminal region of the hybrid tail fibre (from the recipient phage) and allows the formation of viable phage with the host range associated with donor phage's tail fibre C-terminal receptor-binding region. Transplantation of engineered tail fibre hybrid genes into a recipient phage has been demonstrated in the present invention. Using standard molecular genetic techniques, Phi33 has been modified to carry heterologous tail fibre hybrids from the following phage: PTP92, PTP47, LBL3, SPM-1, F8, PB1, KPP12, LMA2, SN, 14-1, NH-4. All modified phage have been shown to be viable and able to plaque on *P. aeruginosa*. (The nomenclature of tail fibre hybrids is as follows: As an example, a hybrid gene such that the N-terminal tail attachment region of Phi33 is hybridised with the C-terminal receptor binding region of PTP47 is Phi33(N)PTP47(C).)

In one such modified phage, Phi33 was engineered such that its tail fibre gene carries the C-terminal receptor binding region of PTP92, creating PTP93 (Phi33(N)PTP92(C)). This was assessed in more detail, by testing the host range against 35 diverse *P. aeruginosa* clinical isolates. Comparing host range of the progenitor phage (Phi33), the tail fibre donor (PTP92) and the hybrid phage (PTP93), the host range of the PTP93 hybrid phage is equivalent to that of the tail fibre donor phage (PTP92) rather than Phi33, but it was surprisingly found that in some instances PTP93 possesses the host range of Phi33 on strains that PTP92 cannot infect, thus PTP93 inherits the host range of both phages (Table 2). PTP93 possesses a broader host range (92%) than either Phi33 (74%) or PTP92 (66%) (Table 2). PTP93 is an example of an obligately lytic bacteriophage which can be considered as "extra-potent" as it possesses a



characteristic above and beyond those exhibited in their unmodified state. Such extra potent phage are suitable for further modification to make SASPject vectors.

Phi33, through assessment of sequence homology by one skilled in the art, can be placed in the group of PB1-like phage (Ceyssens *et al.*, 2009 ), and may be considered a broad host range phage by the definition given earlier. Such a phage could be isolated by the methods described earlier. Phi33 is suitable for genetic modification to introduce a gene for SASP under the control of a promoter. Such a modified phage would be suitable for use in treating infections caused by susceptible *P. aeruginosa* bacteria, either on its own or in combination with other modified bacteriophage. In one arrangement, the invention may not extend to an isolated bacteriophage PTPX31 or PTPX32.

A preferred approach according to the present invention is to use one or more obligately lytic phage, each engineered to carry a SASP gene expressed from a constitutive promoter, each phage being genetically identical other than their tail fibre or tail fibre hybrid gene. Preferred obligately lytic phage for modification and for provision of tail fibre genes to create tail fibre genes or tail fibre hybrid genes are phages carrying tail fibre genes which encode predicted proteins that possess  $\geq 90\%$  amino acid sequence identity in their N-terminal regions compared to N-terminal regions of the tail fibre of other isolated or identified phage.

Another preferred approach according to the present invention is to use one or more obligately lytic phage engineered to express 2 or more HRDs (extra potent obligately lytic phage), each engineered to carry a SASP gene expressed from a constitutive promoter, each phage being genetically identical other than carrying different tail fibre genes, or tail fibre hybrid genes, Preferred obligately lytic phages for modification and for provision of tail fibre genes to create phages carrying multiple tail fibre genes or tail fibre hybrid genes are phages carrying tail fibre genes which encode predicted proteins that possess  $\geq 90\%$  amino acid sequence identity in their N-terminal regions compared to N-terminal regions of the tail fibre of other isolated or identified phage.

Preferred obligate lytic phage meeting these criteria are Phi33, PTP92, PTP47, LBL3, SPM-1, F8, PB1, KPP12, LMA2, SN, 14-1, NH-4, PTP93, JG024, PTP47 and C36. Such phage can be identified by a simple PCR assay, by subjecting plaques of isolated phage to PCR with primers specific to highly conserved regions in the N-terminal region of the tail genes. In such

a way, suitable phage can be identified without whole genome sequencing. Phage PB1 can be obtained from a public strain collection. Phages need not be isolated or provided in order to generate tail fibre sequences as such sequences may be identified in DNA sequence databases, or other sources of DNA sequences, which may provide the information necessary in order to synthesise and clone, by standard methods, such sequences, or to create hybrid tail fibre sequences.

Particularly preferred phage for modification are PTP93, Phi33, PTP92, PTP47 and C36. Particularly preferred extra-potent obligate lytic phage are: Phi33, modified to carry the tail fibre hybrid Phi33(N)PTP92(C) in place of the resident tail fibre; Phi33 modified to carry the tail fibre hybrid Phi33(N)PTP47(C) in place of the resident tail fibre. In one aspect of the present invention, preferred extra-potent non-lytic SASPject derivatives of Phi33 include: Phi33, modified to carry the tail fibre hybrid Phi33(N)PTP92(C) in place of the resident tail fibre and carrying SASP-C from *Bacillus megaterium*, codon-optimised for expression in *P. aeruginosa*, under the control of the *P. aeruginosa* fructose biphosphate aldolase (*fda*) gene promoter; Phi33 modified to carry the tail fibre hybrid Phi33(N)PTP47(C) in place of the resident tail fibre and carrying SASP-C from *Bacillus megaterium*, codon-optimised for expression in *P. aeruginosa*, under the control of the *P. aeruginosa* fructose biphosphate aldolase (*fda*) gene; Phi33 modified to carry SASP-C from *Bacillus megaterium*, codon-optimised for expression in *P. aeruginosa*, under the control of the *P. aeruginosa* fructose biphosphate aldolase (*fda*) gene promoter. In a particularly preferred aspect the present invention provides a mixture of SASPject comprising or consisting of the 3 aforementioned SASPjects formulated together.

A mixture of three modified bacteriophage, designated PT3.9, was constructed and its efficacy in killing *P. aeruginosa* tested. The mixture consists of: Phi33 carrying the Phi33(N)PTP92(C) tail fibre, modified to carry the *fda*-SASP-C (*P. aeruginosa* codon optimised sequence) (PTP388); Phi33 carrying the Phi33(N)PTP47(C) tail fibre, modified to carry the *fda*-SASP-C (*P. aeruginosa* codon optimised sequence) (PTP389); Phi33 carrying the Phi33(N)Phi33(C) tail fibre, modified to carry the *fda*-SASP-C (*P. aeruginosa* codon optimised sequence) (PTP387).

The efficacy of PT3.9 was tested in a 6 hour time-kill curve experiment against a multi-drug resistant (MDR) clinical isolate (trachea isolation site, antibiotic resistance to ceftazidime,

piperacillin-tazobactam and imipenem) of *P. aeruginosa*, strain 3503 and reference strain ATCC 27853. Briefly, cultures were set up in Luria Bertani (LB) broth supplemented with 5 mM calcium chloride, 5 mM magnesium sulphate and 0.1% glucose (LC broth), and grown at 37 °C.  $5 \times 10^5$  colony forming units per millilitre (cfu/ml) of *P. aeruginosa* was incubated with  $3 \times 10^9$  plaque forming units per ml (pfu/ml) of PT3.9, or extra LC broth as a control (untreated culture). Samples were removed at 0, 1, 2, 4, and 6 hours for serial dilution and plating on LC agar plates and then overnight incubation at 32 °C. For both strains, the viable cell count was reduced from  $5 \times 10^5$  cfu/ml to below the limit of detection ( $10^2$  cfu/ml) within 1 hour of treatment, and no viable cells were detected after 6 hours (Figure 14). In contrast, the untreated control culture grew to between  $5 \times 10^8$  and  $1 \times 10^9$  cfu/ml for both strains. This demonstrates the ability of PT3.9 to kill clinical strains of *P. aeruginosa*.

PTP387, a component SASPject of PT3.9, was tested *in vivo* in comparison to PTP284, a SASPject which is equivalent to PTP387 other than lacking one of the lysis genes (endolysin). An immunocompetent murine model of *P. aeruginosa* bacteraemia was used to assess the potency of the two SASPject vectors. Briefly, animals were infected by intravenous injection with an inoculum of  $7.5 \log_{10}$  cfu of *P. aeruginosa* strain ATCC 27853. At 2 hours post infection, the mice were treated either with PTP284, PTP387, vehicle (buffer), or ceftazidime (50 mg/kg) by intravenous injection. PTP284 and PTP387 were administered at the following doses:  $3 \times 10^{10}$ ,  $1 \times 10^{10}$ ,  $3 \times 10^9$ , and  $1 \times 10^9$  pfu. At 22 hours post treatment, mice were euthanised by carbon dioxide asphyxiation, and the livers were removed and weighed. Liver tissue was homogenised in tryptone soya broth (TSB) and the number of viable cells in the liver tissue was enumerated by serial dilution and plating on Ceftrimide agar plates. A control (not treated) group of mice was euthanised at 2 hours post infection and the viable cells in the liver tissue enumerated, to assess the viable cell count in the lung tissue at the time of treatment. A dose response was seen for both PTP284 and PTP387, when assessing the geometric mean of the bioburden levels of *P. aeruginosa* in liver tissue (Figure 15). The potency of PTP387 was greater than that of PTP284 when assessing the log reduction in cfu/g liver tissue compared to the level assessed at the time of treatment: 22 hours post treatment, PTP387 caused a 3-log reduction in liver tissue bioburden at a  $1 \times 10^9$  pfu dose, whilst an equivalent effect of PTP284 was seen at  $1 \times 10^{10}$  pfu. PTP387 caused a greater maximum effect on liver tissue bioburden reduction compared to PTP284: at a dose of  $3 \times 10^{10}$  pfu, PTP387 caused a 5.4-log reduction in liver tissue bioburden at 22 hours post treatment, whilst PTP284 caused a 2.4-log reduction.

This demonstrates the increased potency of the lytic SASPject *in vivo* when compared to equivalent non-lytic SASPject.

The mixture of lytic modified SASPject phage comprising PT3.9 was tested *in vivo* in comparison to the mixture of non-lytic modified SASPject phage comprising PT3.8. The modified phage in PT3.8 are identical to those in PT3.9 other than lacking the lysis gene (endolysin) present in PT3.9. A neutropenic murine model of *P. aeruginosa* pneumonia was used to assess the potency of the two mixtures of SASPject phage. Briefly, animals were rendered neutropenic by immunosuppression with cyclophosphamide 200mg/kg 4 days before infection and 150mg/kg 1 day before infection by intraperitoneal injection. Animals were anaesthetised and infected intranasally with  $4.5 \times 10^3$  cfu of *P. aeruginosa* strain ATCC 27853. Groups of 6 mice were given each treatment. PT3.8 and PT3.9 were administered via the trachea 15 minutes post infection in an aerosolised form at the following doses:  $1 \times 10^9$ ,  $3 \times 10^9$ ,  $1 \times 10^{10}$  and  $1.5 \times 10^{10}$  pfu. Tobramycin (200µg) was administered in an aerosolised form to a control group of mice, and another group was treated with placebo buffer. Animals were euthanised 24 hours post treatment and lung tissue was removed and homogenised in phosphate buffered saline (PBS). The tissue homogenate was serially diluted and plated on agar plates to enumerate the bacteria in the lung tissue. A control (not treated) group of mice was euthanised at 15 minutes post infection and the viable cells in the lung tissue enumerated, to assess the viable cell count in the tissue at the time of treatment. A dose response was seen for both PT3.8 and PT3.9, when assessing the geometric mean of the bioburden levels of *P. aeruginosa* in lung tissue (Figure 16). The potency of PT3.9 was greater than that of PT3.8. When assessing the log reduction in cfu/g lung tissue compared to the level assessed at the time of treatment: 24 hours post treatment, PT3.9 caused a > 2-log reduction in lung tissue bioburden at a  $1 \times 10^9$  pfu dose, whilst an equivalent effect of PT3.8 was seen at doses between  $1 \times 10^{10}$  and  $1.5 \times 10^{10}$  pfu. Thus PT3.9 was more than 10 times more potent than PT3.8.

The ability of PTP387 to propagate in a host cell and yield bacterial lysates suitable for further purification was assessed in comparison to the unmodified phage (Phi33). Briefly, overnight culture of *P. aeruginosa* strain 1868 were used to inoculate 2 X 1 L bioreactor vessels, each containing 0.5 L of rich broth medium, to an OD600 of 0.05. The cultures were grown to OD600 = 0.3-0.4 and then infected with phage Phi33 or PTP387 to a final concentration of  $1 \times 10^7$  pfu/ml, and grown further at 37°C. After 5 hours of growth, the cultures were treated

with benzonase and sterile filtered. The concentration of each phage was determined by plaque assay. The lysate titres yielded for PTP387 were comparable to those obtained for Phi33:  $2 \times 10^{11}$  pfu/ml (PTP387) and  $5 \times 10^{11}$  pfu/ml (Phi33). The titre of PTP387 increased by 4-logs over 5 hours, demonstrating the ability of this phage to complete several cycles of infection, multiplication and lysis, despite the presence of the toxic SASP gene.

Fermentations were performed at 15.5-16L scale for all 3 of the modified phage which comprise PT3.9. Briefly, overnight cultures of *Pseudomonas aeruginosa* were used to inoculate a 16L bioreactor containing 15.5 to 16 L of rich broth medium, to an OD600 of 0.05. Each culture was grown to OD600 = 0.4-0.7 before being infected with either PTP387, PTP388 or PTP389 (SASPject phage which comprise PT3.9) to a final concentration of  $1 \times 10^7$  pfu/ml. Cultures were grown for another 5 hours before Benonzase treatment. Samples were removed, sterile filtered, and analysed by plaque assay. Two fermentations were performed for each SASPject phage. All 3 of the modified SASPject phage comprising PT3.9 were able to propagate to  $5 \times 10^{11}$  to  $1 \times 10^{12}$  pfu/ml. Thus all 3 of the modified SASPject phage are able to complete several cycles of infection, multiplication and lysis, despite the presence of the toxic SASP gene.

The quantities of PTP387 obtained by such manufacturing processes at 1L scale are suitable for effective *in vivo* use, as demonstrated by the use of such preparations in murine infection models (Figure 15 and 16). The levels of PT387, PTP388 and PTP389 obtained by such manufacturing processes at 15.5-16L scale are suitable for effective *in vivo* use, as demonstrated by the use of such preparations, when combined as a mixture (PT3.9), in murine infection models (Figures 15 and 16).

In another embodiment, an obligately lytic phage may be modified to create a SASPject by inserting a SASP gene under the control of a constitutive promoter, and the tail fibre gene could be deleted altogether. Such phage must be propagated in a strain in which a tail fibre gene or tail fibre hybrid gene is expressed *in trans*. In such an instance, the SASPject progeny from such a strain would carry a single tail fibre, derived from the propagation strain, yet would lack in their genomes any tail fibre or tail fibre hybrid gene(s). Several such propagation strains could be constructed and the same tail fibre deleted SASPject expressed in each. In this way several different SASPject derivatives could be made, each carrying a different tail fibre or tail fibre hybrid protein. These SASPjects could be used to formulate a mixture.

In another embodiment, an obligately-lytic phage engineered to carry a SASP gene expressed from a constitutive promoter may be propagated in a host strain carrying the gene(s) for hybrid tail fibre protein(s) *in trans* under the control of a suitable promoter. Suitable promoters for the tail fibre hybrid gene(s) may be a phage promoter, particularly the promoter which drives expression of the tail fibre gene in the engineered, obligately-lytic phage. Other suitable promoters are inducible promoters, such as *lac*, and *trp*, together with their cognate regulatory proteins. The SASPject progeny obtained from such strains are extra-potent, carrying the tail fibre hybrid(s) expressed from the strain *in trans* as well as their own. Alternatively, the tail fibre gene from the obligately lytic phage may be deleted altogether, providing that a strain is used for propagation in which tail fibre gene(s) or tail fibre hybrid gene(s) are expressed *in trans*, allowing for the formation of derivative SASPjects. In such an instance, the SASPject progeny from such a strain would carry multiple tail fibres, yet would lack in their genomes any tail fibre or tail fibre hybrid gene(s).

In a further aspect, the present invention provides a composition for inhibiting or preventing bacterial cell growth, which comprises a modified bacteriophage or mixtures thereof as defined herein and a carrier therefor. The modified bacteriophage may be provided in admixture with at least one other modified bacteriophage which is capable of infecting target bacteria, which includes a toxin gene such as a SASP gene encoding a SASP which is toxic to the target bacteria. Then at least one other modified bacteriophage may or may not express a plurality of different HRDs. Such compositions may have a wide range of uses and are therefore to be formulated according to the intended use. The composition may be formulated as a medicament, especially for human treatment and may treat various conditions, including bacterial infections. Among those infections treatable according to the present invention are localised tissue and organ infections, or multi-organ infections, including blood-stream infections, topical infections, oral infections including dental carries, respiratory infections and eye infections. The carrier may be a pharmaceutically-acceptable excipient or diluent. The exact nature and quantities of the components of such compositions may be determined empirically and will depend in part upon the routes of administration of the composition.

Routes of administration to recipients include intravenous, intra-arterial, oral, buccal, sublingual, intranasal, by inhalation, topical (including ophthalmic), intra-muscular, subcutaneous, intra-vaginal, intrathecal and intra-articular. For convenience of use, dosages

according to the invention will depend on the site and type of infection to be treated or prevented. Respiratory infections may be treated by inhalation administration and eye infections may be treated using eye drops. Oral hygiene products containing the modified bacteriophage are also provided; a mouthwash or toothpaste may be used which contains modified bacteriophage according to the invention formulated to eliminate bacteria associated with dental plaque formation.

A modified bacteriophage, or mixture thereof, according to the invention may be used as a bacterial decontaminant, for example in the treatment of surface bacterial contamination as well as land remediation or water treatment. The bacteriophage may be used in the treatment of medical personnel and/or patients as a decontaminating agent, for example in a handwash. Treatment of work surfaces and equipment is also provided, especially that used in hospital procedures or in food preparation. One particular embodiment comprises a composition formulated for topical use for preventing, eliminating or reducing carriage of bacteria and contamination from one individual to another. This is important to limit the transmission of microbial infections, particularly in a hospital environment where bacteria resistant to conventional antibiotics are prevalent. For such a use the modified bacteriophage may be contained in Tris buffered saline or phosphate buffered saline or may be formulated within a gel or cream. For multiple use a preservative may be added. Alternatively the product may be lyophilised and excipients, for example a sugar such as sucrose, may be added.

### **Detailed description of the invention**

This invention will now be described in more detail, by way of example only, and with reference to the accompanying drawings, in which:

Figure 1 is a schematic diagram showing construction of a plasmid containing *lacZ*ΔM15

Figure 2 is a schematic diagram showing construction of plasmids with replaced tail fibre sections;

Figure 3 is a schematic diagram showing construction of phage with hybrid tail fibre genes, which may be subsequently modified to introduce SASP-C according to the invention;

Figure 4 is a schematic diagram showing construction of phage with further hybrid tail fibre genes, which may be subsequently modified to introduce SASP-C according to the invention;

Figure 5 is a schematic diagram showing construction of bacteriophage with hybrid tail fibre genes, in which the *lacZα* marker has been removed;

Figure 6 is a schematic diagram showing construction of plasmids in which SASP-C is introduced into a suitable Phi33 insertion site;

Figure 7 is a schematic diagram showing production of further bacteriophage according to the invention;

Figure 8 is a schematic diagram showing construction of plasmids in which SASP-C codon optimised for expression in *P. aeruginosa* is introduced into a suitable Phi33 insertion site;

Figure 9 shows the sequence of the SASP-C gene from *Bacillus megaterium* strain KM (ATCC 13632), which has been codon optimised for expression in *P. aeruginosa*;

Figure 10 is a schematic diagram showing production of bacteriophage in which SASP-C which has been codon optimised for expression in *P. aeruginosa* is introduced into a suitable Phi33 insertion site;

Figure 11 is a schematic diagram showing production of further bacteriophage according to the invention;

Figure 12 is a schematic diagram showing production of further bacteriophage according to the invention;

Figure 13 is a CLUSTAL 2.1 multiple sequence alignment of the tail fibre proteins from Phage SPM-1, F8, PB1, C36, LBL3, Phi33, LMA2, KPP12, JG024, PTP92, NH-4, 14-1, PTP47, SN; and

Figure 14. 24 hour time-kill curve showing the in vitro efficacy of PT3.9 against *P. aeruginosa* strains 3503 (A) and ATCC 27853 (B). Cultures were grown in Luria bertani (LB) broth



supplemented with 10 mM calcium chloride, 1 mM magnesium sulphate and 1% glucose, at 37 °C.

Figure 15. In vivo efficacy of PT3.9 in a murine bacteraemia model of infection. Mice were treated IV with vehicle (tris buffered saline containing 1 mM magnesium sulphate, 10 mM calcium chloride and 10% v/v glycerol), PTP284 or PTP387 (2 hours post infection with *P. aeruginosa*). The viable cell counts in liver tissue at 22 hours post treatment are shown for each animal in each group (group size = 6), the geomean for each data set is represented by a horizontal line.

Figure 16. In vivo efficacy of PT3.9 in a neutropenic murine pneumonia model of infection. Mice were treated IT (intra-trachea) with placebo vehicle (tris buffered saline containing 1 mM magnesium sulphate, 10 mM calcium chloride and 10% v/v glycerol), PT3.9, PT3.8 or Tobramycin (15 minutes post infection with *P. aeruginosa*). The viable cell counts in lung tissue at 24 hours post treatment are shown for each animal in each group (group size = 6), the geomean for each data set is represented by a horizontal line.

The product of the invention provides in one aspect a single tail fibre within an individual phage, or a mix of phages where each type of phage has a single, different tail fibre.

This is a summary of the genetic modification of a lytic bacteriophage to render it non-lytic, such that it carries one of a number of possible tail fibre variants, in addition to SASP-C under the control of a promoter that usually controls expression of the *Pseudomonas aeruginosa* 30S ribosomal subunit protein S2 gene (*rpsB*), or SASP-C codon optimised for expression in *P. aeruginosa*, under the control of a promoter that usually controls expression of the *P. aeruginosa* fructose-1,6-bisphosphate aldolase gene (*fda*).

Genes can be removed and added to the phage genome using homologous recombination. There are several ways in which phages carrying foreign genes and promoters can be constructed and the following is an example of such methods.

For the construction of a Phi33 derivative it is shown how, using an *E. coli*/*P. aeruginosa* broad host range vector, as an example only, the existing tail fibre, or a section of the tail fibre, in the

bacteriophage genome may be replaced by an alternative tail fibre or tail fibre section from a different bacteriophage, via homologous recombination. It is also shown as an example only, how additional DNA sequences, such as the SASP-C gene from *B. megaterium* under the control of a *P. aeruginosa rpsB* promoter, or the SASP-C gene from *B. megaterium*, codon optimised for expression in *P. aeruginosa*, under the control of a *P. aeruginosa fda* promoter may be added to the bacteriophage genome via homologous recombination.

A tail fibre gene, or section of a tail fibre gene, from an alternative phage may be cloned between two regions of Phi33 DNA that flank the native tail fibre, or section thereof, along with a *lacZa* genetic marker, in a broad host range *E. coli/P. aeruginosa* vector. This plasmid may be introduced into *P. aeruginosa*, and the resulting strain infected with Phi33. Following harvesting of progeny phage, double recombinants in which the native Phi33 tail fibre or tail fibre section, has been replaced by the new tail fibre or tail fibre section and *lacZa*, may be isolated by plaquing on a suitable *P. aeruginosa* (*lacZΔM15+*) host strain using medium containing a chromogenic substrate that detects the action of β-galactosidase.

In a subsequent step, the *lacZa* marker may be removed from the bacteriophage genomes by making versions of the previously described tail fibre region recombination plasmids that do not contain the *lacZa* marker, introducing the new plasmids into suitable *P. aeruginosa* host strains and infecting with the previously modified bacteriophage derivatives of Phi33 carrying the corresponding alternative tail fibre gene, or section thereof, along with the *lacZa* marker. Recombinants that retain the new tail fibre or tail fibre section, but from which *lacZa* has been removed, may be isolated by plaquing on a suitable *P. aeruginosa* (*lacZΔM15+*) host strain using medium containing a chromogenic substrate that detects the action of β-galactosidase.

In a subsequent step, a similar homologous recombination may be used to introduce the gene for SASP-C, under the control of a *P. aeruginosa rpsB* promoter, while simultaneously adding an *E. coli lacZa* reporter gene for the identification of recombinant phage, into Phi33, or any of the previously described Phi33 derivatives, or similar bacteriophage or similar derivatives. A region consisting of SASP-C controlled by the *rpsB* promoter, and the *E. coli lacZa* allele, may be cloned between two regions of Phi33 that flank a suitable insertion site, such as the intergenic region located immediately downstream of the Phi33 tail fibre operon, in a broad host range *E. coli/P. aeruginosa* vector. This plasmid may be transferred to a suitable *P. aeruginosa* (*lacZΔM15+*) strain, and the resulting strain infected by Phi33 or the previously

constructed Phi33 derivative (from which the initial *lacZa* marker has been removed). Progeny phage may be harvested and double recombinants identified by plaquing on *P. aeruginosa* (*lacZΔM15+*), looking for acquisition of the new *lacZa* reporter on medium containing a chromogenic substrate that detects the action of β-galactosidase.

In an alternative subsequent step, a similar homologous recombination may be used to introduce the gene for SASP-C that has been codon optimised for expression in *P. aeruginosa*, under the control of a *P. aeruginosa fda* promoter, while simultaneously adding an *E. coli lacZa* reporter gene for the identification of recombinant phage, into Phi33, or any of the previously described Phi33 derivatives, or similar bacteriophage or similar derivatives. A region consisting of codon optimised SASP-C controlled by the *fda* promoter, and the *E. coli lacZa* allele, may be cloned between two regions of Phi33 that flank a suitable insertion site, such as the intergenic region located immediately downstream of the Phi33 tail fibre operon, in a broad host range *E. coli/P. aeruginosa* vector. This plasmid may be transferred to a suitable *P. aeruginosa* (*lacZΔM15+*) strain, and the resulting strain infected by Phi33 or the previously constructed Phi33 derivative (from which the initial *lacZa* marker has been removed). Progeny phage may be harvested and double recombinants identified by plaquing on *P. aeruginosa* (*lacZΔM15+*), looking for acquisition of the new *lacZa* reporter on medium containing a chromogenic substrate that detects the action of β-galactosidase.

Since these bacteriophage to be modified are lytic (rather than temperate), another requirement for these described steps of bacteriophage construction is the construction of a suitable host *P. aeruginosa* strain that carries the *E. coli lacZΔM15* gene at a suitable location in the bacterial genome, to complement the *lacZa* phenotypes of the desired recombinant bacteriophage. As an example, the construction of these *P. aeruginosa* strains may be achieved via homologous recombination using an *E. coli* vector that is unable to replicate in *P. aeruginosa*. The genomic location for insertion of the *lacZΔM15* transgene should be chosen such that no essential genes are affected and no unwanted phenotypes are generated through polar effects on the expression of adjacent genes. As an example, one such location may be immediately downstream of the *P. aeruginosa* strain PAO1 *phoA* homologue.

The *E. coli lacZΔM15* allele may be cloned into an *E. coli* vector that is unable to replicate in *P. aeruginosa*, between two regions of *P. aeruginosa* strain PAO1 genomic DNA that flank the 3' end of *phoA*. This plasmid may be introduced into *P. aeruginosa* and isolates having

undergone a single homologous recombination to integrate the whole plasmid into the genome selected according to the acquisition of tetracycline (50 µg/ml) resistance. Isolates (*lacZ*ΔM15+) which have undergone a second homologous recombination event may then be isolated on medium containing 10% sucrose (utilising the *sacB* counter-selectable marker present on the plasmid backbone).

In a subsequent step, a similar homologous recombination may be used to remove the *lacZ* $\alpha$  marker from the previously described, (*lacZ* $\alpha$ +) Phi33 derivatives that have been modified to introduce the gene for SASP-C, under the control of a *P. aeruginosa rpsB* promoter. A region consisting of SASP-C controlled by the *rpsB* promoter, may be cloned between two regions of Phi33 that flank the chosen insertion site, in a broad host range *E. coli*/*P. aeruginosa* vector. This plasmid may be transferred to a suitable *P. aeruginosa* (*lacZ*ΔM15+) strain, and the resulting strain infected by the previously described (*lacZ* $\alpha$ +) Phi33 derivatives that have been modified to introduce the gene for SASP-C, under the control of a *P. aeruginosa rpsB* promoter. Progeny phage may be harvested and double recombinants identified by plaquing on *P. aeruginosa* (*lacZ*ΔM15+), looking for loss of the *lacZ* $\alpha$  reporter on medium containing a chromogenic substrate that detects the action of  $\beta$ -galactosidase.

In an alternative subsequent step, a similar homologous recombination may be used to remove the *lacZ* $\alpha$  marker from the previously described, (*lacZ* $\alpha$ +) Phi33 derivatives that have been modified to introduce the gene for SASP-C, codon optimised for expression in *P. aeruginosa*, under the control of a *P. aeruginosa fda* promoter. A region consisting of SASP-C, codon optimised for expression in *P. aeruginosa*, controlled by the *fda* promoter, may be cloned between two regions of Phi33 that flank the chosen insertion site, in a broad host range *E. coli*/*P. aeruginosa* vector. This plasmid may be transferred to a suitable *P. aeruginosa* (*lacZ*ΔM15+) strain, and the resulting strain infected by the previously described (*lacZ* $\alpha$ +) Phi33 derivatives that have been modified to introduce the gene for SASP-C, codon optimised for expression in *P. aeruginosa*, under the control of a *P. aeruginosa fda* promoter. Progeny phage may be harvested and double recombinants identified by plaquing on *P. aeruginosa* (*lacZ*ΔM15+), looking for loss of the *lacZ* $\alpha$  reporter on medium containing a chromogenic substrate that detects the action of  $\beta$ -galactosidase.

## **Experimental procedures**

PCR reactions to generate DNA for cloning purposes may be carried out using Herculase II Fusion DNA polymerase (Agilent Technologies), depending upon the melting temperatures ( $T_m$ ) of the primers, according to manufacturers instructions. PCR reactions for screening purposes may be carried out using Taq DNA polymerase (NEB), depending upon the  $T_m$  of the primers, according to manufacturers instructions. Unless otherwise stated, general molecular biology techniques, such as restriction enzyme digestion, agarose gel electrophoresis, T4 DNA ligase-dependent ligations, competent cell preparation and transformation may be based upon methods described in Sambrook et al., (1989). Enzymes may be purchased from New England Biolabs or Thermo Scientific. DNA may be purified from enzyme reactions and prepared from cells using Qiagen DNA purification kits. Plasmids may be transferred from *E. coli* strains to *P. aeruginosa* strains by conjugation, mediated by the conjugation helper strain *E. coli* HB101 (pRK2013). A chromogenic substrate for  $\beta$ -galactosidase, S-gal, that upon digestion by  $\beta$ -galactosidase forms a black precipitate when chelated with ferric iron, may be purchased from Sigma (S9811).

Primers may be obtained from Sigma Life Science. Where primers include recognition sequences for restriction enzymes, additional 2-6 nucleotides may be added at the 5' end to ensure digestion of the PCR-amplified DNA.

All clonings, unless otherwise stated, may be achieved by ligating DNAs overnight with T4 DNA ligase and then transforming them into *E. coli* cloning strains, such as DH5 $\alpha$  or TOP10, with isolation on selective medium, as described elsewhere (Sambrook et al., 1989).

An *E. coli*/*P. aeruginosa* broad host range vector, such as pSM1080A, may be used to transfer genes between *E. coli* and *P. aeruginosa*. pSM1080A was previously produced by combining the broad host-range origin of replication from a *P. aeruginosa* plasmid, *oriT* from pRK2, the *tetAR* selectable marker for use in both *E. coli* and *P. aeruginosa*, from plasmid pRK415, and the high-copy-number, *E. coli* origin of replication, *oriV*, from plasmid pUC19.

An *E. coli* vector that is unable to replicate in *P. aeruginosa*, pSM1104, may be used to generate *P. aeruginosa* mutants by allelic exchange. pSM1104 was previously produced by combining *oriT* from pRK2, the *tetAR* selectable marker for use in both *E. coli* and *P. aeruginosa*, from plasmid pRK415, the high-copy-number, *E. coli* origin of replication, *oriV*, from plasmid

pUC19, and the *sacB* gene from *Bacillus subtilis* strain 168, under the control of a strong promoter, for use as a counter-selectable marker.

Detection of Phi33-like phage (PB1-like phage family) conserved N-terminal tail fibre regions by PCR

1. Primers for the detection of Phi33-like phage-like tail fibre genes in experimental phage samples may be designed as follows:

The DNA sequences of the tail fibre genes from all sequenced Phi33-like phage (including Phi33, PB1, NH-4, 14-1, LMA2, KPP12, JG024, F8, SPM-1, LBL3, PTP47, C36, PTP92 and SN) may be aligned using Clustal Omega, which is available on the EBI website, and the approximately 2 kb-long highly conserved region mapping to the gene's 5' sequence may be thus identified (positions 31680-33557 in the PB1 genome sequence, Acc. EU716414). Sections of 100% identity among the 11 tail fibre gene sequences may be identified by visual inspection. Three pairs of PCR primers targeting selected absolutely conserved regions, and amplifying PCR products no longer than 1 kb may be chosen as follows: pair B4500 and B4501, defining a 193 bp-long region; pair B4502 and B4503, defining a 774 bp-long region; and pair B4504 and B4505, defining a 365 bp-long region.

Primer B4500 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 31680 to 31697. Primer B4501 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 31851 to 31872. Primer B4502 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 31785 to 31804. Primer B4503 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 32541 to 32558. Primer B4504 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 32868 to 32888. Primer B4505 consists of sequence of PB1 phage genome (Acc. EU716414) ranging from position 33213 to 33232.

B4500 (SEQ ID NO: 1)

5'-GTGATCACACCCGAACTG-3'

B4501 (SEQ ID NO: 2)

5'-CGATGAAGAAGAGTTGGTTTTG-3'

B4502 (SEQ ID NO: 3)

5'-ACGCCGGACTACGAAATCAG-3'

B4503 (SEQ ID NO: 4)

5'-TCCGGAGACGTTGATGGT-3'

B4504 (SEQ ID NO: 5)

5'-CCTTTCATCGATTTCCACTTC-3'

B4505 (SEQ ID NO: 6)

5'-TTCGTGGACGCCAGTCCCA-3'

2. Phi33-like tail fibre genes may be detected in experimental phage samples as follows:

Plaques of isolated phage of environmental origin may be picked from agar plates and added to water and incubated for 30 minutes, making plaque soak outs. The plaque soak outs may be diluted and a portion added to PCR reactions containing one or all of the above primer pairs, and PCR may be performed according to a standard protocol. PCR products may be visualised on a 1.5 % agarose gel with ethidium bromide staining, and evaluated for their size. PCR products of the correct size for the primer pair used may be gel-extracted and submitted to an external facility for sequencing. Sequencing results may be compared with the available tail fibre gene sequences in order to confirm the identity of the PCR product.

Construction of plasmids to generate *Pseudomonas aeruginosa* strains carrying the *Escherichia coli lacZ*ΔM15 gene, immediately downstream of the *phoA* locus of the bacterial genome

1. Plasmid pSMX200 (Figure 1), comprising pSM1104 carrying DNA flanking the 3' end of the *P. aeruginosa* PAO1 *phoA* homologue, may be constructed as follows.

A region comprising the terminal approximately 1 kb of the *phoA* gene from *P. aeruginosa* may be amplified by PCR using primers B4200 and B4201 (Figure 1). The PCR product may then be cleaned and digested with *SpeI* and *BglII*. A second region comprising approximately 1 kb downstream of the *phoA* gene from *P. aeruginosa*, including the 3' end of the PA3297

open reading frame, may be amplified by PCR using primers B4202 and B4203 (Figure 1). This second PCR product may then be cleaned and digested with BglII and XhoI. The two digests may be cleaned again and ligated to pSM1104 that has been digested with SpeI and XhoI, in a 3-way ligation, to yield plasmid pSMX200 (Figure 1).

Primer B4200 consists of a 5' SpeI restriction site (underlined), followed by sequence located approximately 1 kb upstream of the stop codon of *phoA* from *P. aeruginosa* strain PAO1 (Figure 1). Primer B4201 consists of 5' BglII and AflIII restriction sites (underlined), followed by sequence complementary to the end of the *phoA* gene from *P. aeruginosa* strain PAO1 (the stop codon is in lower case; Figure 1). Primer B4202 consists of 5' BglII and NheI restriction sites (underlined), followed by sequence immediately downstream of the stop codon of the *phoA* gene from *P. aeruginosa* strain PAO1 (Figure 1). Primer B4203 consists of a 5' XhoI restriction site (underlined), followed by sequence within the PA3297 open reading frame, approximately 1 kb downstream of the *phoA* gene from *P. aeruginosa* strain PAO1 (Figure 1).

Primer B4200 (SEQ ID NO:7)

5'-gataACTAGTCCTGGTCCACCGGGGTCAAG-3'

Primer B4201 (SEQ ID NO: 8)

5'-gctcagatcttccttaagtcaGTCGCGCAGGTTTCAG-3'

Primer B4202 (SEQ ID NO: 9)

5'-aggaagatctgagctagcTCGGACCAGAACGAAAAAG-3'

Primer B4203 (SEQ ID NO: 10)

5'-gataCTCGAGGCGGATGAACATTGAGGTG-3'

2. Plasmid pSMX203 (Figure 1), comprising pSMX200 carrying *lacZ*ΔM15 under the control of a *lac* promoter, may be constructed as follows.

The *lacZ*ΔM15 gene under the control of a *lac* promoter may be amplified by PCR from *Escherichia coli* strain DH10B using primers B4208 and B4209 (Figure 1). The resulting PCR product may then be digested with BglII and NheI, and ligated to pSMX200 that has also been digested with BglII and NheI, to yield plasmid pSMX203 (Figure 1).



Primer B4208 consists of a 5' BglII restriction site (underlined), followed by sequence of the *lac* promoter (Figure 1). Primer B4209 consists of a 5' NheI restriction site (underlined), followed by a bi-directional transcriptional terminator and sequence complementary to the 3' end of *lacZΔM15* (underlined, in bold; Figure 1).

Primer B4208 (SEQ ID NO: 11)

5'-gataagatctgagcgcaacgcaattaatgtg-3'

Primer B4209 (SEQ ID NO: 12)

5'-gatagctagcAGTCAAAGCCTCCGGTCGGAGGCTTTTGACTTTATT  
TTTGACACCAGACCAAC-3'

Genetic modification of *Pseudomonas aeruginosa* to introduce the *Escherichia coli lacZΔM15* gene immediately downstream of the *phoA* locus of the bacterial genome

1. Plasmid pSMX203 (Figure 1) may be transferred to *P. aeruginosa* by conjugation, selecting for primary recombinants by acquisition of resistance to tetracycline (50 µg/ml).
2. Double recombinants may then be selected via *sacB*-mediated counterselection, by plating onto medium containing 10% sucrose.
3. Isolates growing on 10% sucrose may then be screened by PCR to confirm that *lacZΔM15* has been introduced downstream of the *P. aeruginosa phoA* gene.
4. Following verification of an isolate (PAX21), this strain may then be used as a host for further modification of bacteriophage, where complementation of a *lacZα* reporter is required.

Construction of a plasmid to replace the 3' section of the Phi33 tail fibre with that of PTP92, utilising a *lacZα* screening process

1. pSMX284 (Figure 2), comprising pSM1080A carrying the region immediately downstream of the Phi33 tail fibre gene, may be constructed as follows.

A 1 kb region of Phi33 sequence covering the terminal 20 bases of the Phi33 tail fibre, and the adjacent downstream region, may be amplified by PCR using primers B4222 and B4249 (Figure 2). The resulting PCR product may then be cleaned and digested with NheI, and ligated to pSM1080A that has also been digested with NheI and then treated with alkaline phosphatase prior to ligation, yielding plasmid pSMX284 (Figure 2).

Primer B4222 consists of a 5' NheI restriction site (underlined), followed by sequence from Phi33, approximately 1 kb downstream of the end of the Phi33 tail fibre gene (Figure 2). B4249 consists of 5' NheI-KpnI-AvrII restriction sites (underlined), followed by sequence complementary to the 3' end of the Phi33 tail fibre and sequence immediately downstream of the tail fibre open reading frame (Figure 2).

B4222 (SEQ ID NO: 13)

5'-gataGCTAGCATGGTTTTTCACGACCATG-3'

B4249 (SEQ ID NO: 14)

5'-GATAGCTAGCGAGGTACCGACCTAGGTTTTCCAGCGAGTGACGTAA  
AATG-3'

2. pSMX285 (Figure 2), comprising pSMX284 carrying *lacZα*, a 3' section of the PTP92 tail fibre gene sequence, and a region of Phi33 sequence comprising the 5' end of the tail fibre gene and sequence located immediately upstream of the Phi33 tail fibre gene, may be constructed as follows.

The *lacZα* open reading frame may be amplified by PCR from pUC19 using primers B4250 and B4252 (Figure 2). The PTP92 tail fibre 3' section may be amplified by PCR from PTP92 using primers B4251 and B4254 (Figure 2). The *lacZα* open reading frame may then be joined to the PTP92 tail fibre gene 3' section by SOEing PCR using the outer primers, B4250 and B4254. A region comprising sequence of the 5' end of the Phi33 tail fibre gene, and sequence located immediately upstream of the Phi33 tail fibre gene, may be amplified by PCR using primers B4253 and B4229 (Figure 2). This PCR product may then be joined to the PCR product comprising *lacZα* and the PTP92 tail fibre gene 3' section, by SOEing PCR using the outer primers B4250 and B4229. The resulting PCR product may then be cleaned and digested with

AvrII and KpnI, and ligated to pSMX284 that has also been digested with AvrII and KpnI, yielding plasmid pSMX285 (Figure 2).

Primer B4250 consists of a 5' AvrII restriction site, followed by sequence complementary to the 3' end of the *lacZα* open reading frame (Figure 2). Primer B4252 consists of a 5' section of sequence that overlaps the 3' end of the PTP92 tail fibre gene (underlined), followed by sequence of the 5' end of the *lacZα* open reading frame. Primer B4251 is the reverse complement of primer B4252 (Figure 2). Primer B4254 consists of 5' sequence from within the Phi33 tail fibre gene (underlined), followed by sequence within the 3' end of the PTP92 tail fibre gene (Figure 2). Primer B4253 is the reverse complement of Primer B4254. Primer B4229 consists of a 5' KpnI restriction site (underlined), followed by sequence that is complementary to a region approximately 1 kb upstream of the tail fibre gene in Phi33 (Figure 2).

Primer B4250 (SEQ ID NO: 15)

5'-GataCCTAGGttagcgccattcgccattc-3'

Primer B4252 (SEQ ID NO: 16)

5'-CTATTCCAGCGGGTAACGTAAAtgaccatgattacgattC-3'

Primer B4251 (SEQ ID NO: 17)

5'-GaatccgtaatcatgtcatTTTACGTTACCCGCTGGAATAG-3'

Primer B4254 (SEQ ID NO: 18)

5'-CAAGCGGGCCGGCTGGTCTCTCGGCAATAACTCCTATGTGATC-3'

Primer B4253 (SEQ ID NO: 19)

5'-GATCACATAGGAGTTATTGCCGAGAGACCAGCCGGCCCGCTTG-3'

Primer B4229 (SEQ ID NO: 20)

5'-gataGGTACCGCGACCGGTCTGTACTTC-3'

Genetic modification of Phi33 to replace the 3' section of the tail fibre gene with that of PTP92

1. Plasmid pSMX285 (Figure 2; Figure 3) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA80.
2. Strain PTA80 may be infected with phage Phi33, and the progeny phage harvested.
3. Recombinant phage in which the 3' end of the Phi33 tail fibre gene has been replaced by that of PTP92, and to which *lacZα* has been added, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for black plaques, which are indicative of β-galactosidase activity.
4. PCR may be carried out to check that the tail fibre gene has been replaced, and that *lacZα* is present.
5. Following identification of a verified isolate (PTPX81; Figure 3), this isolate may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Construction of a plasmid to replace the 3' section of the Phi33 tail fibre with that of PTP47, utilising a *lacZα* screening process

1. pSMX286 (Figure 2), comprising pSMX284 carrying *lacZα*, a 3' section of the PTP47 tail fibre gene sequence, and a region of Phi33 sequence comprising the 5' end of the tail fibre gene and sequence located immediately upstream of the Phi33 tail fibre gene, may be constructed as follows.

The *lacZα* open reading frame may be amplified by PCR from pUC19 using primers B4250 and B4258 (Figure 2). The PTP47 tail fibre 3' section may be amplified by PCR from PTP47 using primers B4259 and B4260 (Figure 2). The *lacZα* open reading frame may then be joined to the PTP47 tail fibre gene 3' section by SOEing PCR using the outer primers, B4250 and B4260. A region comprising sequence of the 5' end of the Phi33 tail fibre gene, and sequence located immediately upstream of the Phi33 tail fibre gene, may be amplified by PCR using primers B4261 and B4229 (Figure 2). This PCR product may then be joined to the PCR product comprising *lacZα* and the PTP47 tail fibre gene 3' section, by SOEing PCR using the outer primers B4250 and B4229. The resulting PCR product may then be cleaned and digested with

AvrII and KpnI, and ligated to pSMX284 that has also been digested with AvrII and KpnI, yielding plasmid pSMX286 (Figure 2).

Primer B4250 consists of a 5' AvrII restriction site, followed by sequence complementary to the 3' end of the *lacZα* open reading frame (Figure 2). Primer B4258 consists of a 5' section of sequence that overlaps the 3' end of the PTP47 tail fibre gene (underlined), followed by sequence of the 5' end of the *lacZα* open reading frame. Primer B4259 is the reverse complement of primer B4258 (Figure 2). Primer B4260 consists of 5' sequence from within the Phi33 tail fibre gene (underlined), followed by sequence within the 3' end of the PTP47 tail fibre gene (Figure 2). Primer B4261 is the reverse complement of Primer B4260. Primer B4229 consists of a 5' KpnI restriction site (underlined), followed by sequence that is complementary to a region approximately 1 kb upstream of the tail fibre gene in Phi33 (Figure 2).

Primer B4250 (SEQ ID NO: 15)

5'-GataCCTAGGttagcgccattcgccattc-3'

Primer B4258 (SEQ ID NO: 21)

5'-CTTTTCCAGCGAGTGACGTAAAatgaccatgattacggattC-3'

Primer B4259 (SEQ ID NO: 22)

5'-gaatccgtaatcatgtgtcatTTTACGTCACTCGCTGGAAAAG-3'

Primer B4260 (SEQ ID NO: 23)

5'-CAAGCGGGCCGGCTGGTCTCTCGGCAATAACTCCTATGTGATC-3'

Primer B4261 (SEQ ID NO: 24)

5'-GATCACATAGGAGTTATTGCCGAGAGACCAGCCGGCCCGCTTG-3'

Primer B4229 (SEQ ID NO: 20)

5'-gataGGTACCGCGACCGGTCTGTACTTC-3'

Genetic modification of Phi33 to replace the 3' section of the tail fibre gene with that of PTP47

1. Plasmid pSMX286 (Figure 2; Figure 4) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA81.
2. Strain PTA81 may be infected with phage Phi33, and the progeny phage harvested.
3. Recombinant phage in which the 3' end of the Phi33 tail fibre gene has been replaced by that of PTP47, and to which *lacZα* has been added, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for black plaques, which are indicative of β-galactosidase activity.
4. PCR may be carried out to check that the tail fibre gene has been replaced, and that *lacZα* is present.
5. Following identification of a verified isolate (PTPX82; Figure 4), this isolate may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Construction of a plasmid to remove the *lacZα* marker from PTPX81

1. pSMX287 (Figure 5), comprising pSM1080A carrying a 3' section of the PTP92 tail fibre gene, and a region of Phi33 sequence located immediately downstream of the Phi33 tail fibre gene, may be constructed as follows.

The region of Phi33 sequence located immediately downstream of the Phi33 tail fibre may be amplified by PCR using primers B4222 and B4255 (Figure 5). The 3' end of the PTP92 tail fibre gene may be amplified by PCR using primers B4256 and B4257 (Figure 5). These two PCR products may then be joined by SOEing PCR, using the two outer primers B4222 and B4257. The resulting PCR product may then be cleaned, digested with *NheI*, cleaned again, and ligated to pSM1080A that has also been digested with *NheI* and then treated with alkaline phosphatase prior to ligation, to yield plasmid pSMX287 (Figure 5).

Primer B4255 consists of a 5' section of the end of the PTP92 tail fibre gene (underlined), followed by sequence immediately downstream of the Phi33 tail fibre gene (Figure 5). Primer B4256 is the reverse complement of primer B4255 (Figure 5). Primer B4257 consists of a 5'

NheI restriction site (underlined), followed by sequence of the terminal 1 kb of the PTP92 tail fibre gene (Figure 5).

Primer B4255 (SEQ ID NO: 25)

5'-CTATTCCAGCGGGTAACGTAAAATGAAATGGACGCGGATCAG-3'

Primer B4256 (SEQ ID NO: 26)

5'-CTGATCCGCGTCCATTTTACGTTACCCGCTGGAATAG-3'

Primers B4257 (SEQ ID NO: 27)

5'-gataGCTAGCGGCAATAACTCCTATGTGATC-3'

Genetic modification of PTPX81 to remove the *lacZα* marker

1. Plasmid pSMX287 (Figure 5; Figure 3) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA82.
2. Strain PTA82 may be infected with phage PTPX81, and the progeny phage harvested.
3. Recombinant phage in which the *lacZα* marker has been removed may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for white plaques, which are indicative of loss of β-galactosidase activity.
4. PCR may be carried out to check that the tail fibre gene has been retained, and that *lacZα* has been removed.
5. Following identification of a verified isolate (PTPX83; Figure 3), this isolate may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Construction of a plasmid to remove the *lacZα* marker from PTPX82

1. pSMX288 (Figure 5), comprising pSM1080A carrying a 3' section of the PTP47 tail fibre gene, and a region of Phi33 sequence located immediately downstream of the Phi33 tail fibre gene, may be constructed as follows.

The region of Phi33 sequence located immediately downstream of the Phi33 tail fibre may be amplified by PCR using primers B4222 and B4262 (Figure 5). The 3' end of the PTP47 tail fibre gene may be amplified by PCR using primers B4263 and B4264 (Figure 5). These two PCR products may then be joined by SOEing PCR, using the two outer primers B4222 and B4264. The resulting PCR product may then be cleaned, digested with *NheI*, cleaned again, and ligated to pSM1080A that has also been digested with *NheI* and then treated with alkaline phosphatase prior to ligation, to yield plasmid pSMX288 (Figure 5).

Primer B4262 consists of a 5' section of the end of the PTP47 tail fibre gene (underlined), followed by sequence immediately downstream of the Phi33 tail fibre gene (Figure 5). Primer B4263 is the reverse complement of primer B4262 (Figure 5). Primer B4264 consists of a 5' *NheI* restriction site (underlined), followed by sequence of the terminal 1 kb of the PTP47 tail fibre gene (Figure 5).

Primer B4262 (SEQ ID NO: 28)

5'-CTTTTCCAGCGAGTGACGTAAAATGAAATGGACGCGGATCAG-3'

Primer B4263 (SEQ ID NO: 29)

5'-CTGATCCGCGTCCATTTTACGTCCTCGCTGGAAAAG -3'

Primers B4264 (SEQ ID NO: 30)

5'-gataGCTAGCGGCAATAACTCCTATGTGATC-3'

Genetic modification of PTPX82 to remove the *lacZα* marker

1. Plasmid pSMX288 (Figure 5; Figure 4) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA83.



2. Strain PTA83 may be infected with phage PTPX82, and the progeny phage harvested.
3. Recombinant phage in which the *lacZ $\alpha$*  marker has been removed may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for white plaques, which are indicative of loss of  $\beta$ -galactosidase activity.
4. PCR may be carried out to check that the tail fibre gene has been retained, and that *lacZ $\alpha$*  has been removed.
5. Following identification of a verified isolate (PTPX84; Figure 4), this isolate may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Construction of a plasmid to introduce *rpsB*-SASP-C and *lacZ $\alpha$*  into the phage genome of Phi33, PTPX83, PTPX84, and similar phage

1. Plasmid pSMX251 (Figure 6), comprising pSM1080A containing regions of Phi33 flanking the chosen insertion site for *rpsB*-SASP-C, such as the intergenic region immediately downstream of the tail fibre operon, may be constructed as follows.

The region of Phi33 sequence immediately downstream of the chosen insertion site may be amplified by PCR using primers B4900 and B4901 (Figure 6). This PCR product may then be cleaned and digested with *NheI* and *AvrII*. The region of Phi33 sequence immediately upstream of the chosen insertion site may be amplified by PCR using primers B4902 and B4903 (Figure 6). This second PCR product may then be cleaned and digested with *AvrII* and *NheI*. The two PCR product digests may then be cleaned again and ligated to pSM1080A that has been digested with *NheI* and treated with alkaline phosphatase prior to ligation. Clones carrying one insert of each of the two PCR products may be identified by PCR using primers B4900 and B4903, and *NheI* restriction digest analysis of the purified putative clones, to identify plasmid pSMX251 (Figure 6).

Primer B4900 consists of a 5' *NheI* restriction site (underlined), followed by Phi33 sequence located approximately 500bp downstream of the Phi33 insertion site that is within the intergenic region immediately downstream of the tail fibre operon (Figure 6). Primer B4901 consists of 5' *AvrII* and *XhoI* restriction sites (underlined), followed by sequence of Phi33 that

is complementary to sequence located immediately downstream of the Phi33 insertion site (Figure 6). Primer B4902 consists of a 5' AvrII restriction site (underlined), followed by Phi33 sequence located immediately upstream of the insertion site (Figure 6). Primer B4903 consists of a 5' NheI site (underlined), followed by Phi33 sequence that is complementary to sequence located approximately 500bp upstream of the Phi33 insertion site (Figure 6).

Primer B4900 (SEQ ID NO: 31)

5' gatagctagcTTTCTCGTTTAAATGTCG 3'

Primer B4901 (SEQ ID NO: 32)

5' gataCCTAGGtgCTCGAGTATTCGCCCAAAGAAAAG 3'

Primer B4902 (SEQ ID NO: 33)

5' gataCCTAGGTCAGGAGCCTTGATTGATC 3'

Primer B4903 (SEQ ID NO: 34)

5' gatagctagcGGACTGGTAAGTCTGGTG 3'

2. Plasmid pSMX252 (Figure 6), comprising pSMX251 containing SASP-C under the control of an *rpsB* promoter, may be constructed as follows.

The SASP-C gene from *Bacillus megaterium* strain KM (ATCC 13632) may be amplified by PCR using primers B4904 and B4270 (Figure 6). The resulting PCR product may then be digested with XhoI and NcoI. The *rpsB* promoter may be amplified by PCR from *P. aeruginosa* using primers B4271 and B4905 (Figure 6). The resulting PCR product may then be digested with NcoI and AvrII. The two digested PCR products may then be cleaned and ligated to pSMX251 that has been digested with XhoI and AvrII, yielding plasmid pSMX252 (Figure 6).

Primer B4904 comprises a 5' XhoI restriction site, followed by 5 bases, and then a bi-directional transcriptional terminator, and then sequence complementary to the 3' end of the SASP-C gene from *B. megaterium* strain KM (ATCC 13632) (underlined, in bold; Figure 6). Primer B4270 comprises a 5' NcoI restriction site (underlined), followed by sequence of the 5' end of the SASP-C gene from *B. megaterium* strain KM (ATCC 13632) (Figure 6). Primer B4271 comprises a 5' NcoI restriction site (underlined), followed by sequence complementary

to the end of the *rpsB* promoter from *P. aeruginosa* PAO1 (Figure 6). Primer B4905 comprises a 5' AvrII restriction site (underlined), followed by sequence of the beginning of the *rpsB* promoter from *P. aeruginosa* PAO1 (Figure 6).

Primer B4904 (SEQ ID NO: 35)

5'-gataCTCGAGGATCTAGTCAAAAGCCTCCGACCGGAGGCTTTTGACT  
ttagtacttgccgcctag-3'

Primer B4270 (SEQ ID NO: 36)

5'- gataccATGGcaaattatcaaaacgcatc-3'

Primer B4271 (SEQ ID NO: 37)

5'-gataCCATggTAGTTCCTCGATAAGTCG-3'

Primer B4905 (SEQ ID NO: 38)

5'-gataCCTAGGCCTAGGgatctGACCGACCGATCTACTCC-3'

3. pSMX253 (Figure 6), comprising pSMX252 containing *lacZα*, may be constructed as follows.

*lacZα* may be PCR amplified using primers B4906 and B4907 (Figure 6). The resulting PCR product may then be digested with XhoI and ligated to pSMX252 that has also been digested with XhoI and treated with alkaline phosphatase prior to ligation, to yield pSMX253 (Figure 6).

Primer B4906 consists of a 5' XhoI restriction site (underlined), followed by sequence complementary to the 3' end of *lacZα* (Figure 6). Primer B4907 consists of a 5' XhoI restriction site (underlined), followed by sequence of the *lac* promoter driving expression of *lacZα* (Figure 6).

Primer B4906 (SEQ ID NO: 39)

5'-gataCTCGAGttagcgccattcgccattc-3'

Primer B4907 (SEQ ID NO: 40)

5'-gataCTCGAGgcgcaacgcaattaatgtg-3'

Genetic modification of Phi33, PTPX83, PTPX84, and similar phage, to introduce *rpsB*-SASP-C and *lacZa*

1. Plasmid pSMX253 (Figure 6; Figure 3; Figure 4; Figure 7) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA51.
2. Strain PTA51 may be infected in individual experiments with phage Phi33, or PTPX83, or PTPX84, or other similar phage, and the progeny phage harvested.
3. Recombinant phage, in which *rpsB*-SASP-C and *lacZa* have been introduced into the chosen insertion site, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for black plaques, which are indicative of β-galactosidase activity.
4. PCR may be carried out to check that *rpsB*-SASP-C and *lacZa* are present.
5. Following identification of verified isolates (for example, PTPX85 (Figure 7), PTPX86 (Figure 3), PTPX87 (Figure 4)), the isolates may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Genetic modification to remove the *lacZa* marker from PTPX85, PTPX86, PTPX87, and similar derivatives of Phi33

1. Plasmid pSMX252 (Figure 6; Figure 3; Figure 4; Figure 7) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA85.
2. Strain PTA85 may be infected in individual experiments with phage PTPX85, or PTPX86, or PTPX87, or other similar phage, and the progeny phage harvested.

3. Recombinant phage, in which *lacZα* marker has been removed, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for white plaques, which are indicative of loss of β-galactosidase activity.
4. PCR may be carried out to confirm removal of the *lacZα* marker, while ensuring that *rpsB*-SASP-C is still present.
5. Following identification of verified isolates (for example, PTPX88 (Figure 7), PTPX89 (Figure 3), PTPX90 (Figure 4)), the isolates may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Construction of a plasmid to introduce *fda*-SASP-C (codon optimised) and *lacZα* into a chosen insertion site, located in an intergenic region immediately downstream of the tail fibre operon, within the genome of Phi33, PTPX83, PTPX84, and similar phage

1. Plasmid pSMX254 (Figure 8), comprising pSMX251 containing SASP-C codon optimised for expression in *P. aeruginosa*, under the control of an *fda* promoter, may be constructed as follows.

The SASP-C gene from *Bacillus megaterium* strain KM (ATCC 13632) may be codon optimised for expression in *P. aeruginosa* (Figure 9) and synthesised *in vitro*. The codon optimised SASP-C gene may then be amplified by PCR using primers B4312 and B4313 (Figure 8). The *fda* promoter may be amplified by PCR from *P. aeruginosa* using primers B4314 and B4315 (Figure 8). The resulting two PCR products may then be joined by splicing by overlap extension (SOEing) PCR, using the outer primers B4312 and B4314 (Figure 8). The resulting *fda*-codon optimised SASP-C-terminator PCR product may then be digested with XhoI and AvrII, cleaned, and ligated to pSMX251 that has been digested with XhoI and AvrII, yielding plasmid pSMX254 (Figure 8).

Primer B4312 comprises a 5' XhoI restriction site, followed by a bi-directional transcriptional terminator, and then sequence complementary to the 3' end of the SASP-C gene from *B. megaterium* strain KM (ATCC 13632) that has been codon optimised for expression in *P. aeruginosa* (underlined, in bold; Figure 8). Primer B4313 comprises sequence of the 3' end of the *fda* promoter from *P. aeruginosa* PAO1 (in bold) followed by sequence of the 5' end of the codon optimised SASP-C gene. Primer B4314 comprises sequence complementary to the 5'

end of the codon optimised SASP-C gene followed by sequence complementary to the 3' end of the *fda* promoter from *P. aeruginosa* PAO1 (Figure 8). Primer B4315 comprises a 5' *AvrII* restriction site (underlined), followed by sequence of the beginning of the *fda* promoter from *P. aeruginosa* PAO1 (Figure 8).

Primer B4312 (SEQ ID NO: 41)

5'-

gataCTCGAGAGTCAAAAGCCTCCGACCGGAGGCTTTTGACTTCAGTACTTGCCGC  
CCAG-3'

Primer B4313 (SEQ ID NO: 42)

5'- GATTGGGAGATACGAGAACCATGGCCAACTACCAGAACGC -3'

Primer B4314 (SEQ ID NO: 43)

5'- GCGTTCTGGTAGTTGGCCATGGTTCTCGTATCTCCCAATC-3'

Primer B4315 (SEQ ID NO: 44)

5'- GATACCTAGGAACGACGAAGGCCTGGTG-3'

3. pSMX255 (Figure 8), comprising pSMX254 containing *lacZα*, may be constructed as follows.

*lacZα* may be PCR amplified using primers B4906 and B4907 (Figure 8). The resulting PCR product may then be digested with *XhoI* and ligated to pSMX254 that has also been digested with *XhoI* and treated with alkaline phosphatase prior to ligation, to yield pSMX255 (Figure 8).

Primer B4906 consists of a 5' *XhoI* restriction site (underlined), followed by sequence complementary to the 3' end of *lacZα* (Figure 8). Primer B4907 consists of a 5' *XhoI* restriction site (underlined), followed by sequence of the *lac* promoter driving expression of *lacZα* (Figure 8).

Primer B4906 (SEQ ID NO: 40)

5'-gataCTCGAGGttagcgccattcgccattc-3'

Primer B4907 (SEQ ID NO: 41)

5'-gataCTCGAGgcgcaacgcaattaatgtg-3'

Genetic modification of Phi33, PTPX83, PTPX84, and similar phage, to introduce *fda*-codon optimised SASP-C and *lacZα*

1. Plasmid pSMX255 (Figure 8; Figure 10; Figure 11; Figure 12) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA86.
2. Strain PTA86 may be infected in individual experiments with phage Phi33, or PTPX83, or PTPX84, or other similar phage, and the progeny phage harvested.
3. Recombinant phage, into which *fda*-codon optimised SASP-C and *lacZα* have been introduced, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for black plaques, which are indicative of β-galactosidase activity.
4. PCR may be carried out to check that *fda*-codon optimised SASP-C and *lacZα* are present.
5. Following identification of verified isolates (for example, PTPX91 (Figure 12), PTPX92 (Figure 10), PTPX93 (Figure 11)), the isolates may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.

Genetic modification to remove the *lacZα* marker from PTPX91, PTPX92, PTPX93, and similar derivatives of Phi33

1. Plasmid pSMX254 (Figure 8; Figure 10; Figure 11; Figure 12) may be introduced into *P. aeruginosa* strain PAX21 by conjugation, selecting transconjugants on the basis of tetracycline resistance (50 µg/ml), yielding strain PTA87.
2. Strain PTA87 may be infected in individual experiments with phage PTPX91, or PTPX92, or PTPX93, or other similar phage, and the progeny phage harvested.

3. Recombinant phage, in which *lacZα* marker has been removed, may be identified by plaquing the lysate from step (2) on *P. aeruginosa* strain PAX21, onto medium containing S-gal, looking for white plaques, which are indicative of loss of β-galactosidase activity.
4. PCR may be carried out to confirm removal of the *lacZα* marker, while ensuring that *fda*-codon optimised SASP-C is still present.
5. Following identification of verified isolates (for example, PTP387 (Figure 12), PTP388 (Figure 10), PTP389 (Figure 11)), the isolates may be plaque purified twice more on *P. aeruginosa* strain PAX21, prior to further use.



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**Table 1. Host range of Phi33, PTP92, C36 and PTP47 against 44 European clinical isolates of *Pseudomonas aeruginosa*.**

Strains were tested for sensitivity to each phage by dropping 10 µl of crude phage lysate onto a soft agar overlay plate inoculated with bacteria. Plates were grown overnight at 32°C and the strains were scored for sensitivity to each phage by assessing clearance zones at the point of inoculation. Where phage inhibited growth, as seen by clearance of the bacterial lawn, the strain was marked as sensitive (+), and where no inhibition of growth was seen, the strain was marked as not-sensitive (-)

Bacterial Strain no.	Phi33	PTP47	PTP92	C36
2019	+	+	-	+
2020	+	+	-	+
2021	+	+	+	+
2029	+	+	-	+
2031	+	+	+	+
2039	+	+	+	+
2040	+	+	-	+
2041	+	+	+	+
2042	+	+	+	+
2045	-	-	+	-
2046	+	+	+	+
2047	+	+	+	+
2048	+	+	+	+
2049	+	+	+	+
2050	+	+	+	+
2051	+	+	-	-
2052	-	-	-	-
2053	+	+	-	+
2054	-	+	-	+
2055	+	+	-	+
2056	+	+	+	+
2057	+	+	+	+
2058	+	+	+	+
2483	-	-	+	-
2484	+	+	-	+
2705	+	+	-	+
2706	+	+	-	+
2707	+	+	+	+
2708	+	+	+	+
2709	+	+	+	+
2710	-	+	+	-
2711	+	+	+	+
2712	+	+	-	+
2713	-	+	+	+
2714	+	+	+	+
2715	+	+	+	+
2716	+	+	-	-
2717	-	+	+	+
2718	-	+	+	+
2719	+	+	-	+
2720	+	+	+	+
2721	+	+	+	+
2722	+	+	+	+
2723	+	+	-	+

**Table 2. Host range of Phi33, PTP92 and PTP93 against 35 European clinical isolates of *Pseudomonas aeruginosa*.** Strains were tested for sensitivity to each phage by dropping 10 µl of crude phage lysate onto a soft agar overlay plate inoculated with bacteria. Plates were grown overnight at 32°C and the strains were scored for sensitivity to each phage by assessing clearance zones at the point of inoculation. Where phage inhibited growth, as seen by clearance of the bacterial lawn, the strain was marked as sensitive (+), and where no inhibition of growth was seen, the strain was marked as not-sensitive (-)

Isolate	Phi33	PTP93	PTP92
2019	+	+	-
2020	+	+	-
2029	+	+	-
2040	+	+	-
2045	-	+	+
2053	+	+	-
2483	-	+	+
2484	+	+	-
2705	+	-	-
2710	-	+	+
2711	+	+	+
2712	+	+	-
2713	-	+	+
2716	+	+	-
2717	-	+	+
2718	-	+	+
2720	+	+	+
2721	+	+	+
2722	+	+	+
2723	+	-	-
2728	-	+	+
2733	+	+	-
2734	+	+	+
2740	-	+	+
2741	+	+	+
2742	+	+	+
2743	+	+	+
2747	+	+	+
2748	+	+	+
2749	+	+	-
2750	+	+	+
2752	+	+	+
2753	-	+	+
2754	+	+	+
2756	+	+	+

**Claims:**

1. A modified bacteriophage capable of infecting a plurality of different target bacteria, which bacteriophage includes a toxin gene encoding a toxin protein which is toxic to the target bacteria; wherein the bacteriophage is lytic; and wherein the bacteriophage expresses host range determinant proteins which have a plurality of bacterial host specificities.
2. A modified bacteriophage according to claim 1, wherein the toxin gene comprises an  $\alpha/\beta$  small acid-soluble spore protein (SASP) gene encoding a SASP.
3. A modified bacteriophage according to claim 1 or claim 2, wherein the SASP is: (i) SASP-C; or (ii) SASP-C from *Bacillus megaterium*.
4. A modified bacteriophage according to claim 1, wherein the bacterial host specificity of the host range determinant is within the same bacterial species.
5. A modified bacteriophage according to any one of the preceding claims, wherein the toxin gene is under the control of a constitutive promoter.
6. A modified bacteriophage according to claim 5, wherein: (i) the constitutive promoter is selected from *pdhA*, *rpsB*, *pgi*, *fda*, *lasB* and promoters having more than 90% sequence identity thereto; or (ii) the constitutive promoter is *fda*.
7. A modified bacteriophage according to any one of the preceding claims, wherein the plurality of different target bacteria:
  - (i) comprises at least one that is a *Pseudomonas* bacteria;
  - (ii) comprises at least one that is *Pseudomonas aeruginosa*;
  - (iii) is a plurality of different *Pseudomonas* bacteria; or
  - (iv) is a plurality of different *Pseudomonas* bacteria comprising *Pseudomonas aeruginosa*.
8. A modified bacteriophage according to any one of the preceding claims, wherein the host range determinant proteins: (i) have a broad host range as defined by more than 50% of a collection of at least 35 and preferably more than 50 clinical isolates, from a

plurality of different infection sites and including a range of antibiotic resistance phenotypes; or (ii) comprise tail fibre proteins.

9. A modified bacteriophage according to claim 8, wherein: (i) each tail fibre protein comprises a receptor binding region for binding to the target bacteria and a region linking the receptor binding region to the body of the bacteriophage; or (ii) each tail fibre protein comprises a receptor binding region for binding to the target bacteria and a region linking the receptor binding region to the body of the bacteriophage, wherein the receptor binding region is a C-terminal receptor binding region and the region linking the C-terminal receptor binding region to the body of the bacteriophage is an N-terminal region.

10. A modified bacteriophage according to claim 9, wherein: (i) the N-terminal region comprises amino acids 1 to 628 of the tail fibre protein and the C-terminal region comprises amino acids 629 to 964 of the tail fibre protein, based on the amino acid sequence of bacteriophage Phi33 tail fibre protein as set out in SEQ ID NO 50; (ii) the C-terminal region has no more than 96% amino acid sequence identity with the C-terminal region of the tail fibre protein of bacteriophage Phi33 having SEQ ID NO 50; and/or (iii) the C-terminal region is from a tail fibre protein having SEQ ID NO 50, SEQ ID NO 49, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 52, SEQ ID NO 51, SEQ ID NO 58, SEQ ID NO 56, SEQ ID NO 53, SEQ ID NO 55, SEQ ID NO 57, SEQ ID NO 54, or SEQ ID NO 48 .

11. A modified bacteriophage according to claim 10, wherein the C-terminal region amino acid sequence has less than 80%, less than 70%, or less than 60% sequence identity with the C-terminal region of the tail fibre protein of bacteriophage Phi33 having SEQ ID NO: 50.

12. A modified bacteriophage according to any one of claims 9 to 11, wherein: (i) the N-terminal region has at least 95% amino acid sequence identity with the N-terminal region of the tail fibre protein of bacteriophage Phi33 having SEQ ID NO 50; or (ii) the N-terminal region is from a tail fibre protein having SEQ ID NO 50, SEQ ID NO 49, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 52, SEQ ID NO 51, SEQ ID NO 58, SEQ ID NO 56, SEQ ID NO 53, SEQ ID NO 55, SEQ ID NO 57, SEQ ID NO 54, or SEQ ID NO 48; or (iii) the bacteriophage is bacteriophage PTP387, which comprises Phi33, modified to carry *fda*-SASP-C (*Pseudomonas aeruginosa* codon optimised

sequence), wherein Phi33 is a bacteriophage comprising a tail fibre protein having SEQ ID NO: 50.

13. A modified bacteriophage according to any one of the preceding claims wherein: (i) the host range determinant proteins are hybrid host range determinant proteins each comprising an amino acid sequence from a plurality of different bacteriophages; or (ii) the host range determinant proteins are hybrid host range determinant proteins each comprising an amino acid sequence from a plurality of different bacteriophages, wherein the hybrid host range determinant proteins comprise hybrid tail fibre proteins comprising a C-terminal receptor binding region and an N-terminal region linking the C-terminal receptor binding region to the body of the bacteriophage, wherein the C-terminal and N-terminal regions are each from a different bacteriophage.

14. A modified bacteriophage according to claim 13, wherein each hybrid tail fibre protein comprises: (i) the C-terminal receptor binding region of the tail fibre protein having SEQ ID NO 57 and the N-terminal region of the tail fibre protein having SEQ ID NO 50; or (ii) the C-terminal receptor binding region of the tail fibre protein having SEQ ID NO 54 and the N-terminal region of the tail fibre protein having SEQ ID NO 50.

15. A modified bacteriophage according to any one of claims 1 to 14, wherein: (i) the bacteriophage expresses a plurality of different host range determinants, and wherein each host range determinant has a different bacterial host specificity; or (ii) the bacteriophage expresses a plurality of different host range determinants, wherein each host range determinant has a different bacterial host specificity, and wherein each host range determinant protein comprises a tail fibre protein having a sequence selected from SEQ ID NO 50, SEQ ID NO 49, SEQ ID NO 45, SEQ ID NO 46, SEQ ID NO 47, SEQ ID NO 52, SEQ ID NO 51, SEQ ID NO 58, SEQ ID NO 56, SEQ ID NO 53, SEQ ID NO 55, SEQ ID NO 57, SEQ ID NO 54, SEQ ID NO 48 and a sequence having amino acids 1-638 of SEQ ID NO 50 and amino acids 629-962 of SEQ ID NO 54.

16. A modified bacteriophage according to any one of the preceding claims in admixture with at least one other modified bacteriophage which is capable of infecting target bacteria, which includes a SASP gene encoding a SASP which is toxic to the target bacteria.



17. A modified bacteriophage according to any one of the preceding claims, for use as a medicament.
18. A method of treating or preventing a bacterial infection or of therapeutic inhibition or prevention of bacterial cell growth, the method comprising administering a modified bacteriophage according to any one of the preceding claims to a subject.
19. A method according to claim 18, wherein: (i) the bacterial infection comprises a localised organ infection or a multi-organ infection; (ii) the bacterial infection comprises a topical infection, oral infection, respiratory infection, eye infection or blood stream infection; and/or (iii) the subject is a human.
20. A composition for inhibiting or preventing bacterial cell growth, which comprises a modified bacteriophage according to any one of claims 1 to 16, and a carrier therefor.
21. A composition according to claim 20, which comprises: (i) a plurality of the modified bacteriophages, at least two of which have different host specificities, or (ii) bacteriophage PTP387, bacteriophage PTP388 and bacteriophage PTP389, wherein bacteriophage PTP387 comprises Phi33, modified to carry *fda*-SASP-C (*P. aeruginosa* codon optimised sequence); bacteriophage PTP388 comprises Phi33 modified to carry *fda*-SASP-C (*P. aeruginosa* codon optimised sequence) and carries a Phi33 tail fibre in which amino acids 629-964 are replaced by amino acids 629-962 of the PTP92 tail fibre (SEQ ID NO:54); and bacteriophage PTP389 comprises Phi33 modified to carry *fda*-SASP-C (*P. aeruginosa* codon optimised sequence) and carries a Phi33 tail fibre in which amino acids 629-964 are replaced by amino acid 629-962 of the PTP47 tail fibre (SEQ ID NO:57) , wherein Phi33 is a bacteriophage comprising a tail fibre protein having SEQ ID NO: 50.
22. A composition according to claim 20 or claim 21, which is formulated: (i) for pharmaceutical use; and/or (ii) for topical use, or for delivery to the respiratory tract.
23. Use of a modified bacteriophage according to any one of claims 1 to 16, as a bacterial decontaminant.
24. Use according to claim 23, which comprises treating surface bacterial contamination, land remediation or water treatment.

25. Use of a modified bacteriophage according to any one of claims 1 to 16 in the manufacture of a medicament for treating or preventing a bacterial infection, or for the therapeutic inhibition or prevention of bacterial cell growth, in a subject.

Figure 1 (Part 1 of 2)

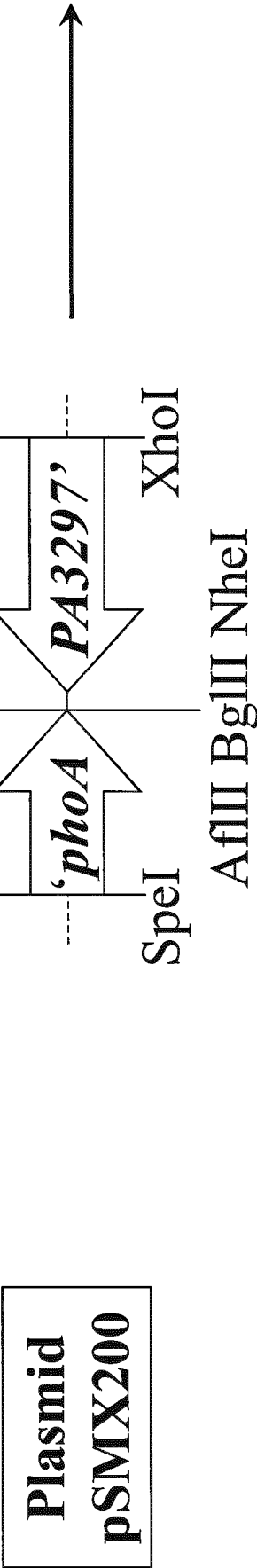


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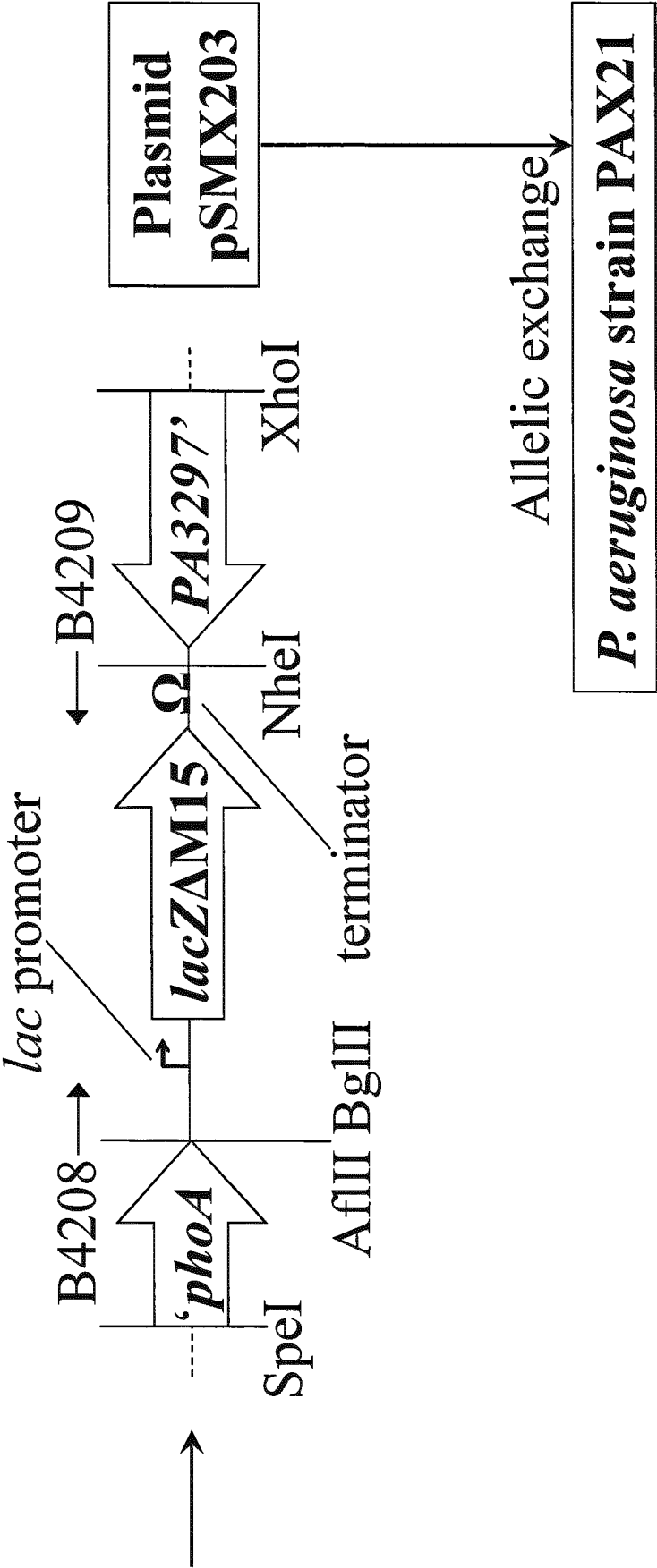


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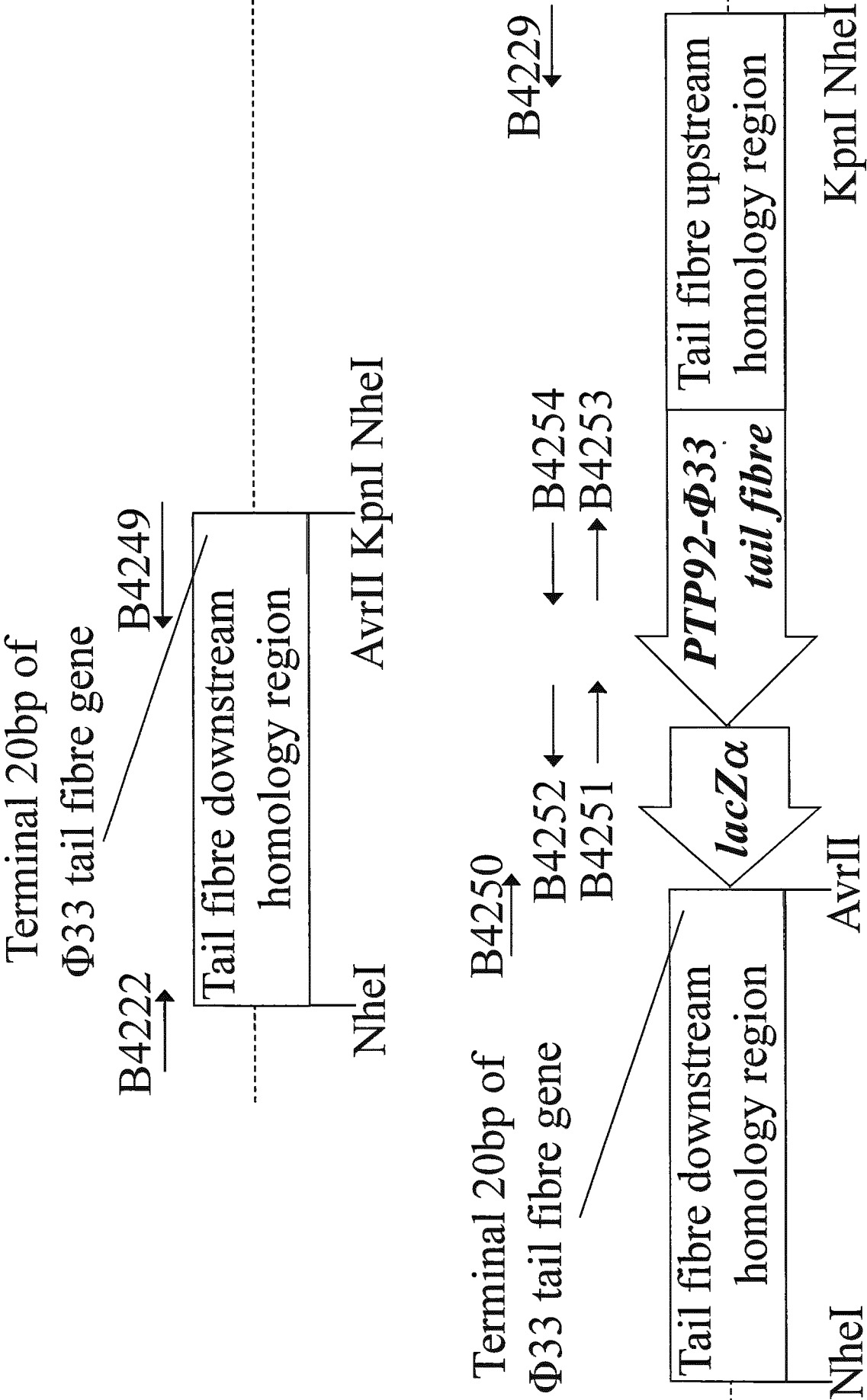


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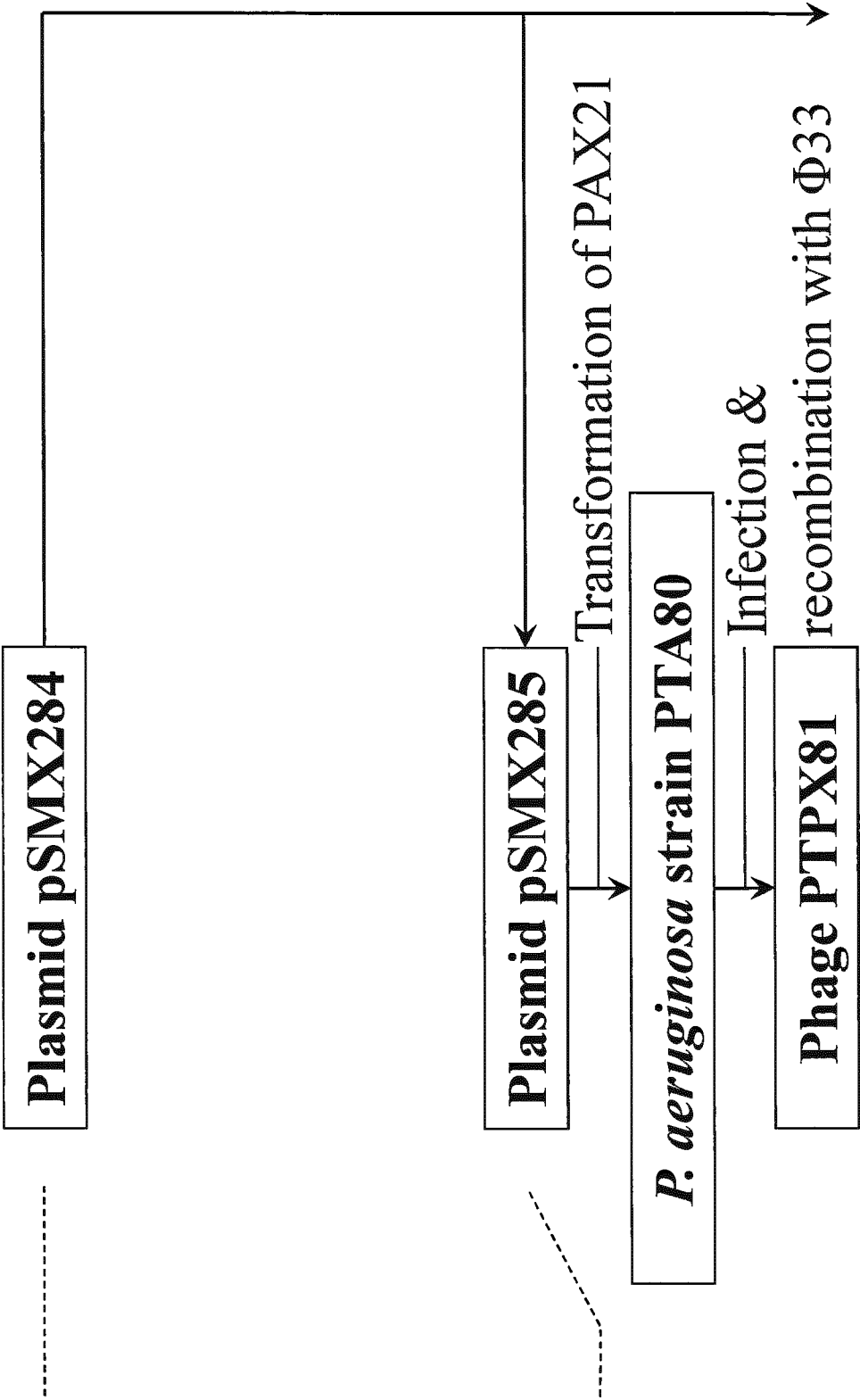


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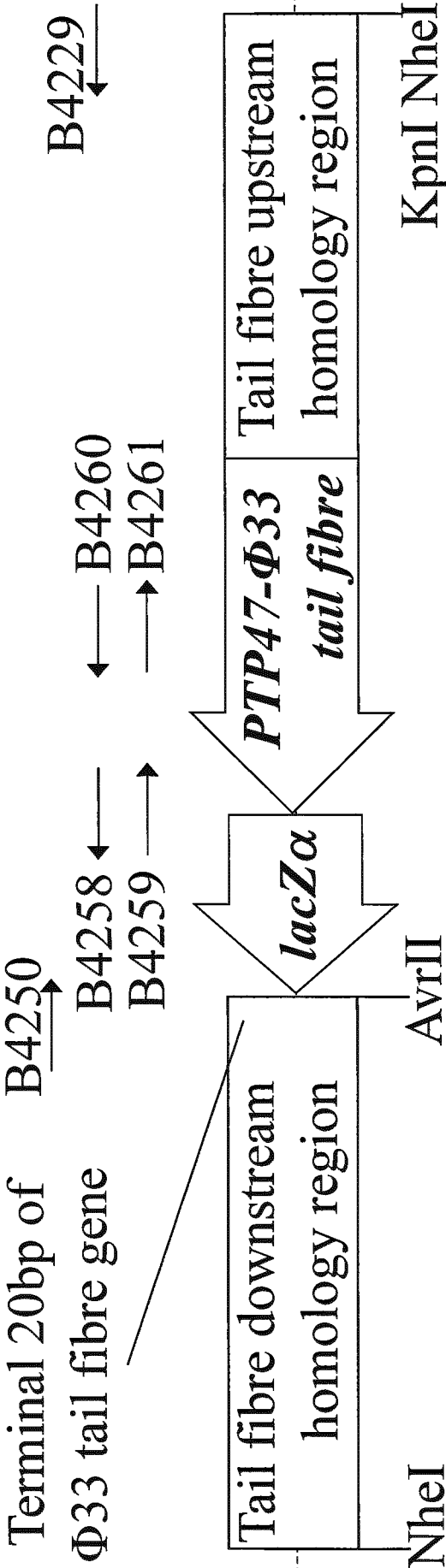


Figure 2 (Part 4 of 4)





Figure 3 (Part 1 of 4)

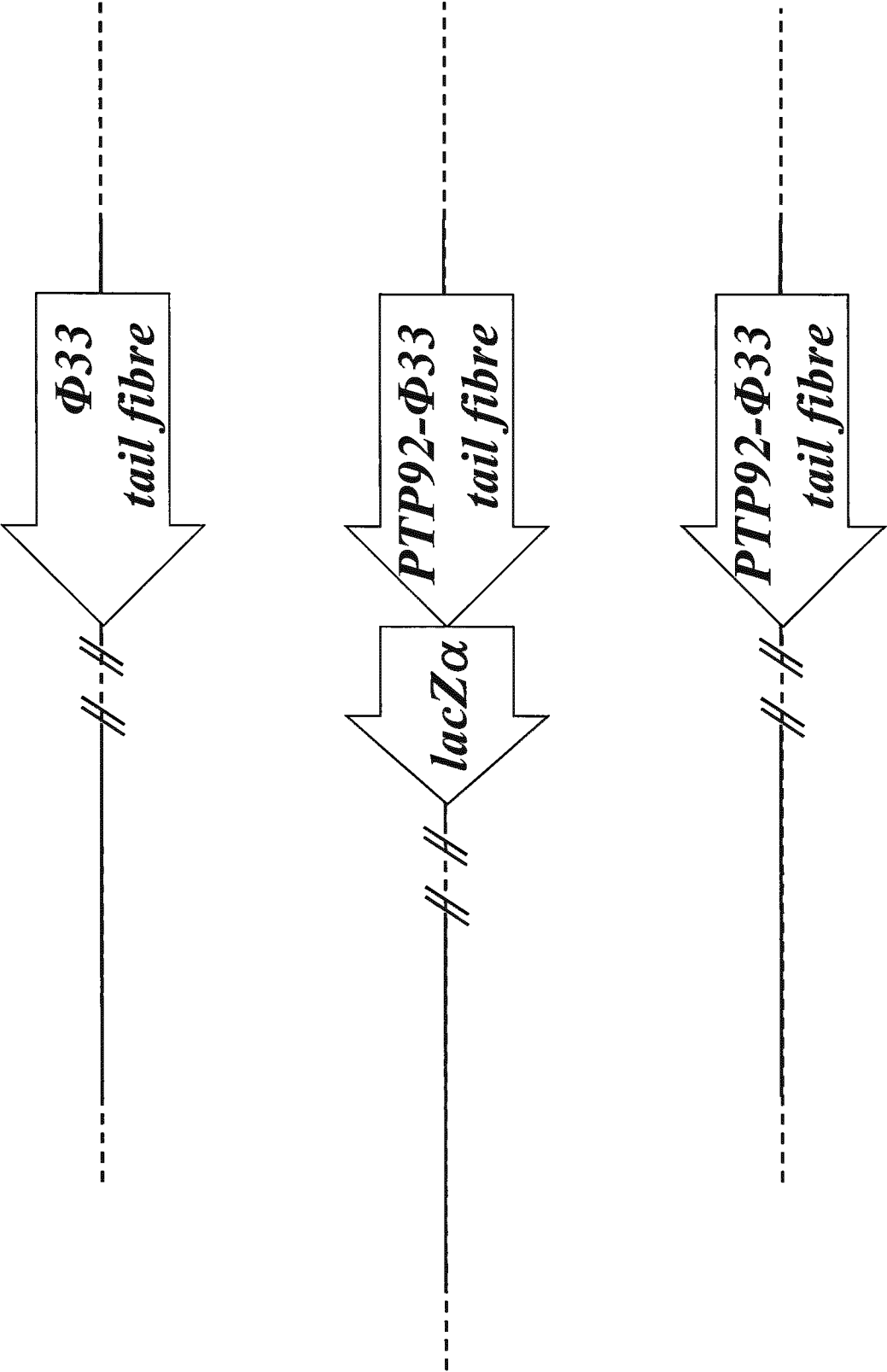


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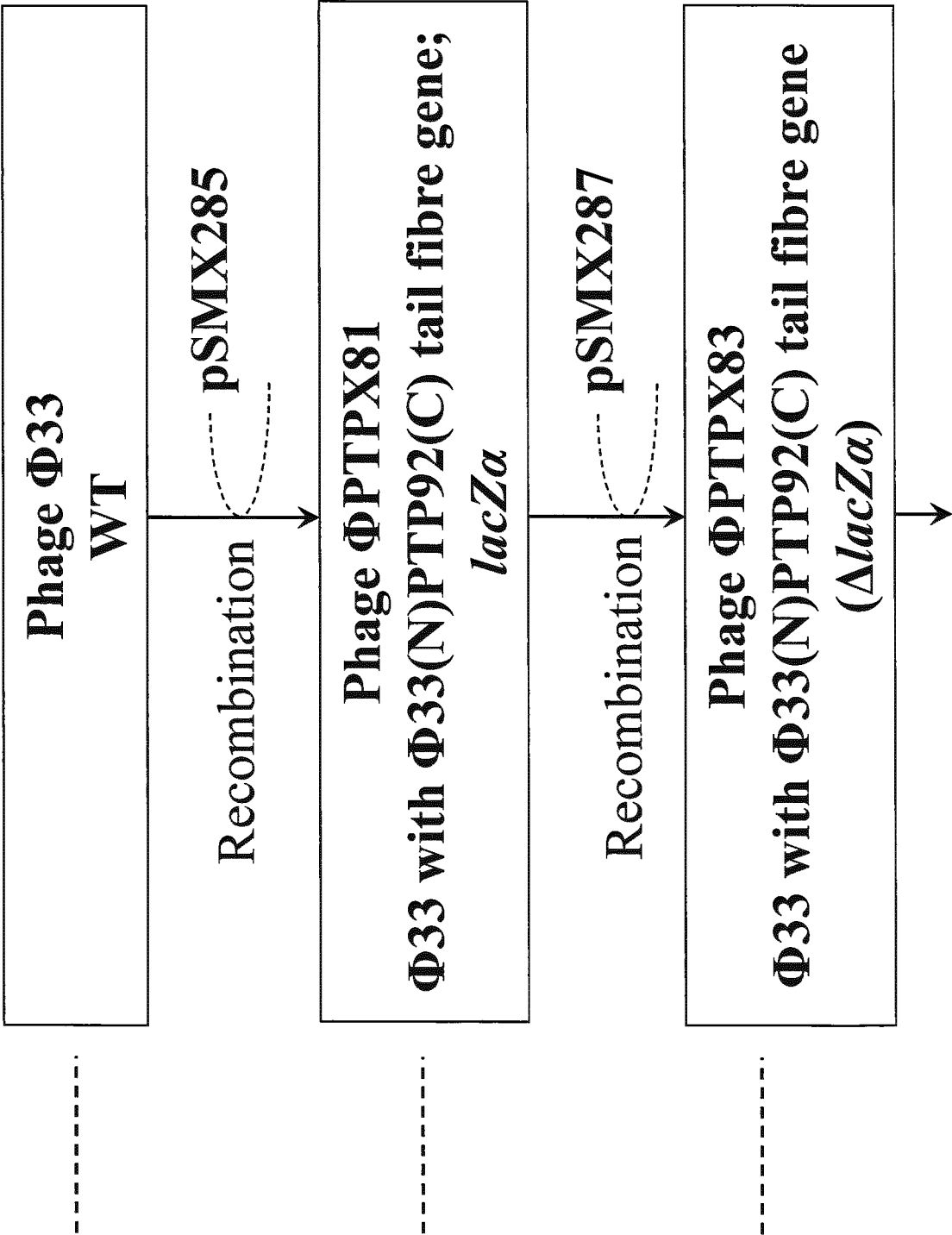


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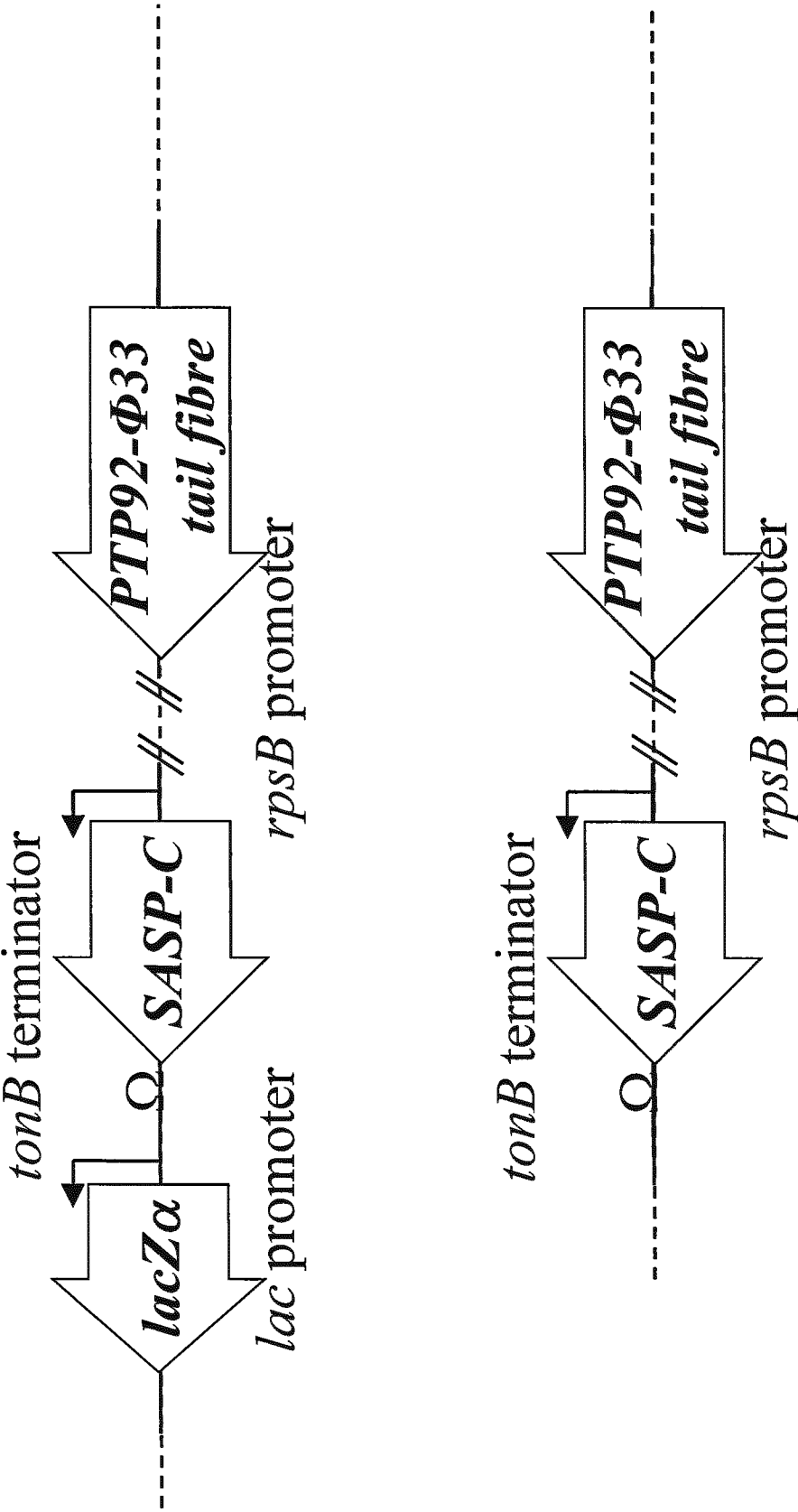


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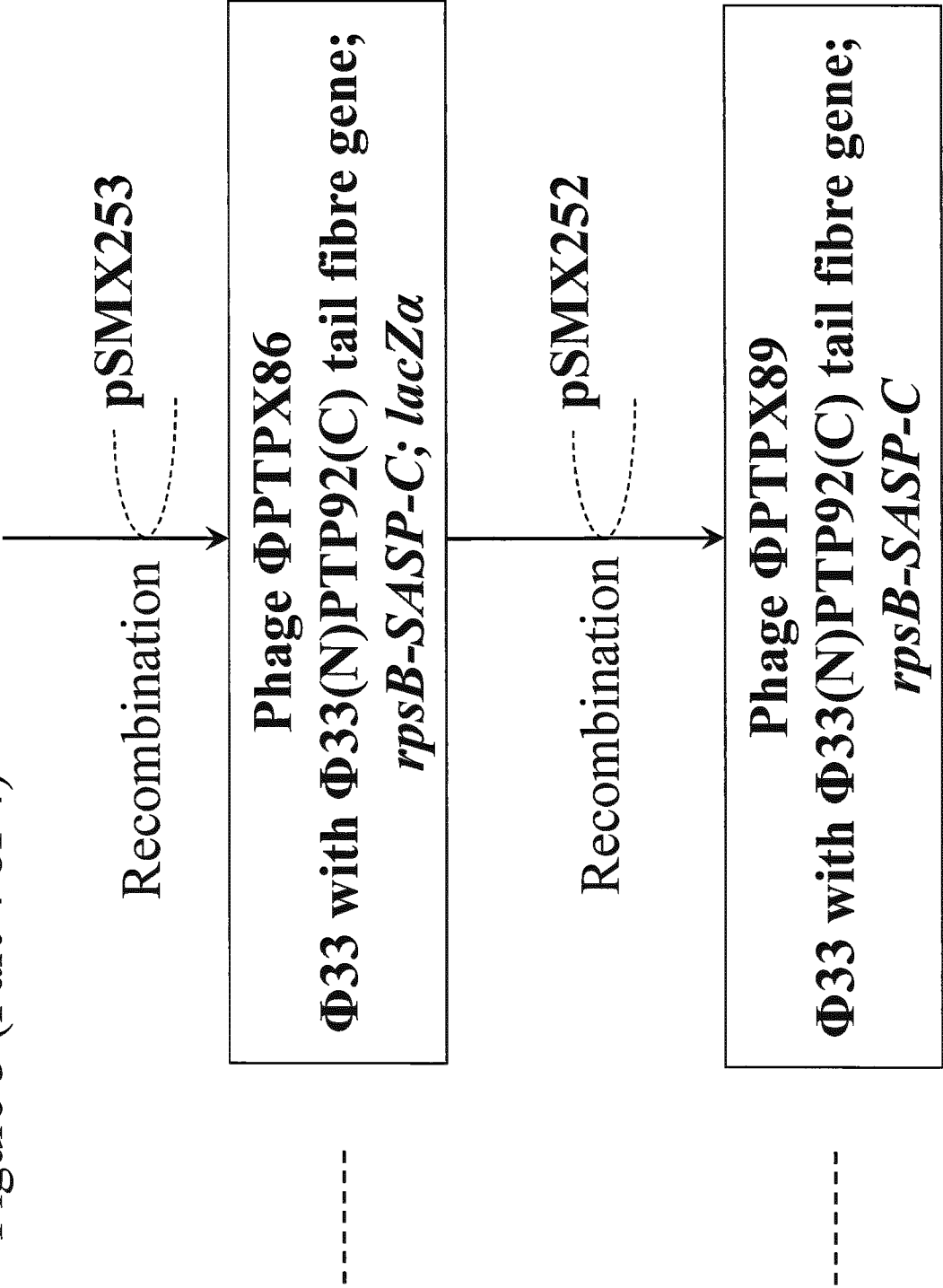


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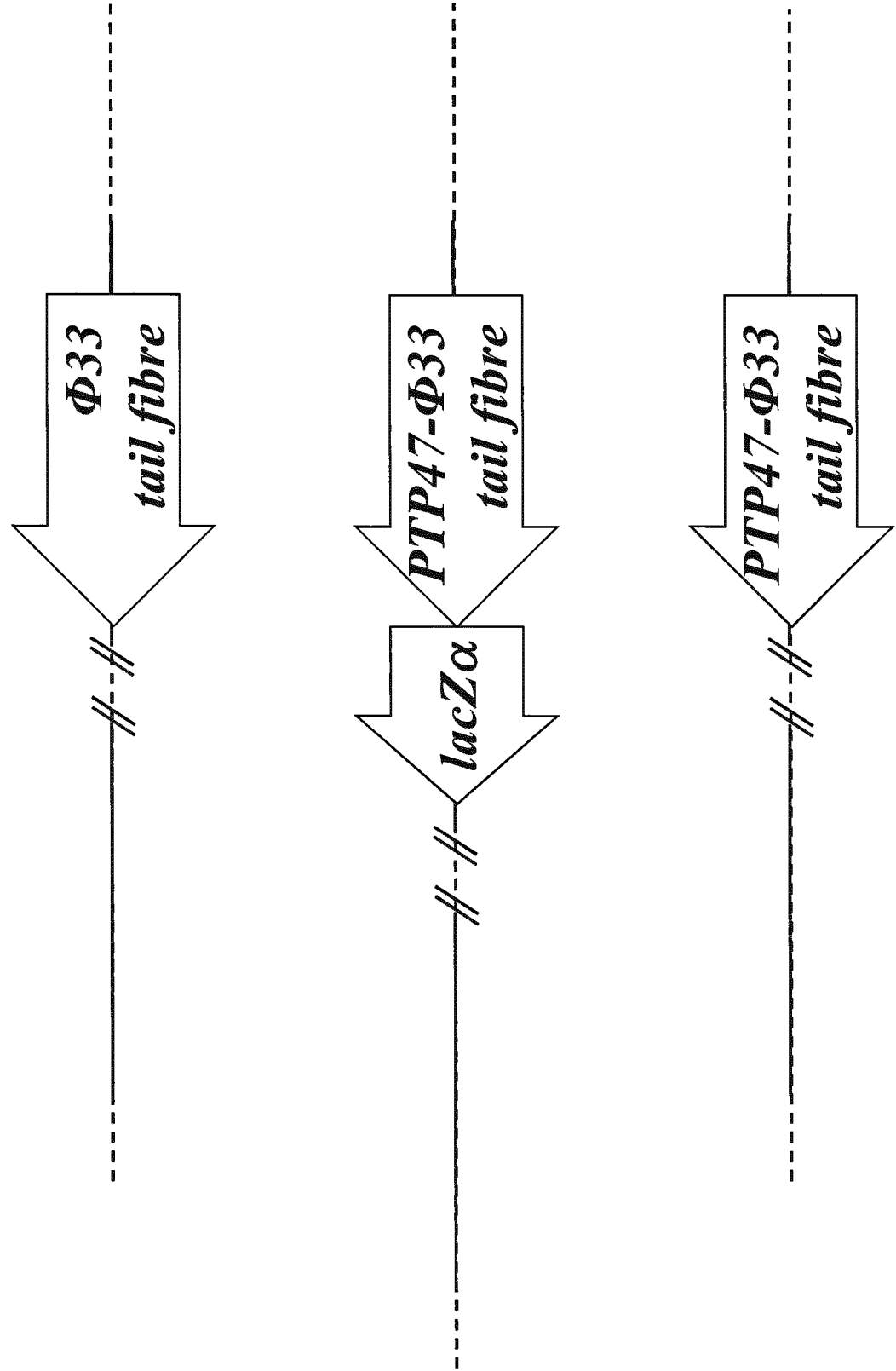


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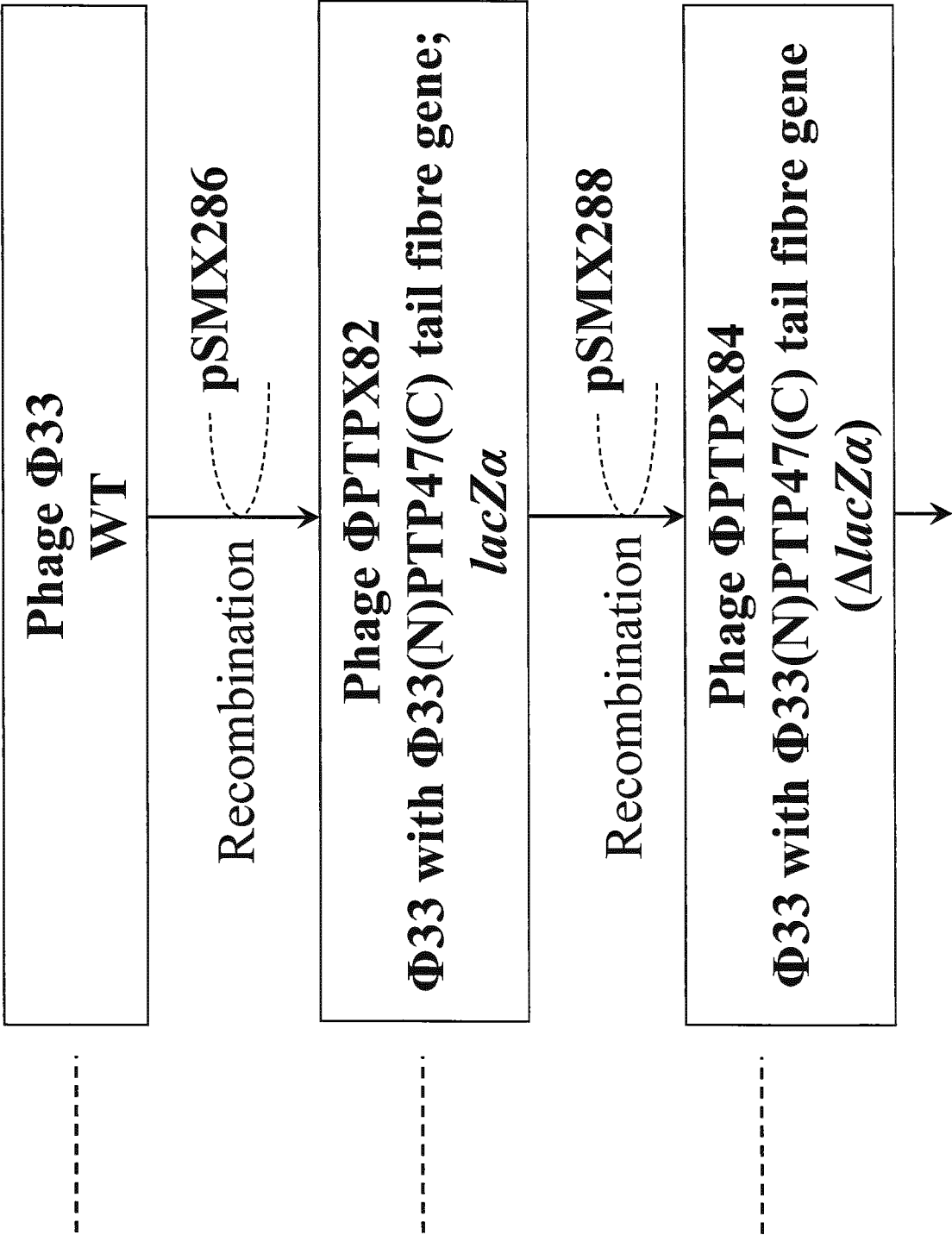


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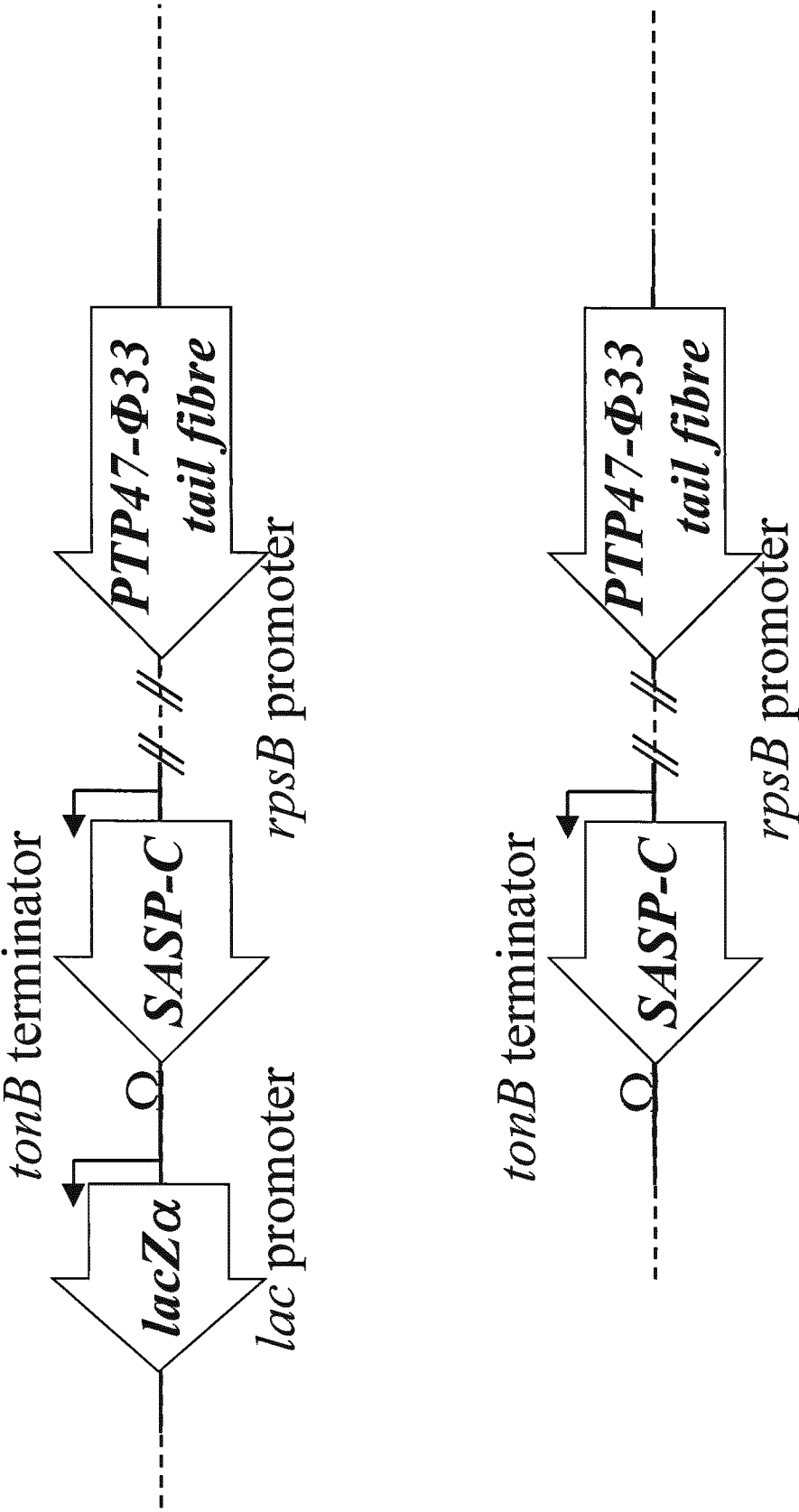


Figure 4 (Part 4 of 4)





Figure 5 (Part 1 of 2)

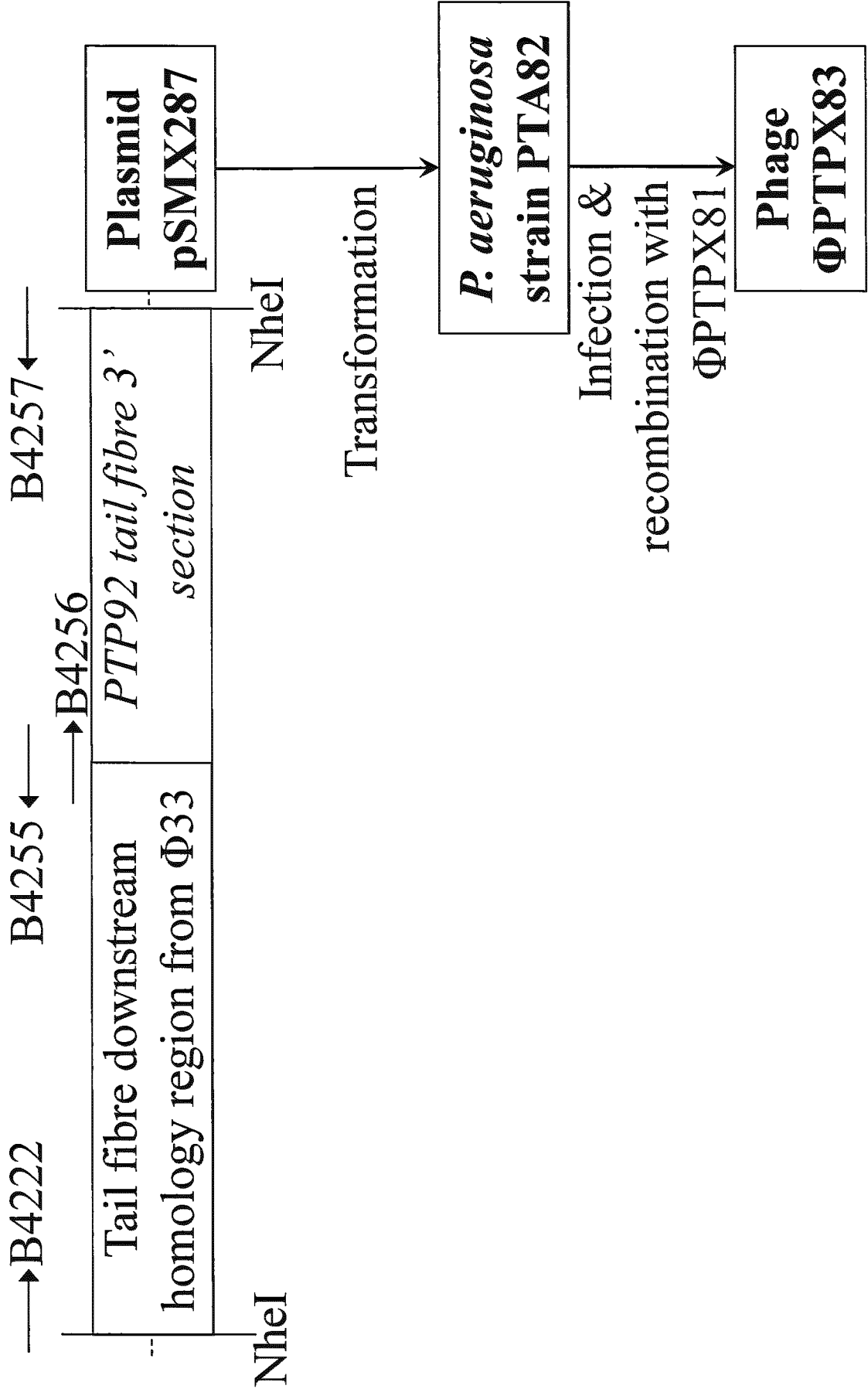


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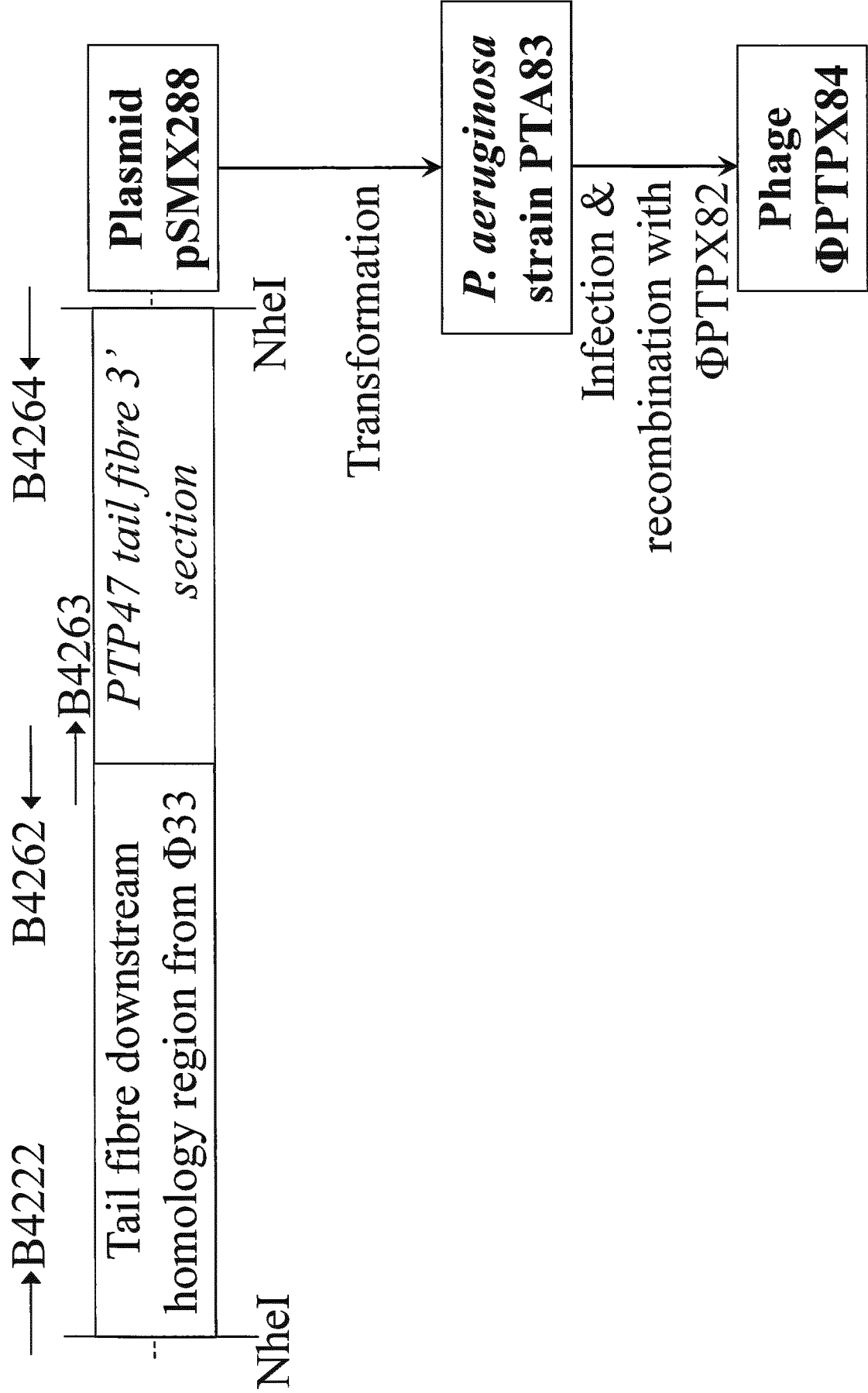


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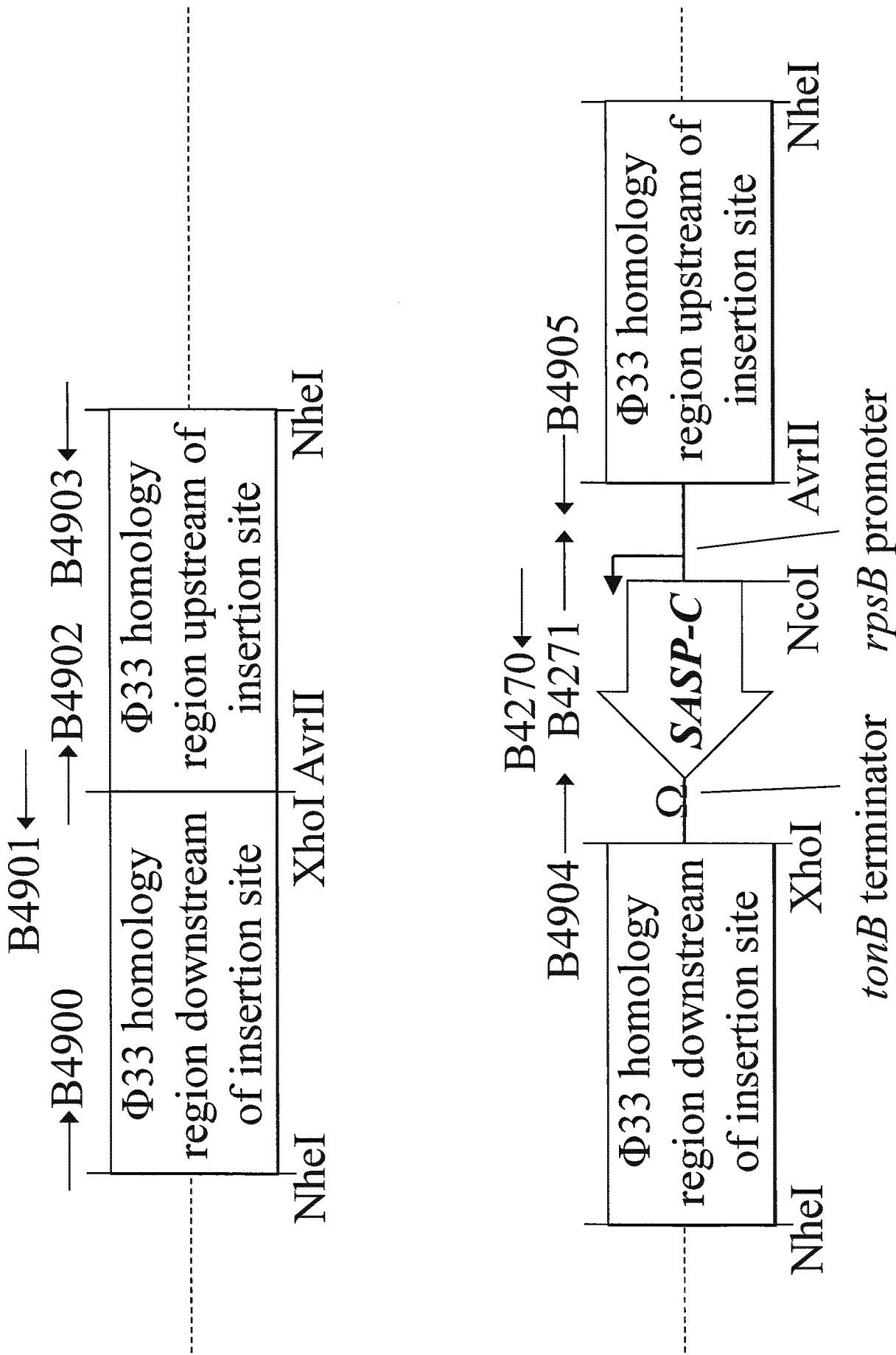


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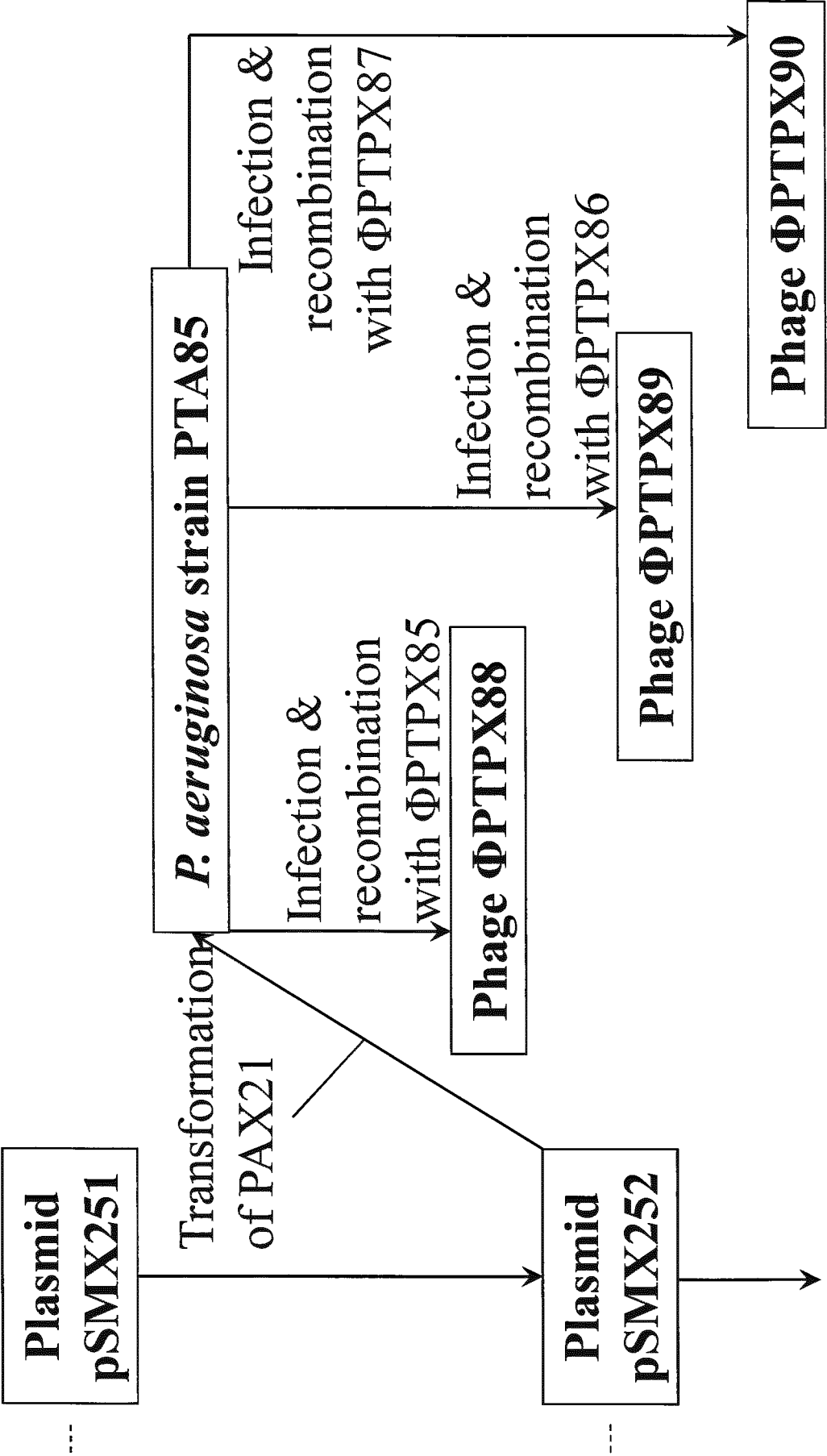


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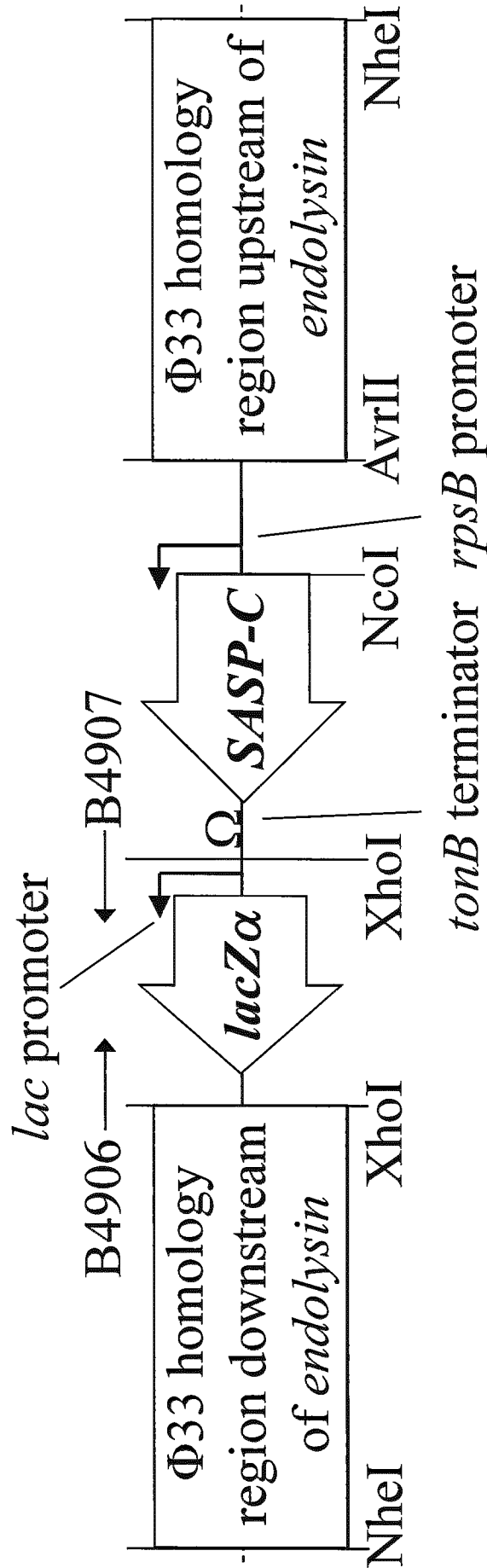


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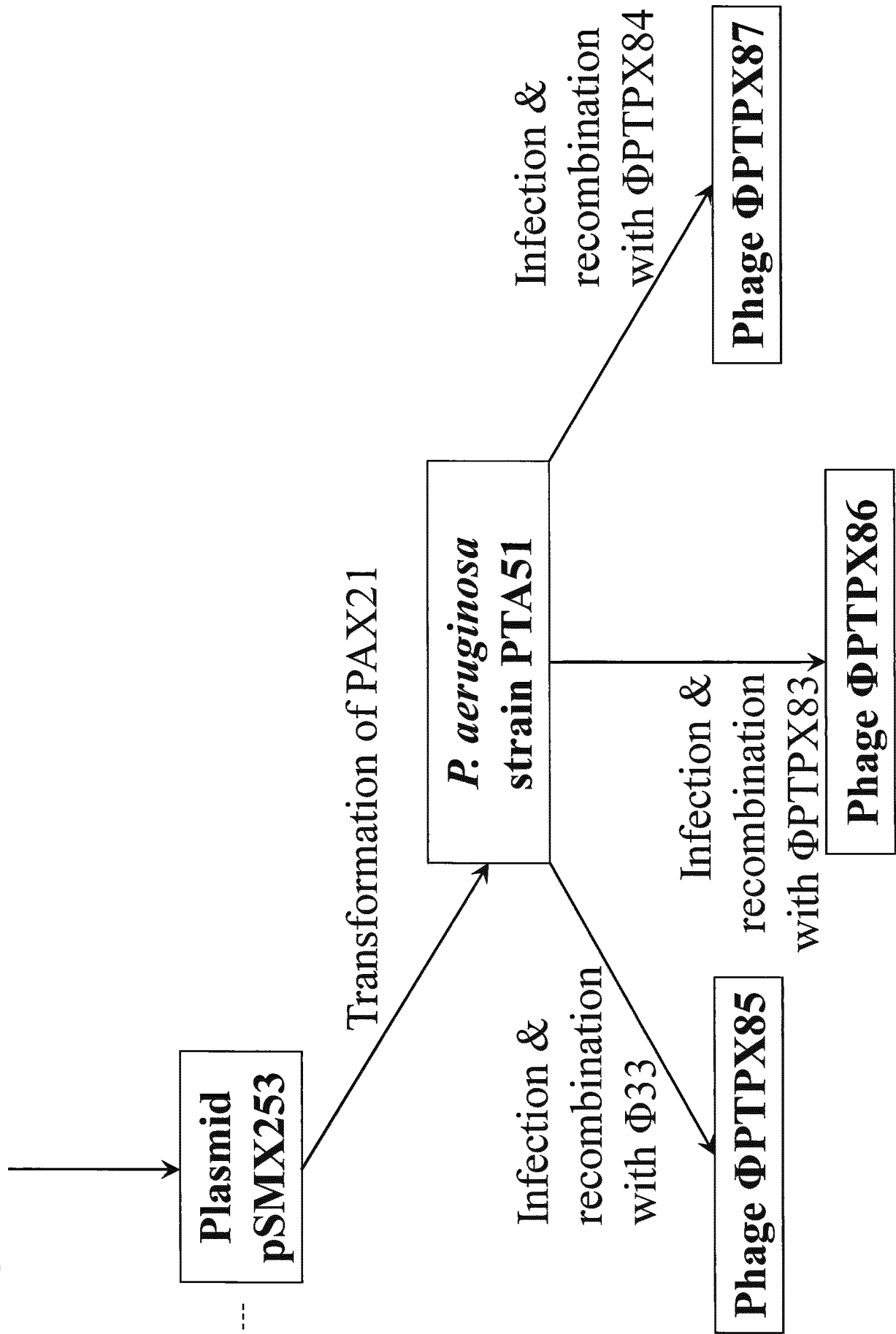


Figure 7 (Part 1 of 2)

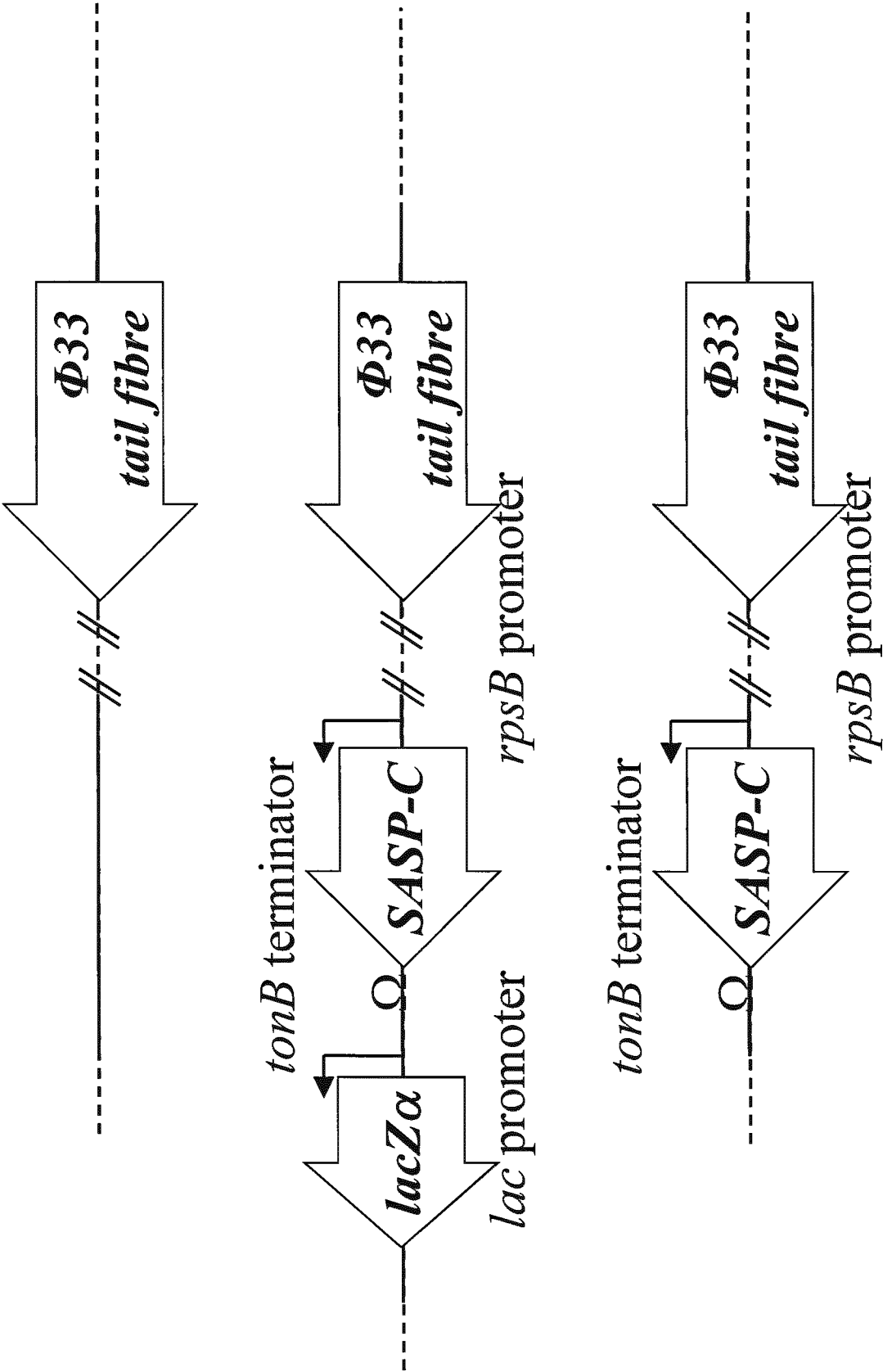


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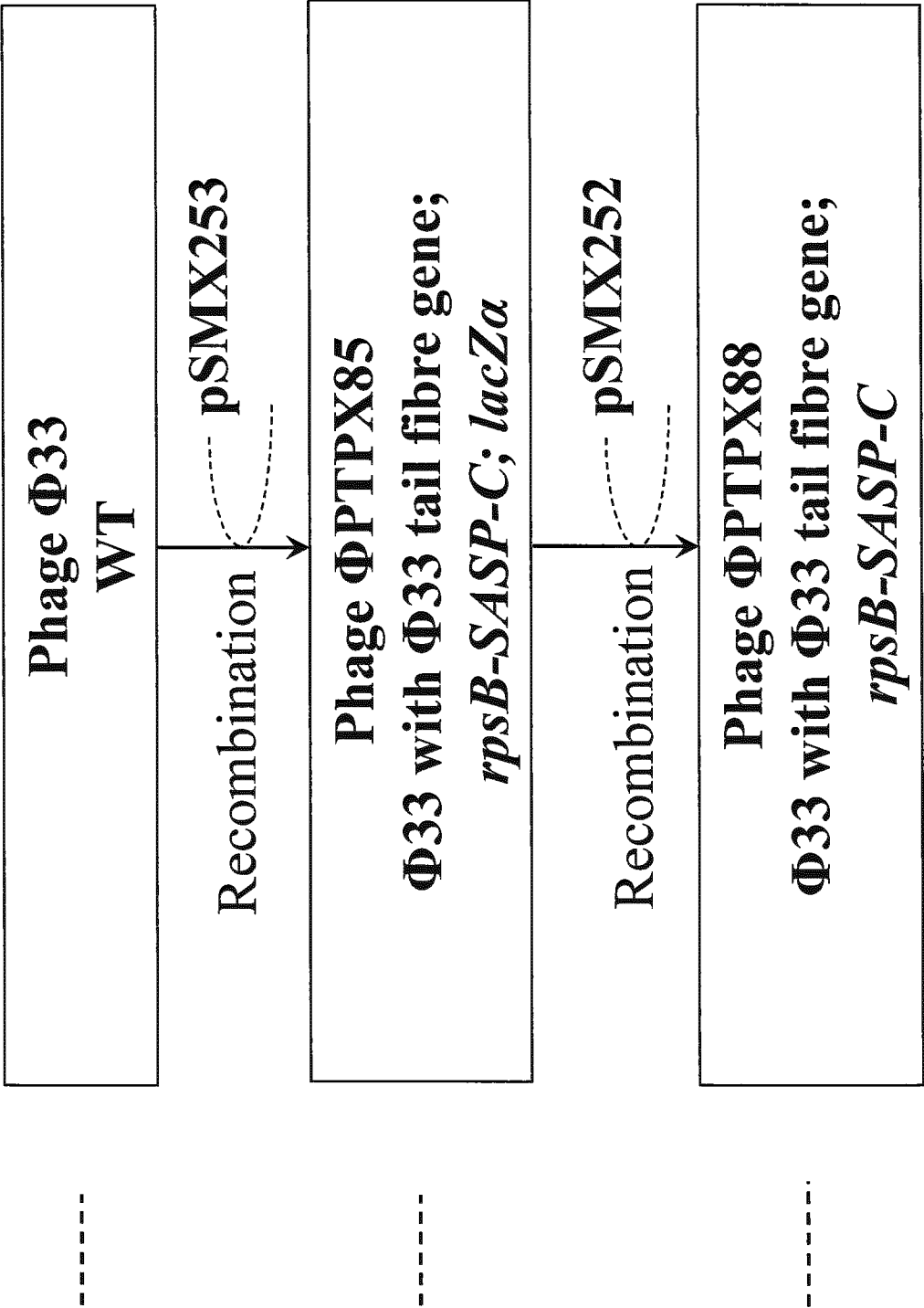




Figure 8 (Part 1 of 4)

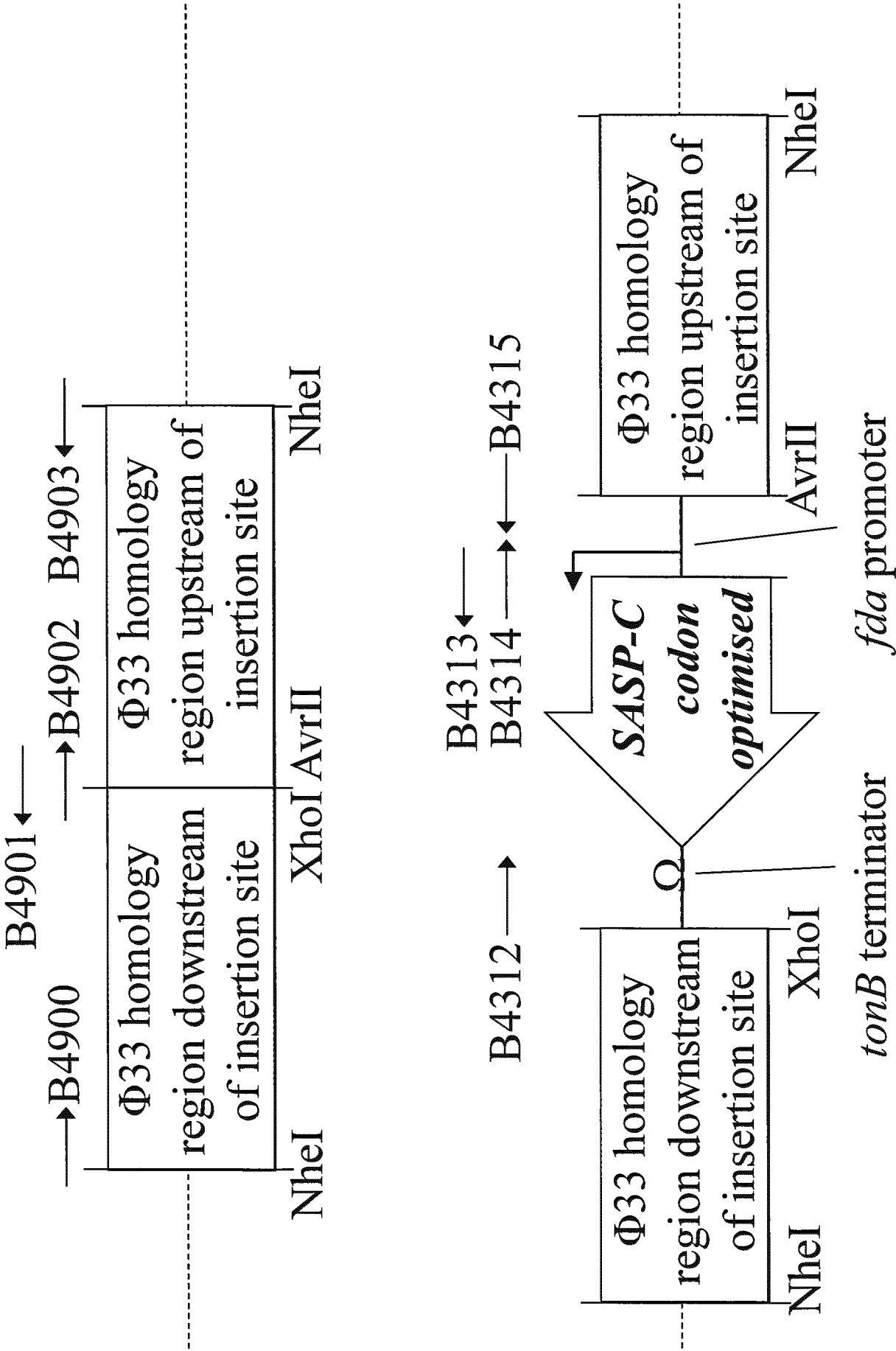


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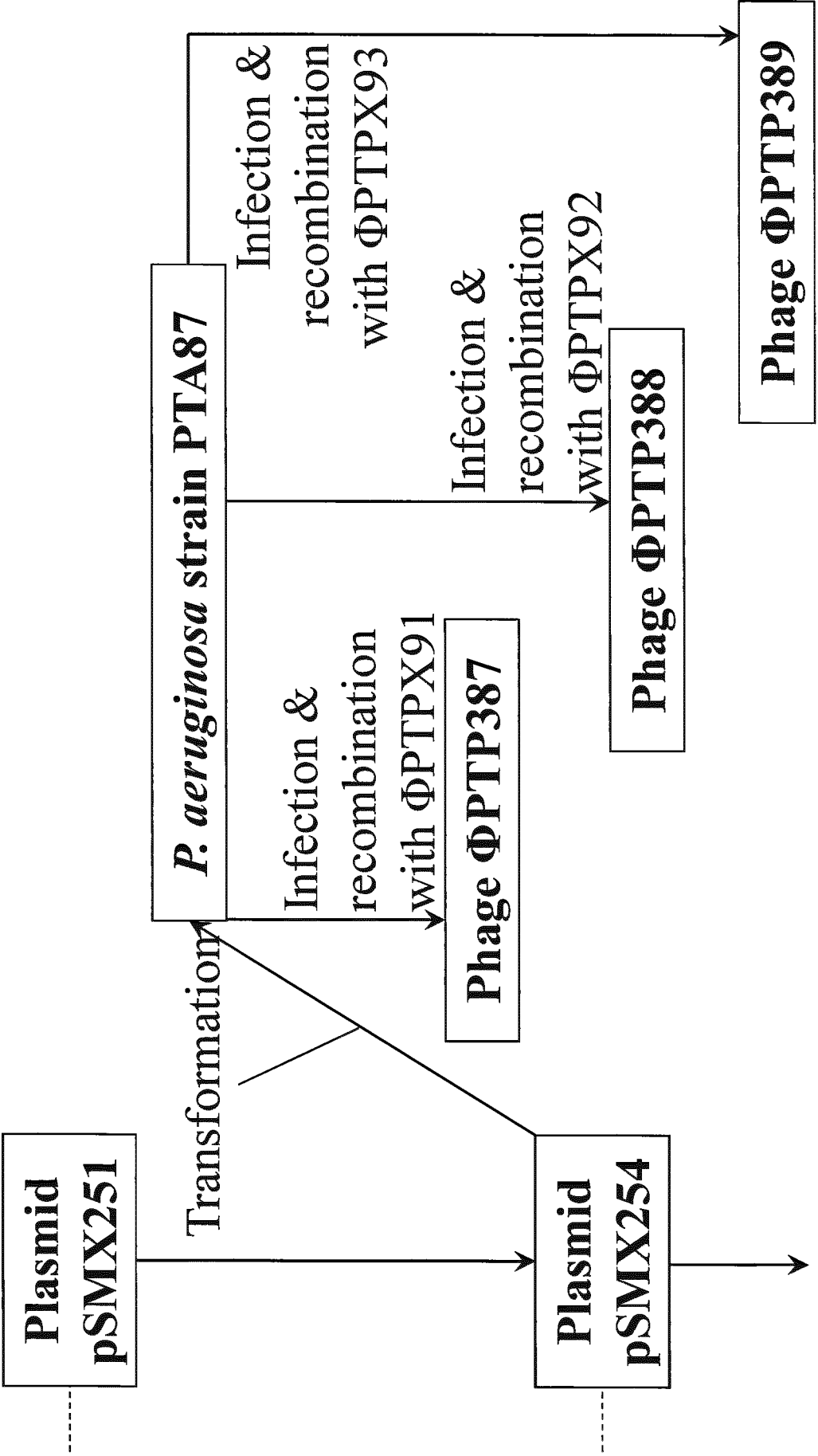


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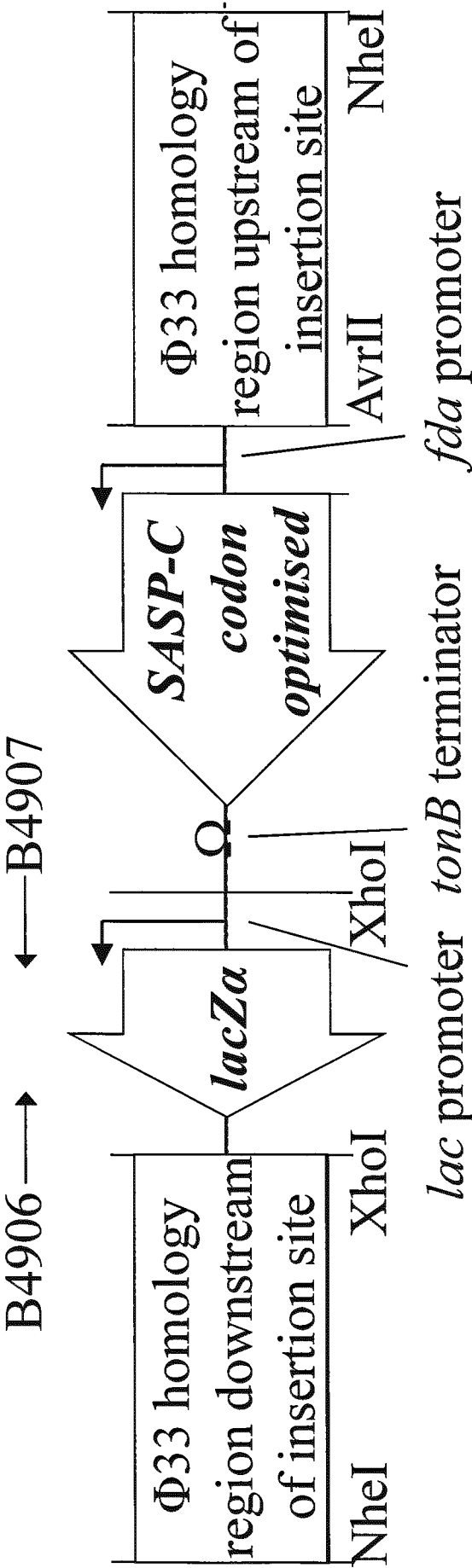


Figure 8 (Part 4 of 4)

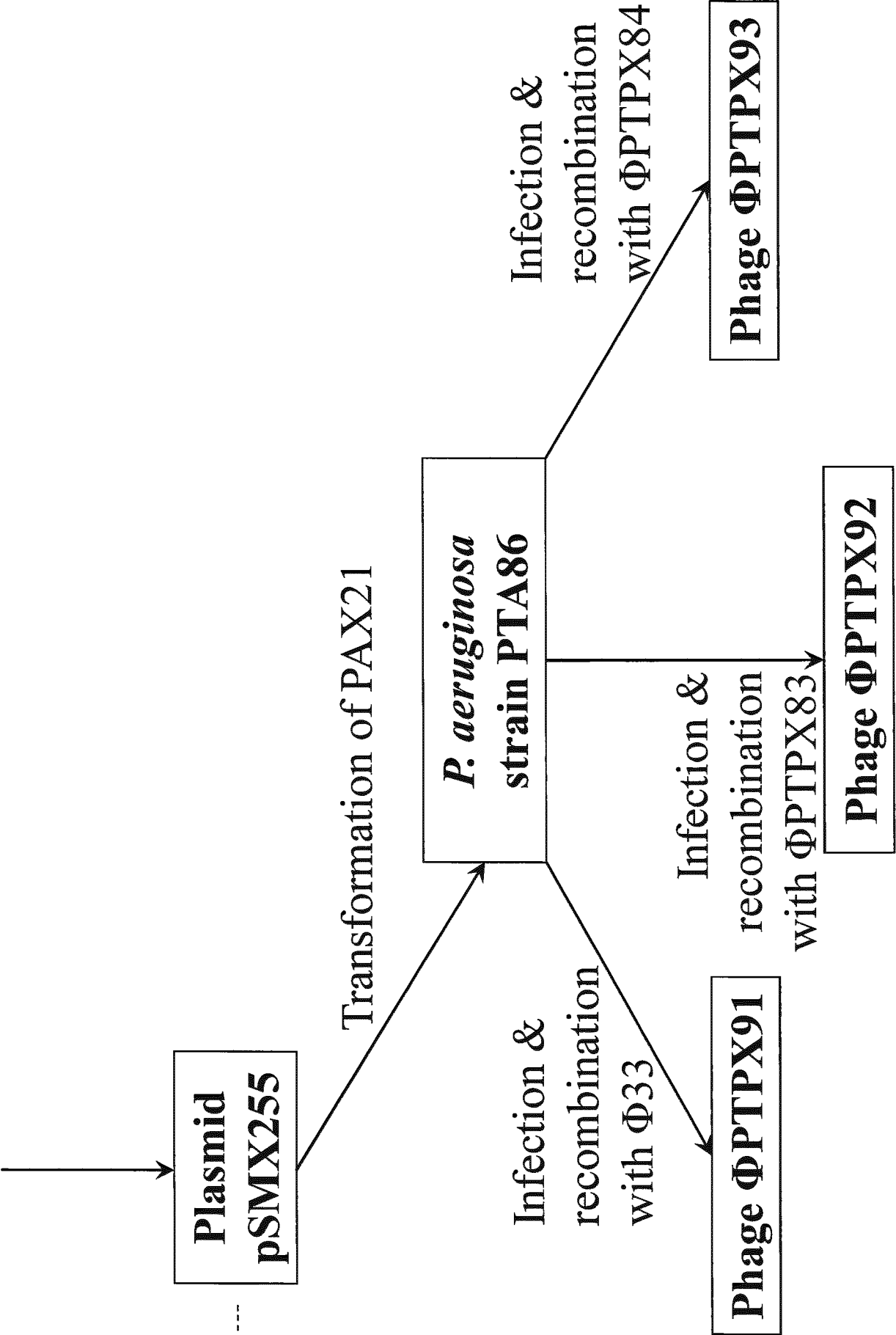


Figure 9

```
>codon_optimised_SASP-C
ATGGCCAAC TACCAGAA CCGAGCAA CCGCAAC AGCAGCA AC
AAGCTGGT CCGCGCC GCGCCAG GCGCCAT CCGACC AGATG
AAGTTCGA GATCGCG AGCGAGT TCGGCGT GAACCT CGGCCG
GACGCCAC CGCCCGT GCGCAAC GGTCTCG GTCGGC GGAATC
ACCAAGCG CCTGGTG CAGCTGG CGGAAC AGAACCT GGGCGG C
AAGTACTGA
```

Figure 10 (Part 1 of 4)

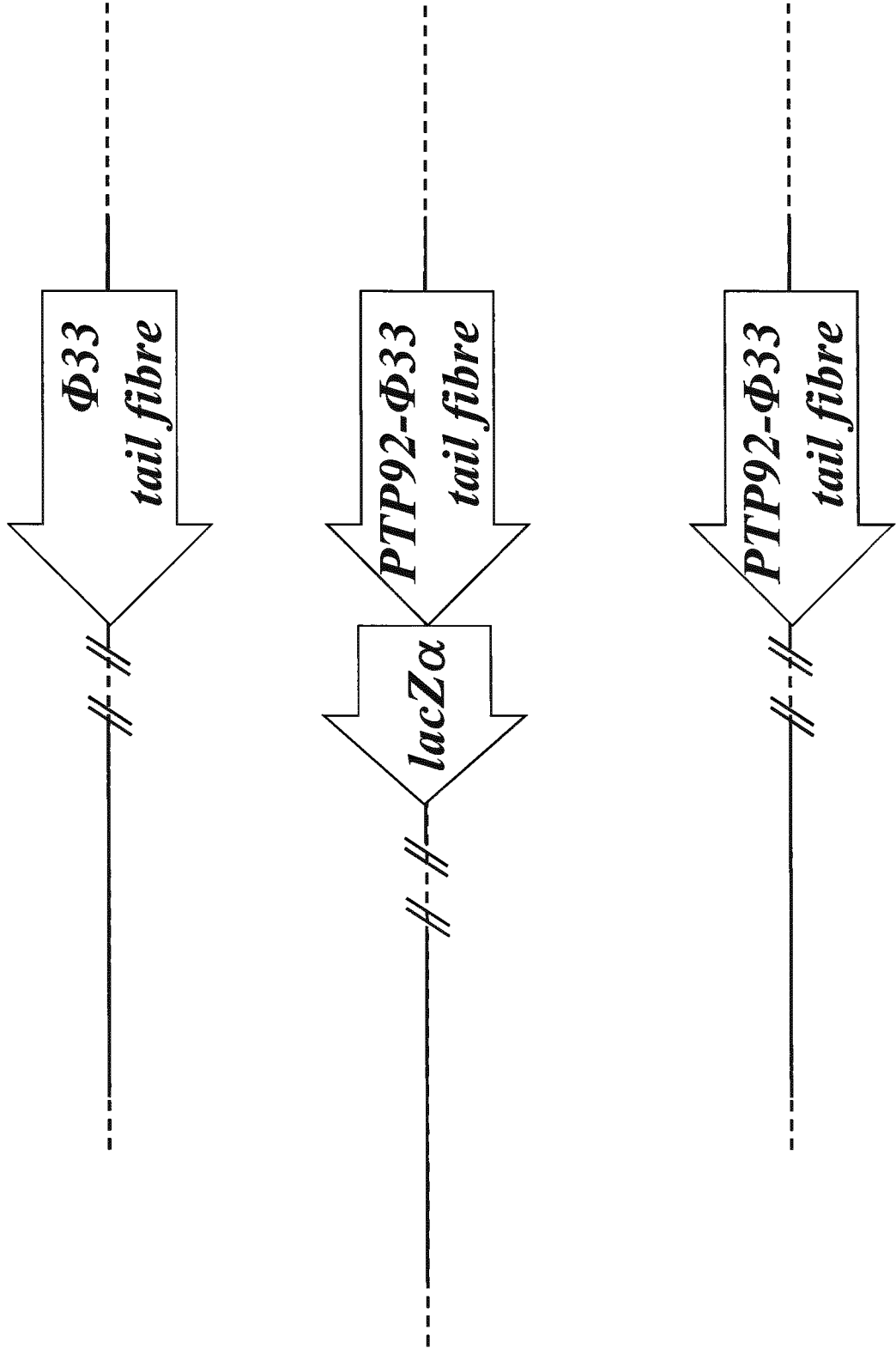


Figure 10 (Part 2 of 4)

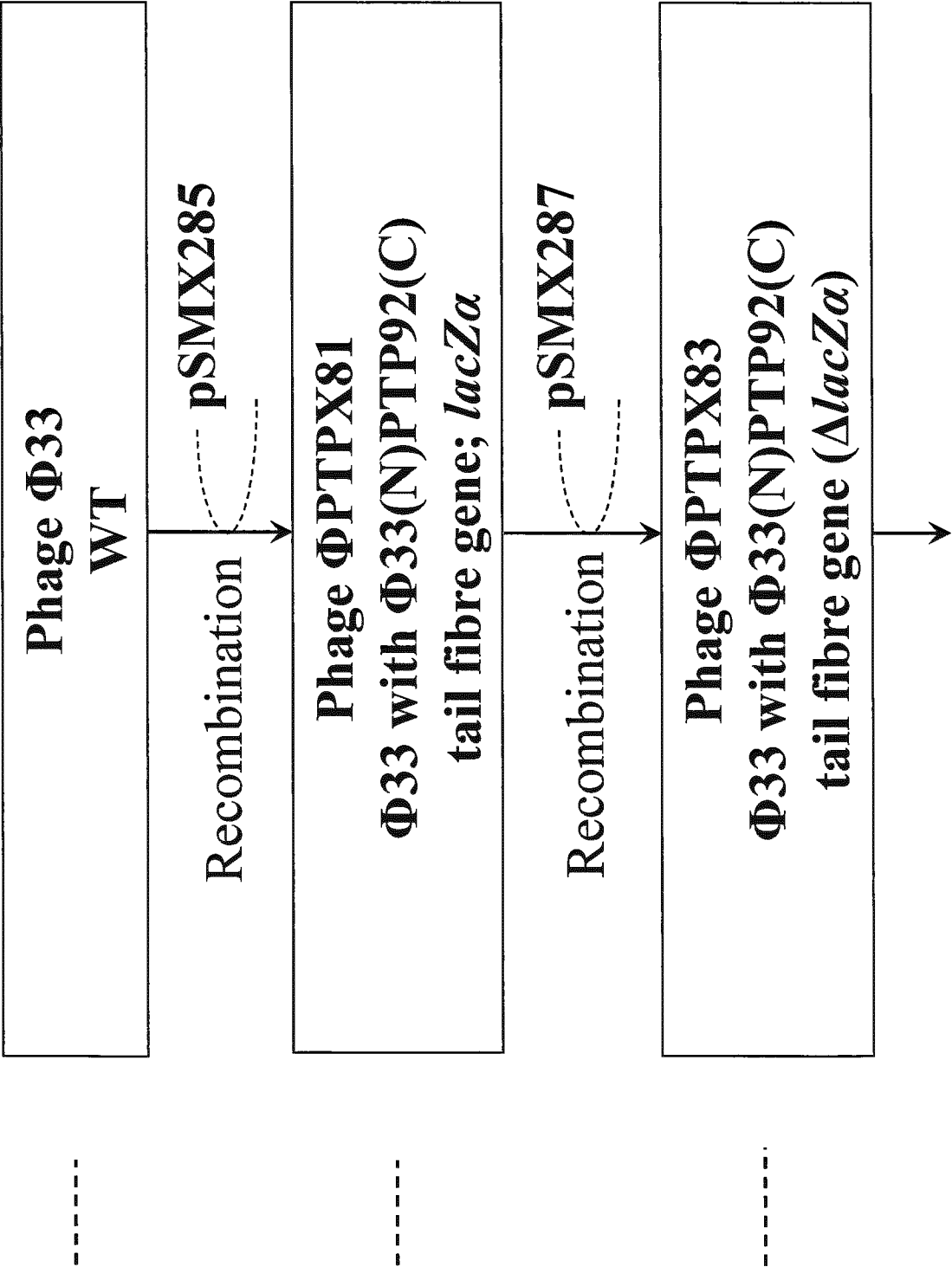


Figure 10 (Part 3 of 4)

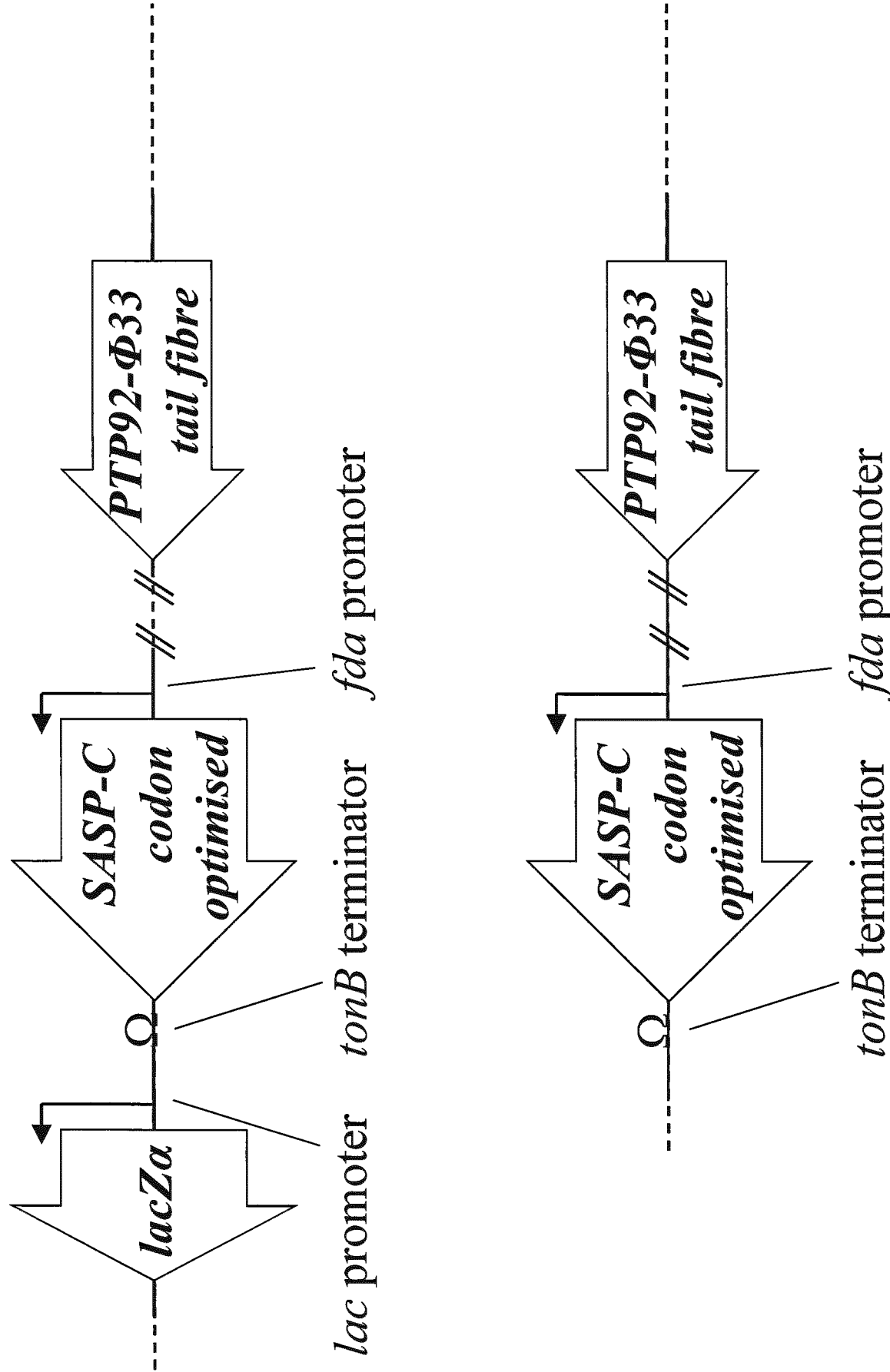




Figure 10 (Part 4 of 4)

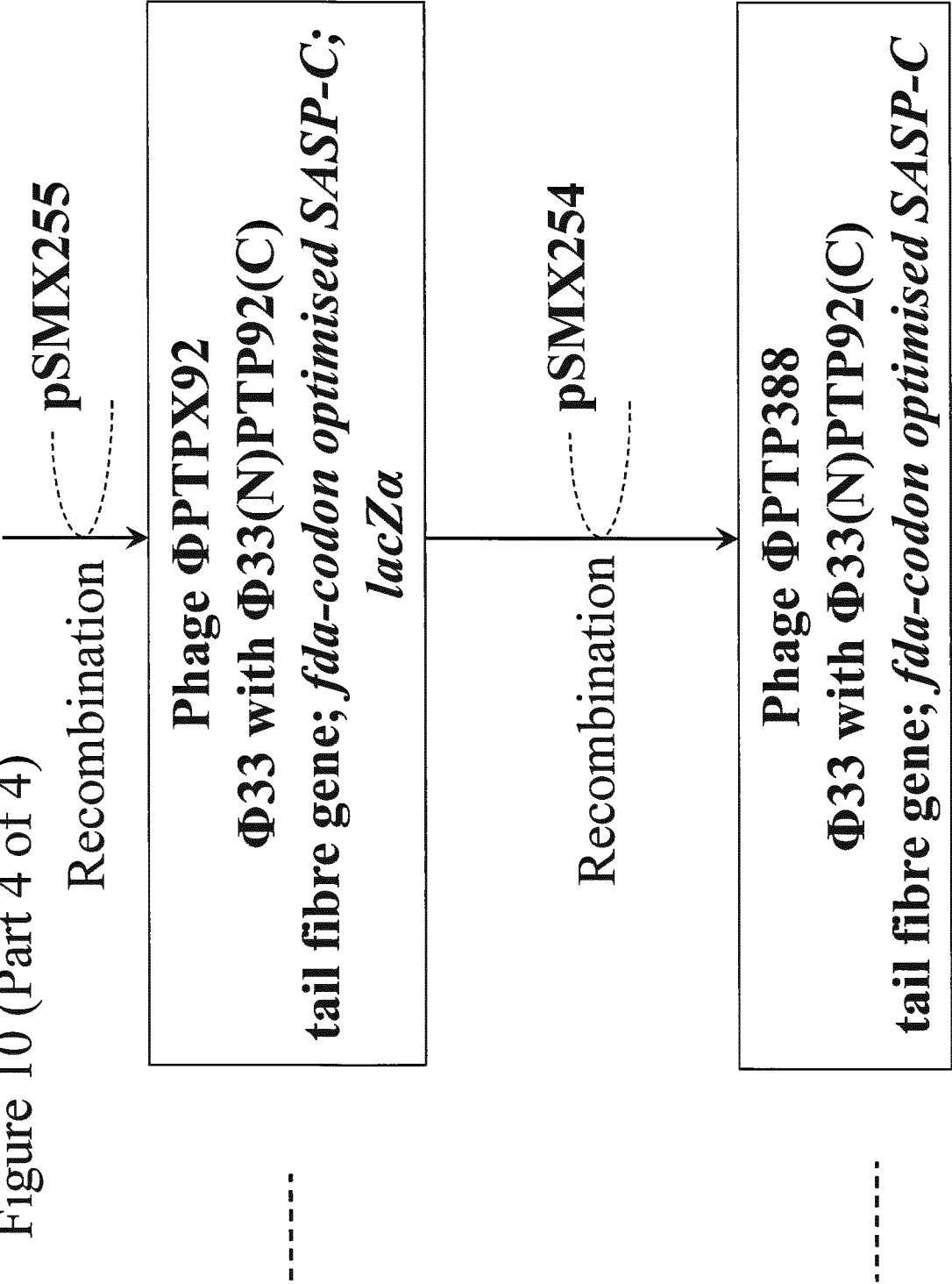


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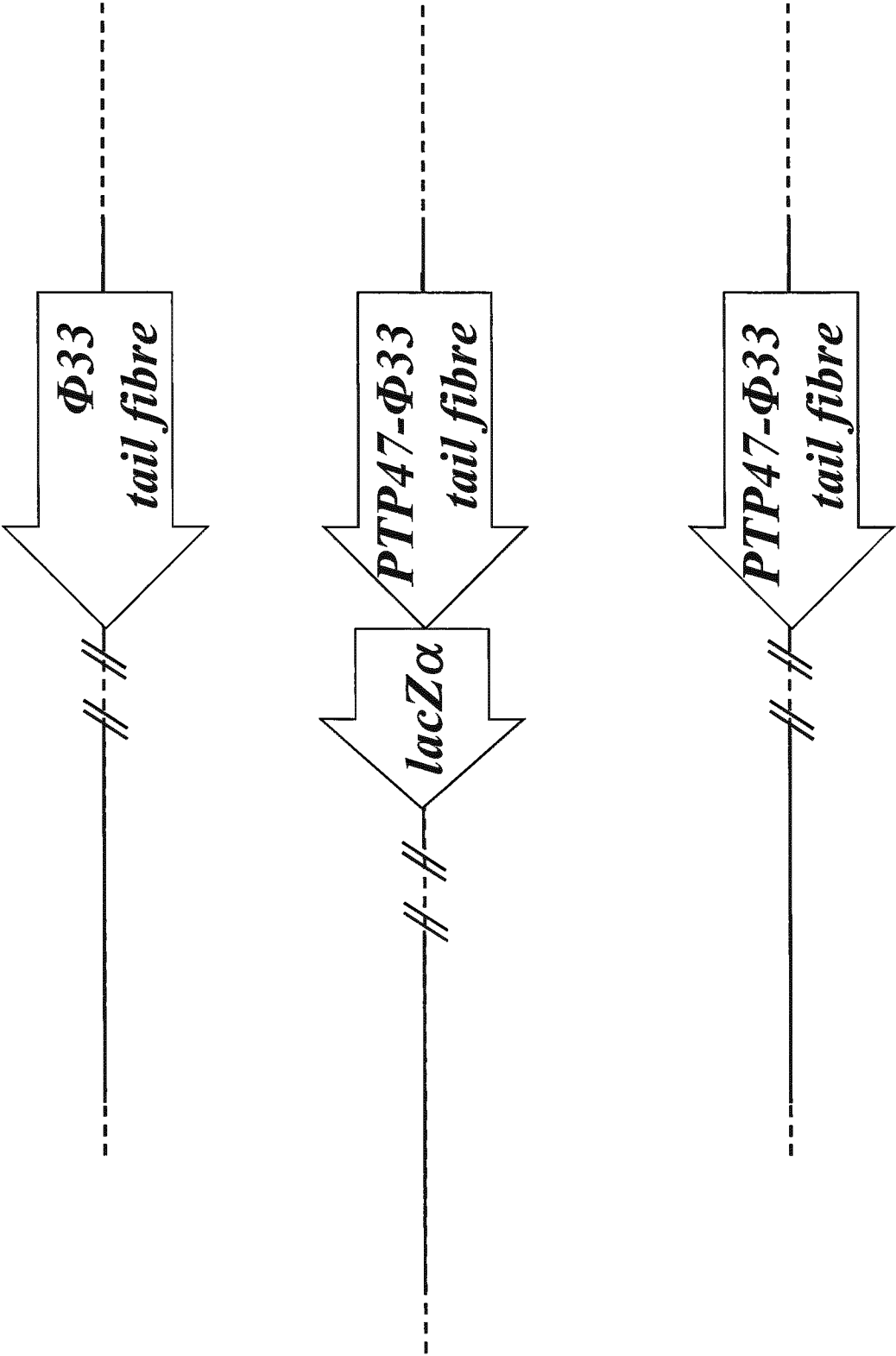


Figure 11 (Part 2 of 4)

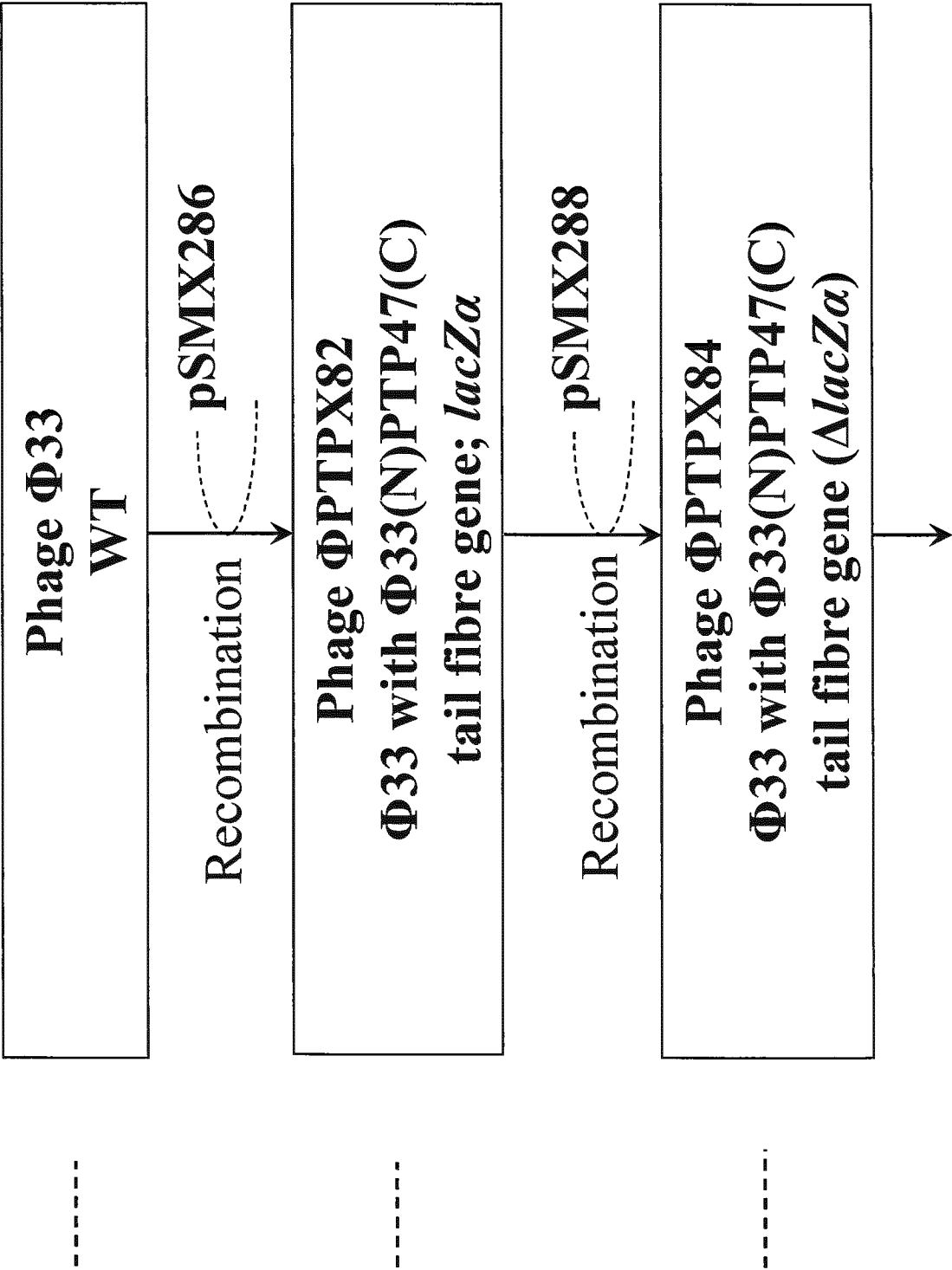


Figure 11 (Part 3 of 4)

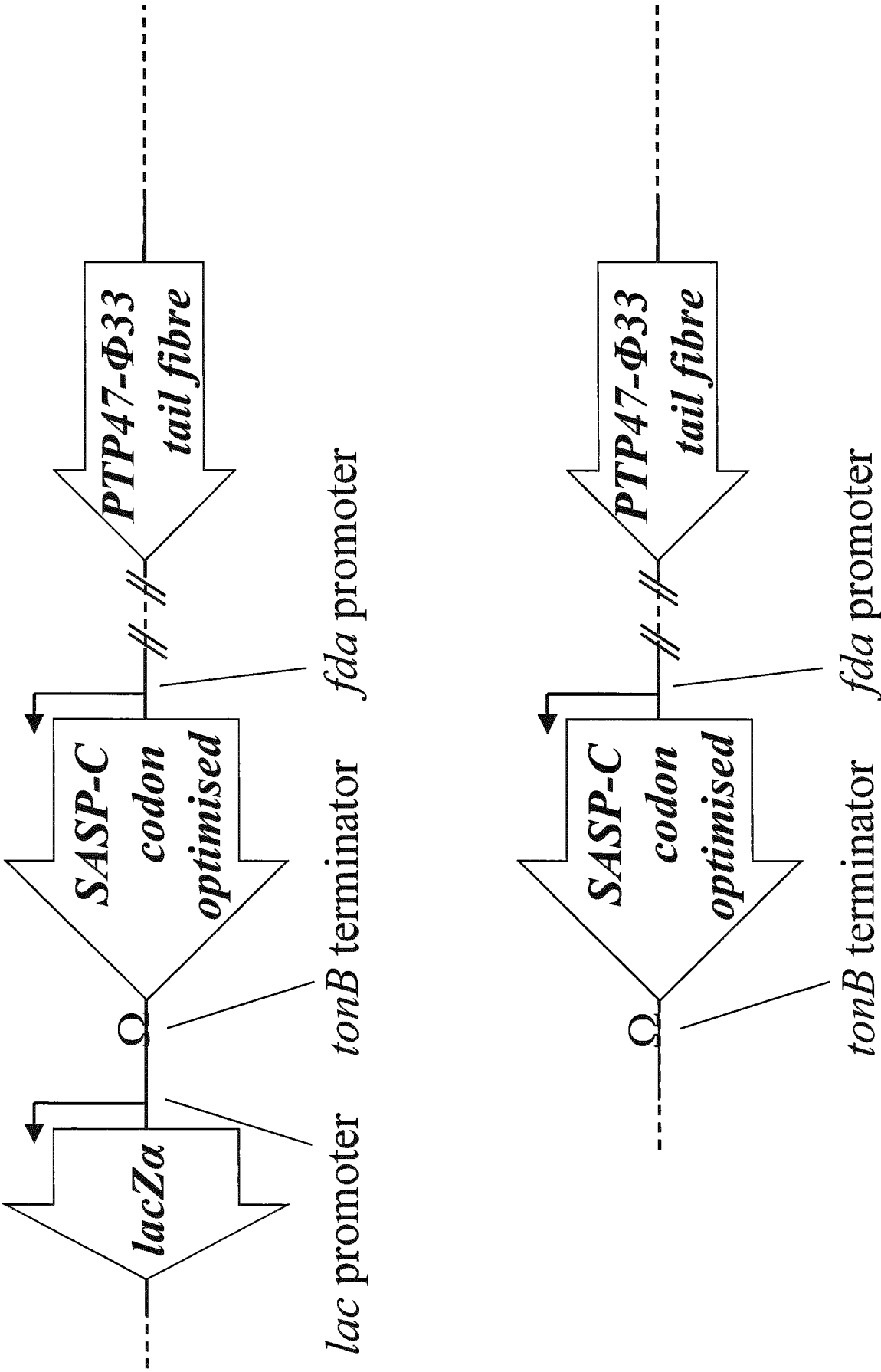


Figure 11 (Part 4 of 4)

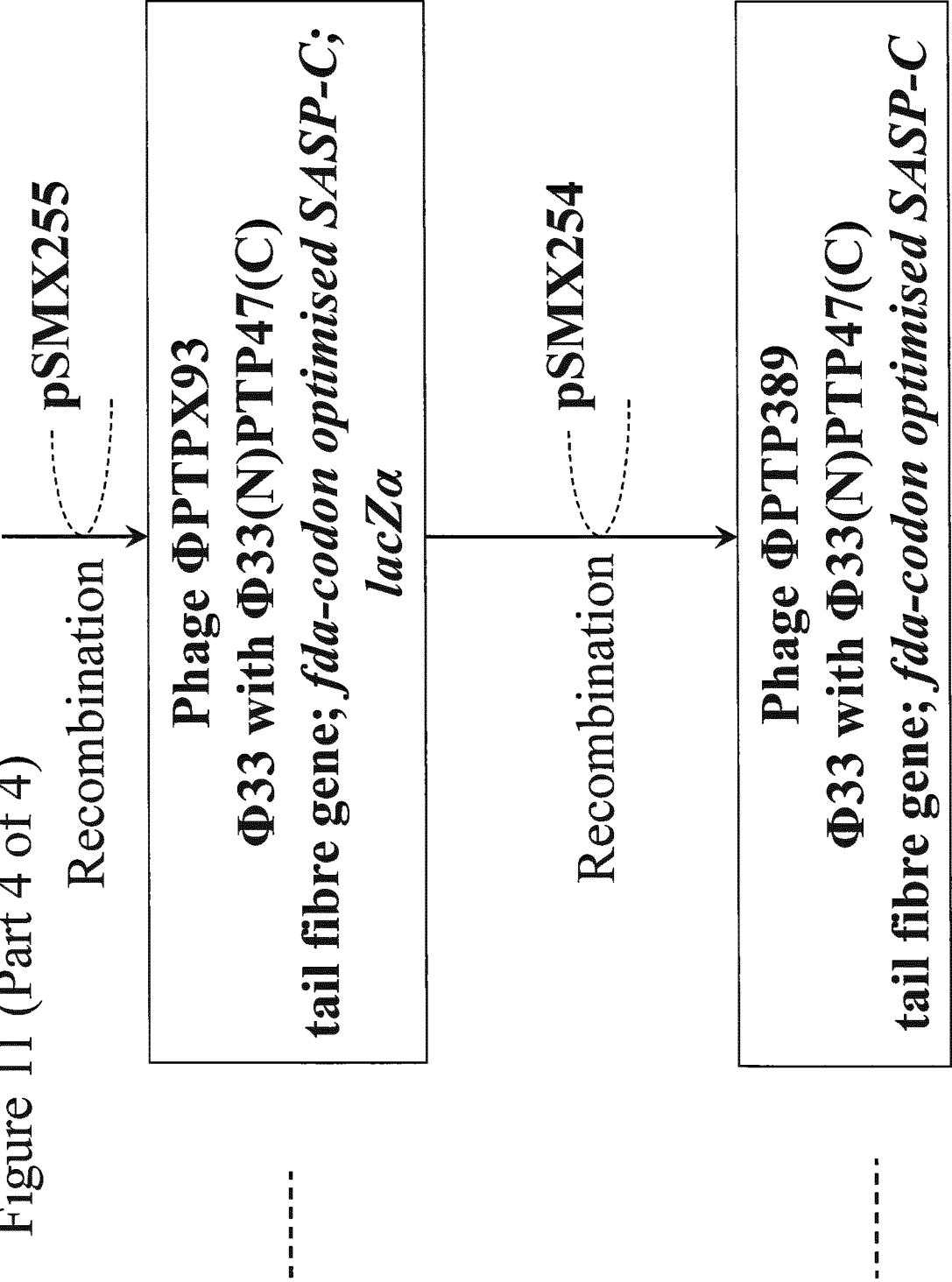


Figure 12 (Part 1 of 2)

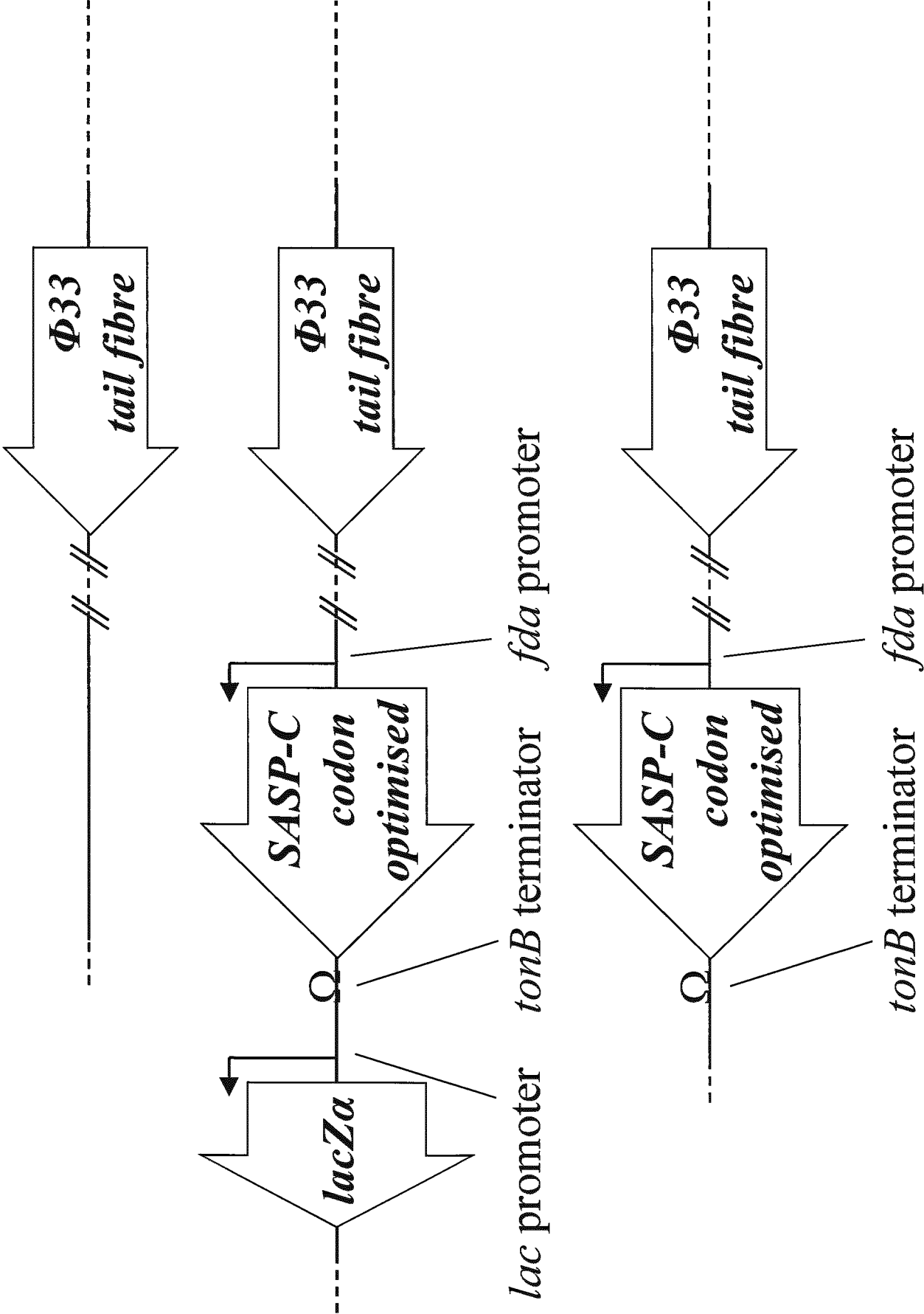


Figure 12 (Part 2 of 2)

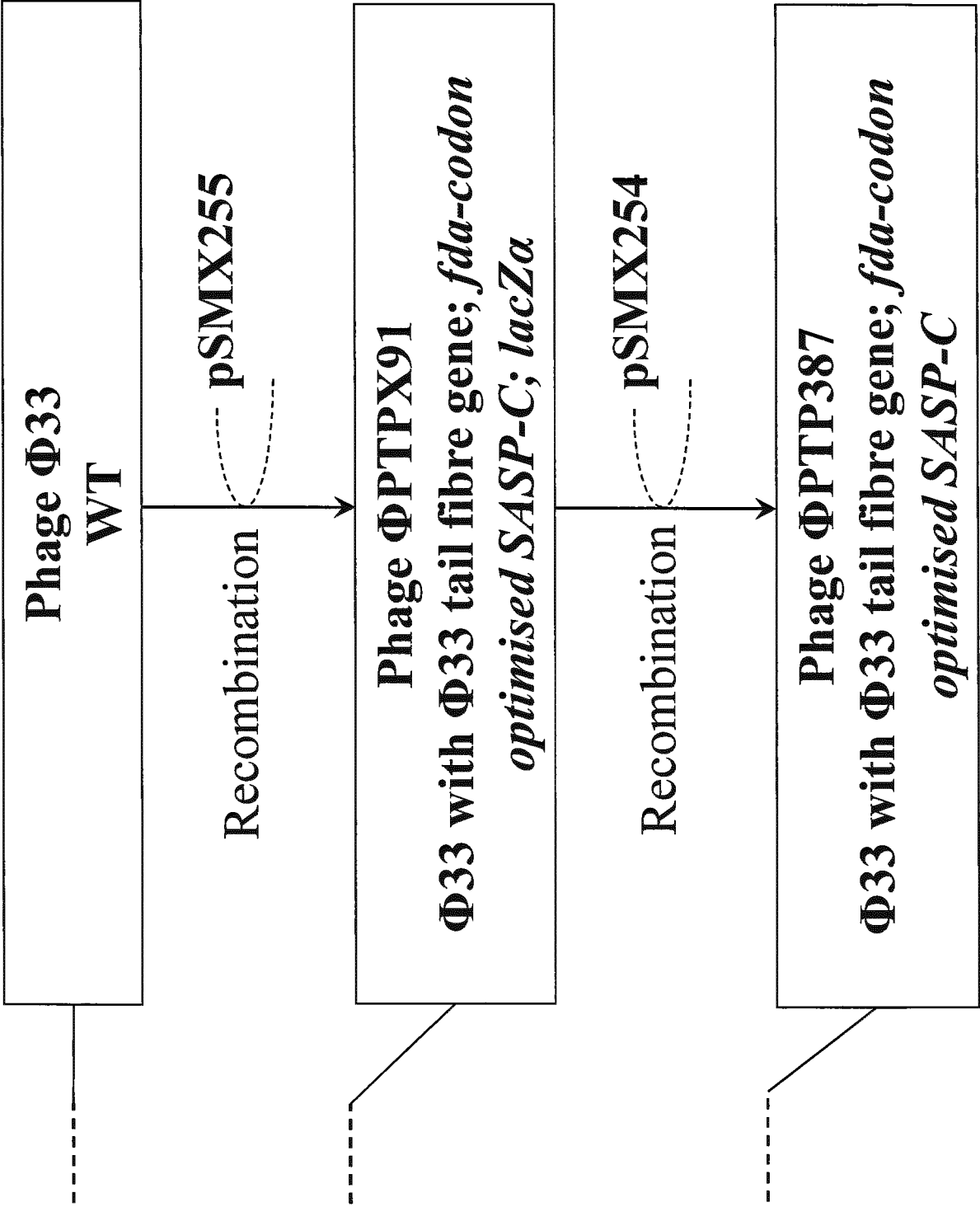


Figure 13

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SPM-1      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
F8         MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
PB1        MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
C36        MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
LBL3       MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
Phi33      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
LMA2       MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
KPP12      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
JG024      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
PTP92      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
NH-4       MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
14-1       MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
PTP47      MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
SN         MITPELIPSPFAAQGDKDPIPQTSSTGFANLRDGYTPDYEISLASNNPQAKAVERKIQNQ 60
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SPM-1      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
F8         LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
PB1        LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
C36        LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
LBL3       LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
Phi33      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
LMA2       LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
KPP12      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
JG024      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
PTP92      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
NH-4       LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
14-1       LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
PTP47      LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
SN         LFFIATQNAQAWQRQMAPPWFQGMPPGGYEQNAEVVRVGNDGIMRRYRSMVNANASDPLSS 120
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F8         TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
PB1        TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
C36        TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
LBL3       TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
Phi33      TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
LMA2       TTWEEQPAWSAMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
KPP12      TTWEEQPAWSAMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
JG024      TTWEEQPAWSVMRTNIPMPAGGSGLSGGEVITTGRNFNELLNGTWEFFSDAIVVASQNA 180
PTP92      TTWEEQPAWSVMRTNIPMPAGGSGLSGGEVITTGRNFNELLNGTWEFFSDAIVVASQNA 180
NH-4       TTWEEQPAWSVMRTNIPMPAGGSGLSGGEVITTGRNFNELLNGTWEFFSDAIVVASQNA 180
14-1       TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
PTP47      TTWEEQPAWSAMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
SN         TTWEEQPAWSVMRSNIPMPAGGSGLSGGEVITTGRNFNDLLNGTWEFFSDSVVVASQNA 180
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SPM-1	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
F8	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
PB1	PVYPASAGAAAGMLEAKSWISGSNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
C36	PVYPASAGAAAGMLEAKSWISGSNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
LBL3	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
Phi33	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
LMA2	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
KPP12	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVALRGLNAGAWTNWMYAVNVMAL	240
JG024	PVYPASAGAAAGMLEAKSWVSGNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
PTP92	PVYPASAGAAAGMLEAKSWVSGNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
NH-4	PVYPASAGAAAGMLEAKSWVSGNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
14-1	PVYPASAGAAAGMLEAKSWISRSNTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
PTP47	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
SN	PVYPASAGAAAGMLEAKSWVSGANTFCVQRYTDRVGNVAVRGLNAGAWTNWMYAVNVMAL	240
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SPM-1	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNAMNTGASTINVSFGFSKAIV	300
F8	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNAMNTGASTINVSFGFSKAIV	300
PB1	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNTVNTGASTINVSFGFKAIAIV	300
C36	QQGRVTYGVAAGPANAYTLTLPVQLQGGLVDGMILRVKFNTVNTGASTINVSFGFKAIAIV	300
LBL3	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNMTNTGASTINVSFGFKAIAIV	300
Phi33	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNTMTNTGASTINVSGLGAKAIV	300
LMA2	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNTMTNTGATTINVSGLGAKAIV	300
KPP12	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNTMTNTGASTINVSGLGAKAIV	300
JG024	QHGRVTYGTAAGPANAYTLTLPVQIQGGLVDGMILRVKFNTMTNTGATTINVSGLGAKAIV	300
PTP92	QHGRVTYGTAAGPANAYTLTLPVQIQGGLVDGMILRVKFNMTNTGATTINVSGLGAKAIV	300
NH-4	QHGRVTYGTAAGPANAYTLTLPVQIQGGLVDGMILRVKFNTMTNTGATTINVSGLGAKAIV	300
14-1	QQGRVTYGVAAGPANAYTLTLPVQLQGGLVDGMILRVKFNTVNTGASTINVSGLGAKAIV	300
PTP47	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNTMTNTGATTINVSGLGAKAIV	300
SN	QQGRVTYGVAAGSANAYTLTLPVQLQGGLVDGMILRVKFNMTNTGASTINVSGLGAKAIV	300
	*.*.....*.**.*.....*****.*.....*.....*.....*.....*	

SPM-1	GAANFPLTGGELGQGLIAELVFDATGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
F8	GAANFPLTGGELGQGLIAELVFDATGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
PB1	GAANFPLTGGELGQGLIAELVFDATGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
C36	GAANFPLTGGELGQGLIAELVFDATGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
LBL3	GAANFPLTGGELGQGLIAELVFDATGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
Phi33	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
LMA2	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
KPP12	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
JG024	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVE	360
PTP92	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVE	360
NH-4	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
14-1	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
PTP47	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
SN	GAANFPLTGGELGQGLIAELVFDAAGDRWRILAGAPRIQVGNADQDYQAPSWKQVKDYVA	360
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F8	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFNNNRAKDFDYRFISEAD	420
PB1	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFNNNRAKDFDYRFISEAD	420
C36	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFNNNRAKDFDYRFISEAD	420
LBL3	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFNNNRAKDFDYRFISEAD	420
Phi33	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
LMA2	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
KPP12	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFNNNRAKDFDYRFISEAD	420
JG024	SQKLTEVDWDTVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
PTP92	SQKLTEVDWDTVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
NH-4	SQKLTEVDWDTVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
14-1	SQKLTEVDWDTVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
PTP47	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
SN	SQKLTEVDWADVVNKPNAIQDTPWFANLELSARPFDHFHFSNRAKDFDYRLISEAD	420
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F8 GSMAFYSRQGSAGPTQDILFSRSNVTFLLQPRLDVAKNLAYIANSGLPWQNTTADQPGWKF 480

SPM-1	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
F8	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
PB1	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
C36	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
LBL3	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
Phi33	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYVPWDSGNFD	540
LMA2	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
KPP12	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	IMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
JG024	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
PTP92	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
NH-4	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
14-1	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNDRLPLFAGQYTPWDSGNFD	540
PTP47	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
SN	TFAQGVDANNNAVI	AVNTTNP	PDGSYRSQ	VMRWDASTN	VFNNRPLFAGQYTPWDSGNFD	540
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SPM-1	PATKLTVGTTNNISGPTGIRNTTSNTGNMNTWGSSTTASYGNAALQIFGRGGGEPAAIY	600
F8	PATKLTVGTTNNISGPTGIRNTTSNTGNMNTWGSSTTASYGNAALQIFGRGGGEPAAIY	600
PB1	PATKLTVGTTNNISGPTGIRNTTSNTGNMNTWGSSTTASYGNAALQIFGRGGGEPAAIY	600
C36	PATKLTVGTTNNISGPTGIRNTTSNTGNMNTWGSSTTASYGNAALQIFGRGGGEPAAIY	600
LBL3	PATKLTVGTTNNISRPTGIRNTTSNTGNMNTWGSSTTASYGNAALQIFGRGGGEPAAIY	600
Phi33	PSTKLTVNATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
LMA2	PSTKLTVNATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
KPP12	PSTKLTVNATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
JG024	PSTKLTVSATNQISGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
PTP92	PSTKLTVSATNQISGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
NH-4	PSTKLTVSATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
14-1	PSTKLTVSATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
PTP47	PSTKLTVSATNQIAGPTGIRNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
SN	PSTKLTVRATNQIAGPTGIQNTNGNTGNMNTWGSSTTASYGNAALQIFGKGGGEPAAIY	600
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F8          FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVVTDESNIRNHVNGMSGAPVWGGQWFWGEW 660
PB1        FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVVTDESNIRNHVNGMSGAPVWGGQWFWGEW 660
C36        FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVVTDESNIRFHVNSMAGTPVWGGNEFWGPW 660
LBL3       FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVVTDESNIRFHVNSMAGTPVWGGNEFWGPW 660
Phi33      FDNSQTGWYLGMDKDGQLKRAGWSLGNNAVITDESNIRFHVNSMAGTPVWGGNEFWGPW 660
LMA2       FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDELNIRNHINGMAARPVWGGNEFWGPW 660
KPP12      FDNSQTGWYLGMDKDGQLKRAGWSLGNNAVITDESNIRFHVNSMAGTPVWGGNEFWGSW 660
JG024      FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGNVEFWGPW 660
PTP92      FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGNVEFWGPW 660
NH-4       FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGNVEFWGPW 660
14-1       FDNSQTGWYLGMDKDGRLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGNVEFWGPW 660
PTP47      FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGNVEFWGPW 660
SN         FDNSQTGWYLGMDKDGQLKRAGWSLGNNSYVITDESNIRTHINTMAARPIWGGVEFWGPW 660
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SPM-1	NFNPNNTKLTIKAGTQETSSTAIFSGTLPFAPIASLSDYSQAPLTIYN--SPTGPSAKPAV	718
F8	NFNPNNTKLTIKAGTQETSSTAIFSGTLPFAPIASLSDYSQAPLTIYN--SPTGPSAKPAV	718
PB1	NFNPNNTKLTIKAGTQETSSTAIFSGTLPFAPIASLSDYSQAPLTIYN--SPTGPSAKPAV	718
C36	NFNPNNTKLTIKAGTQETSSTAIFSGTMPFAPIASLSDYSQAPLTIYN--SPTGPSAKPAV	718
LBL3	NFNPNNTKLTIKAGTQETSSTAIFSGTMPFAPIASLSDYSQAPLTVYN--SPTGPSAKPAV	718
Phi333	NFNPNNTKLTIKAGTOETSSTAIFSGTMPFAPIASLSDYSQAPLTVYN--APTGPSAKPAV	718

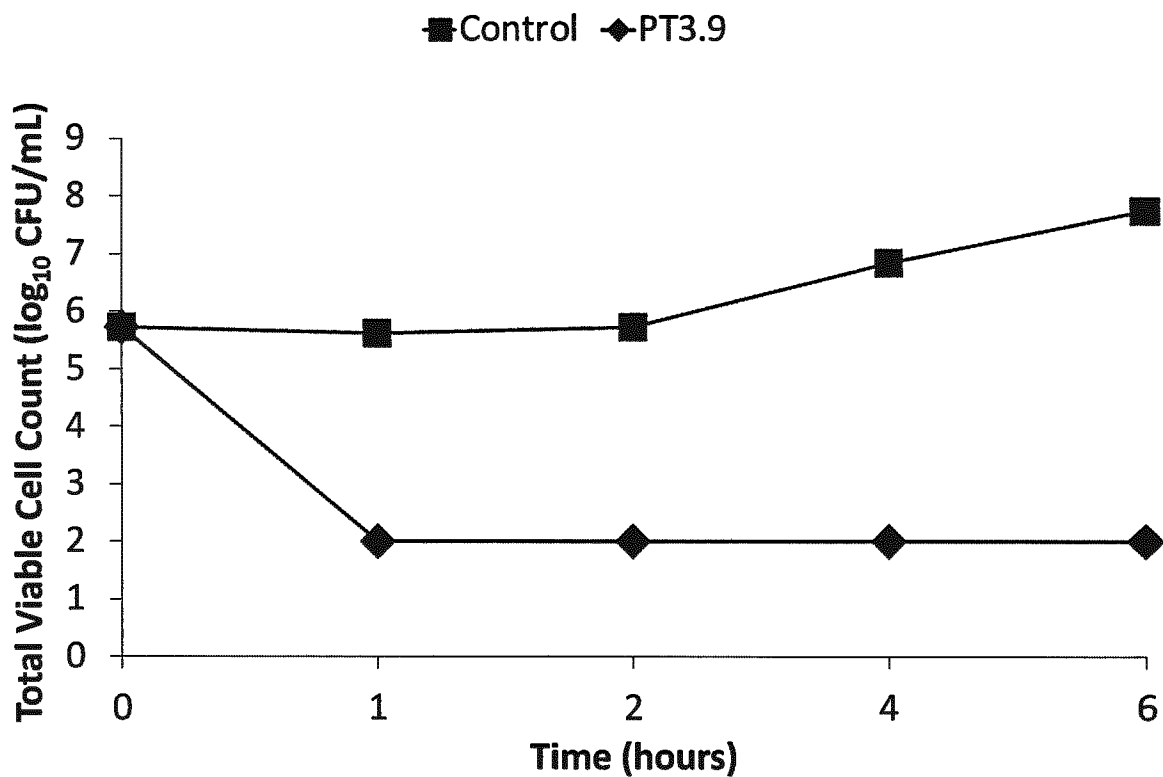
LMA2	NFNPNTKLTIKAGTQETSSTAISYSGTMPFAPIASLSDYSQAPLTIYN--APTGPSAKPAV	718
KPP12	NFNPNTKLTIKAGTQETSSTAIFSETMPFAPIASLSDYSQAPLTIYN--APTGPSAKPAV	718
JG024	NFDPNLKLTNLAFNDSSYTRMTNSGAKDVG- IASMTSYADAAMSFFNYEASNPTGPRAAV	719
PTP92	NFDPNLKLTNLAFNDSSYTRMTNSGAKDVG- IASMTSYADAAMSFFNYEASNPTGPRAAV	719
NH-4	NFNPNTKLTLGSFNDSQHTRMVNSAAKDVG- IASMTSYADAAMSFFNYEASNPTGNRAAV	719
14-1	NFDPNLKLTNLAFNDSSYTRMTNSGAKDVG- IASMTSYADAAMSFFNYEASNPTGPRAAV	719
PTP47	NFNPNTKLTLGSFNDSQHTRMVNSAAKDVG- IASMTSYADAAMSFFNYEASNPTGNRAAV	719
SN	NFNPNTKLTLGSFNDSQHTRMVNSAAKDVG- IASMTSYADAAMSFFNYEASNPTGNRAAV	719
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SPM-1	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
F8	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
PB1	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
C36	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
LBL3	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
Phi33	IAFIRPGNWGAFFGIDTDNKLKWGGGSLGNNSREIADSSNIMNLWASNPTAPSWNGQTVW	778
LMA2	IAFIRPGNWGAFFGLDTDNKLKWGGGSLGNSSMEIADSSNIMNLWASNPTAPSWNGQTVW	778
KPP12	IAFIRPGNWGAFFGLDTDNKLKWGGGSLGNSSREIADSSNIMNLWASNPTAPSWNGQTVW	778
JG024	ISFVRNGSRGVLFGLDSNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
PTP92	ISFVRNGSRGVLFGLDSNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
NH-4	ISFVRNGARGVLFGLDTDNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
14-1	ISFVRNGSRGVLFGLDSNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
PTP47	ISFVRNGARGVLFGLDTDNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
SN	ISFVRNGARGVLFGLDTDNKLKWGGYSLGAVAFEIADSSNLMSLWSSHAAAPNWNQGTIW	779
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SPM-1	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
F8	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
PB1	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
C36	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
LBL3	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
Phi33	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
LMA2	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
KPP12	RSGNFDPATKVDLNAANATNGSMIFNRISGTGSGIASSGRVGA INLQNGAHSGQAAAVTF	838
JG024	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
PTP92	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
NH-4	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
14-1	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
PTP47	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
SN	RSGNFNPDTKATLAARNTTSSPTIFS---YGASGIASGTQVGVGVVENSNTAAAITF	836
	*****: * * . * * * : * . . : * . . *****: : * : : . : * : * *	
SPM-1	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
F8	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
PB1	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
C36	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
LBL3	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
Phi33	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
LMA2	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
KPP12	ERGGSI FVNFGLDTDNVLKVGGGNLGANAYPVIHAGNYNNYINQALVQVGLGGVGSYGIF	898
JG024	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
PTP92	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
NH-4	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
14-1	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
PTP47	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
SN	HSPQKYQVNFGLDADNVVKIGGGTMGGVAYPI IHSGNYNNYINQALVQVGLGGVGSYAIL	896
	. *****: * *: * : * : * : * : * : * : * : * : * : * : * : * : * : *	
SPM-1	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
F8	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
PB1	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
C36	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
LBL3	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
Phi33	AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQKPA GTWRCMGYVVNRDANTADSAT	958
LMA2	AVYDTSAPASSVPGTILDGSLFYSSFNANFRSGTKPTGTWRCMGYVILNRDGTNPDSAT	958
KPP12	AVYDTSAPASSVPGTILDGSLFYSSFNANFRSGTKPTGTWRCMGYVILNRDGTNPDSAT	957
JG024	AVLDTSAPAASIAPGTIMDSSKLFYSSCDSTYRSSASPTGTWRCMGYVILNRDGTNPDSAT	956

PTP92 AVLDTSAPAASIAPGTIMDSSKLFYSSCDSTYRSSASPTGTWRCMGYVYNRDSTNGDSAS 956  
 NH-4 AVLDTSAPAASIAPGTIMDSSKLFYSSCDSTYRSSARPTGTWRCMGYVYNRDSTNGDSAS 956  
 14-1 AVLDNAAPIATVQPGVVVDGSILYSSCAANYNSGQRPAGTWRCMGYVYNRDANTPDSAT 956  
 PTP47 AVLDYAAPTATVRPGVVVDGSILYSSCAANYNSGQRPAGTWRCMGYVYNRDANTPDSAT 956  
 SN AVLDNAAPTATVQPGVVVDGSILYSSCAANYNSGQRPAGTWRCMGYVYNRDANTPDSAT 956  
 \*\* \* : \*\* : : : \*\* . : : \* . \* \* : \* \* \* : : . \* . \* : \* \* \* \* \* : \* \* . \* \* :

SPM-1 LFQRTV 964 (SEQ ID NO: 45)  
 F8 LFQRTV 964 (SEQ ID NO: 46)  
 PB1 LFQRTV 964 (SEQ ID NO: 47)  
 C36 LFQRTV 964 (SEQ ID NO: 48)  
 LBL3 LFQRTV 964 (SEQ ID NO: 49)  
 Phi33 LFQRTV 964 (SEQ ID NO: 50)  
 LMA2 LFQRTV 964 (SEQ ID NO: 51)  
 KPP12 LFQRTV 963 (SEQ ID NO: 52)  
 JG024 LFQRTV 962 (SEQ ID NO: 53)  
 PTP92 LFQRTV 962 (SEQ ID NO: 54)  
 NH-4 LFQRTV 962 (SEQ ID NO: 55)  
 14-1 LFQRTV 962 (SEQ ID NO: 56)  
 PTP47 LFQRTV 962 (SEQ ID NO: 57)  
 SN LFQRTV 962 (SEQ ID NO: 58)

Figure 14

(A)



(B)

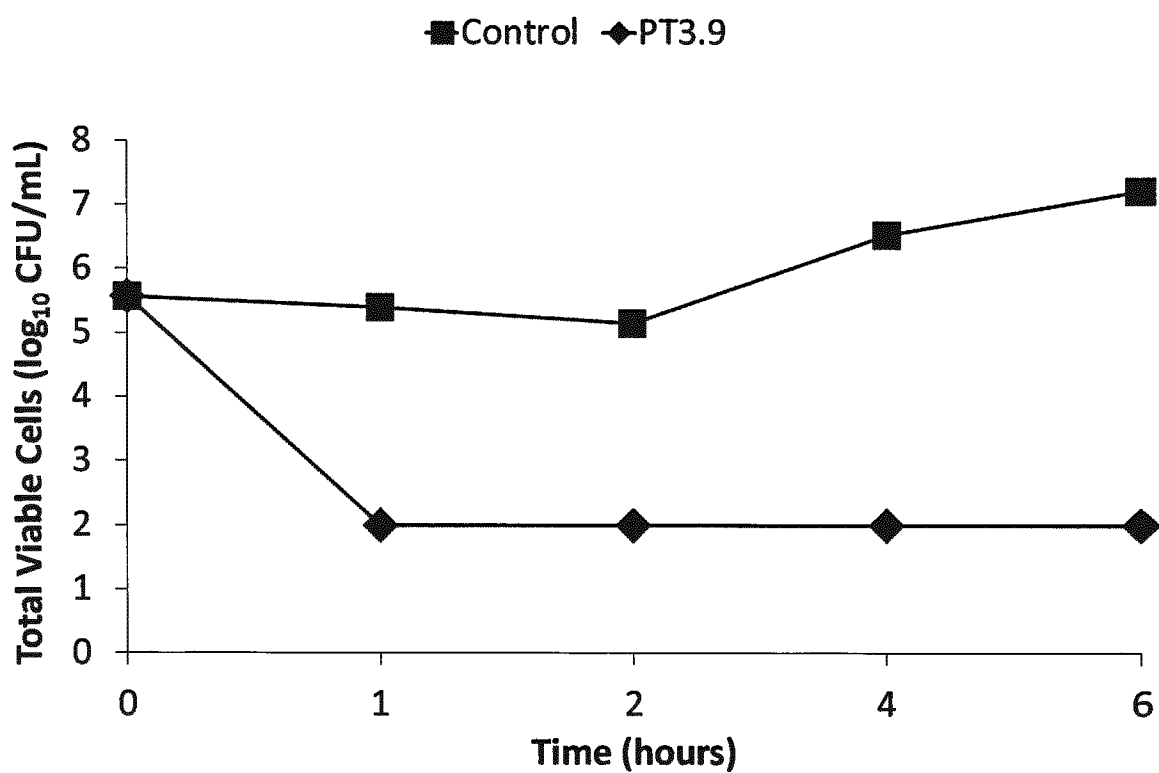
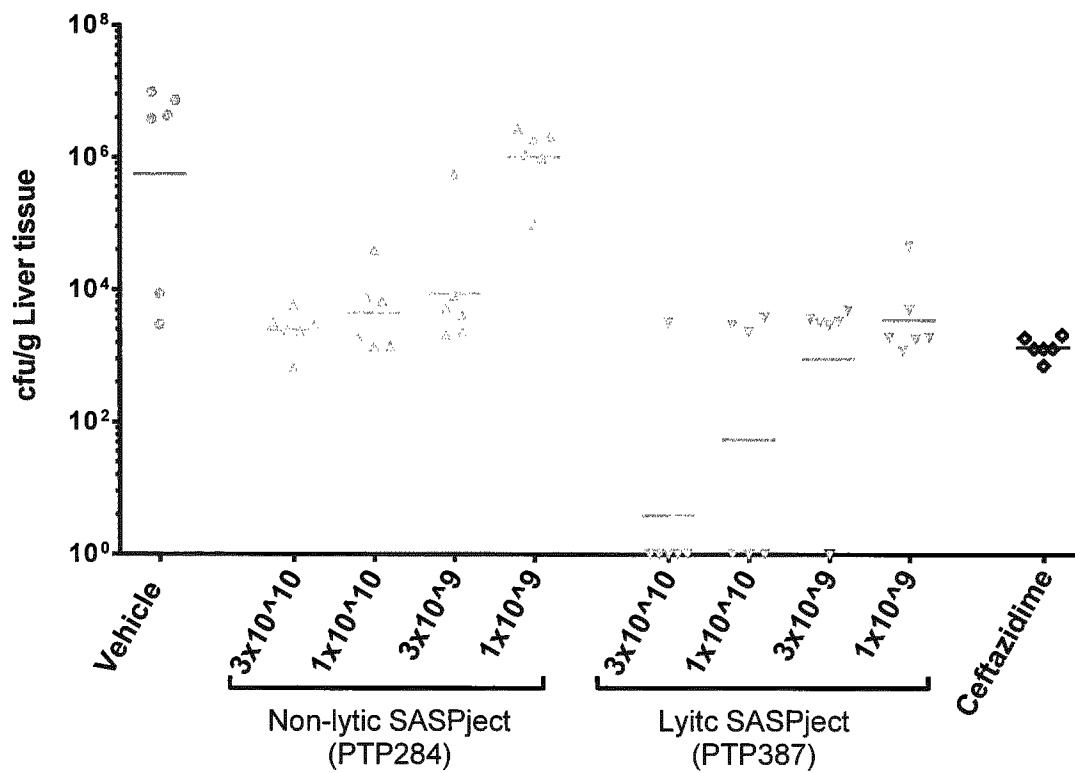


Figure 15



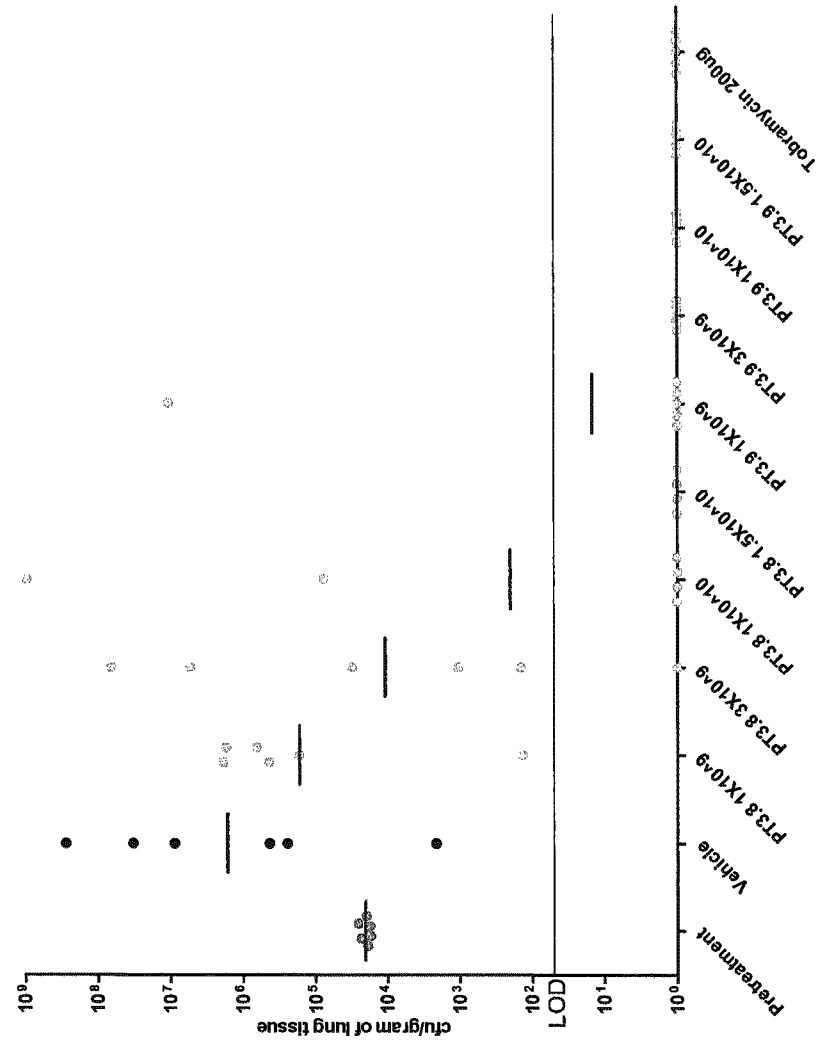


Figure 16



CASEDOCS-#2318074-v1-Sequence\_listing  
SEQUENCE LISTING

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## CASEDOCS-#2318074-v1-Sequence\_listing

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# CASEDOCS-#2318074-v1-Sequence\_listing

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caac 64

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# CASEDOCS-#2318074-v1-Sequence\_listing

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<220>



## CASEDOCS-#2318074-v1-Sequence\_listing

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&lt;210&gt; 23

&lt;211&gt; 43

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; primer

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&lt;211&gt; 43

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&lt;223&gt; primer

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&lt;211&gt; 42

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

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&lt;223&gt; primer

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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; primer

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&lt;211&gt; 31

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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; primer

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## CASEDOCS-#2318074-v1-Sequence\_listing

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## CASEDOCS-#2318074-v1-Sequence\_listing

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cctag 65

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<210> 37  
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<220>  
<223> primer

<400> 38  
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<210> 39  
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# CASEDOCS-#2318074-v1-Sequence\_listing

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<210> 40
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<210> 41
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## CASEDOCS-#2318074-v1-Sequence\_listing

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 <212> PRT  
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<400> 45

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 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Ser Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Val Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
 210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
 225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala



## CASEDOCS-#2318074-v1-Sequence\_listing

245

250

255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
                   260                  265                  270

Met Val Leu Arg Val Lys Phe Asn Ala Met Asn Thr Gly Ala Ser Thr  
                   275                  280                  285

Ile Asn Val Ser Gly Phe Gly Ser Lys Ala Ile Val Gly Ala Ala Asn  
                   290                  295                  300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
                   305                  310                  315                  320

Val Phe Asp Ala Thr Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
                   325                  330                  335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
                   340                  345                  350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
                   355                  360                  365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
                   370                  375                  380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
                   385                  390                  395                  400

Phe His Phe Asn Asn Asn Arg Ala Lys Asp Phe Asp Tyr Arg Phe Ile  
                   405                  410                  415

Ser Glu Ala Asp Gly Ser Met Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
                   420                  425                  430

Gly Pro Thr Gln Asp Ile Leu Phe Ser Arg Ser Asn Val Thr Phe Leu  
                   435                  440                  445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
                   450                  455                  460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
                   465                  470                  475                  480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
                   485                  490                  495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Ile Met Arg Trp  
                   500                  505                  510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala



## CASEDOCS-#2318074-v1-Sequence\_listing

515

520

525

Gly Gln Tyr Val Pro Trp Asp Ser Gly Asn Phe Asp Pro Ala Thr Lys  
 530 535 540

Leu Thr Val Gly Thr Thr Asn Asn Ile Ser Gly Pro Thr Gly Ile Arg  
 545 550 555 560

Asn Thr Thr Ser Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Ser Ser  
 565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Arg Gly  
 580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
 595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
 610 615 620

Leu Gly Asn Asn Ser Tyr Val Val Thr Asp Glu Ser Asn Ile Arg Asn  
 625 630 635 640

His Val Asn Gly Met Ser Gly Ala Pro Val Trp Gly Gly Gln Trp Phe  
 645 650 655

Trp Gly Glu Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
 660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Leu Pro  
 675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
 690 695 700

Ile Tyr Asn Ser Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
 705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
 725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Asn Ser Arg Glu  
 740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ser Asn Pro Thr  
 755 760 765

Ala Pro Ser Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
 770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Ser



## CASEDOCS-#2318074-v1-Sequence\_listing

785 790 795 800

Met Ile Phe Asn Arg Ile Ser Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815Gly Arg Val Gly Ala Ile Asn Leu Gln Asn Gly Ala His Ser Gly Gln  
820 825 830Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Ser Ile Phe Val Asn Phe  
835 840 845Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
865 870 875 880Asn Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly  
885 890 895Ile Phe Ala Val Leu Asp Asn Ala Ala Pro Ile Ala Thr Val Gln Pro  
900 905 910Gly Val Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ala Ala  
915 920 925Asn Tyr Asn Ser Gly Gln Lys Pro Ala Gly Thr Trp Arg Cys Met Gly  
930 935 940Tyr Val Val Asn Arg Asp Ala Asn Thr Ala Asp Ser Ala Thr Leu Phe  
945 950 955 960

Gln Arg Val Thr

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 <211> 964  
 <212> PRT  
 <213> bacteriophage F8

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20 25 30Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
35 40 45Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
50 55 60



CASEDOCS-#2318074-v1-Sequence\_listing

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
115 120 125

Trp Ser Val Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Ser Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ala Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Val Leu Arg Val Lys Phe Asn Ala Met Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Phe Gly Ser Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Thr Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335



CASEDOCS-#2318074-v1-Sequence\_listing

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Asn Asn Arg Ala Lys Asp Phe Asp Tyr Arg Phe Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Met Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Ser Arg Ser Asn Val Thr Phe Leu  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Ile Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Val Pro Trp Asp Ser Gly Asn Phe Asp Pro Ala Thr Lys  
530 535 540

Leu Thr Val Gly Thr Thr Asn Asn Ile Ser Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Thr Ser Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Ser Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Arg Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605



CASEDOCS-#2318074-v1-Sequence\_listing

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Val Thr Asp Glu Ser Asn Ile Arg Asn  
625 630 635 640

His Val Asn Gly Met Ser Gly Ala Pro Val Trp Gly Gly Gln Trp Phe  
645 650 655

Trp Gly Glu Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Leu Pro  
675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Ile Tyr Asn Ser Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Asn Ser Arg Glu  
740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ser Asn Pro Thr  
755 760 765

Ala Pro Ser Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Ser  
785 790 795 800

Met Ile Phe Asn Arg Ile Ser Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Asn Leu Gln Asn Gly Ala His Ser Gly Gln  
820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Ser Ile Phe Val Asn Phe  
835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
865 870 875 880



CASEDOCS-#2318074-v1-Sequence\_listing

Asn Gln Ala Leu Val<sub>885</sub> Gln Val Gly Leu Gly<sub>890</sub> Gly Val Gly Ser Tyr Gly<sub>895</sub>

Ile Phe Ala Val<sub>900</sub> Leu Asp Asn Ala Ala<sub>905</sub> Pro Ile Ala Thr Val<sub>910</sub> Gln Pro

Gly Val Val<sub>915</sub> Val Asp Gly Ser Ile<sub>920</sub> Leu Ile Tyr Ser Ser<sub>925</sub> Cys Ala Ala

Asn Tyr Asn Ser Gly Gln Lys<sub>935</sub> Pro Ala Gly Thr Trp<sub>940</sub> Arg Cys Met Gly

Tyr Val Val Asn Arg Asp<sub>950</sub> Ala Asn Thr Ala Asp<sub>955</sub> Ser Ala Thr Leu Phe<sub>960</sub>

Gln Arg Val Thr

<210> 47  
<211> 964  
<212> PRT  
<213> bacteriophage PB1

<400> 47

Met Ile Thr Pro Glu<sub>5</sub> Leu Ile Pro Ser Pro<sub>10</sub> Phe Ala Ala Gln Gly<sub>15</sub> Asp

Lys Asp Pro Ile Pro Gln Thr Ser Ser<sub>25</sub> Thr Gly Phe Ala Asn<sub>30</sub> Leu Arg

Asp Gly Tyr Thr Pro Asp Tyr Glu<sub>40</sub> Ile Ser Leu Ala Ser<sub>45</sub> Asn Asn Pro

Gln Ala Lys Ala Val Glu Arg<sub>55</sub> Lys Ile Gln Asn Gln<sub>60</sub> Leu Phe Phe Ile

Ala Thr Gln Asn Ala Gln<sub>70</sub> Ala Trp Gln Arg Gln<sub>75</sub> Met Ala Pro Pro Trp<sub>80</sub>

Phe Gln Gly Met Pro<sub>85</sub> Gly Gly Tyr Glu Gln<sub>90</sub> Asn Ala Glu Val Val<sub>95</sub> Arg

Val Gly Asn Asp<sub>100</sub> Gly Ile Met Arg Arg<sub>105</sub> Tyr Arg Ser Met Val<sub>110</sub> Asn Ala

Asn Ala Ser Asp Pro Leu Ser Ser<sub>120</sub> Thr Thr Trp Glu Glu<sub>125</sub> Gln Pro Ala

Trp Ser<sub>130</sub> Val Met Arg Ser Asn<sub>135</sub> Ile Pro Met Pro Ala<sub>140</sub> Gly Gly Pro Gly



## CASEDOCS-#2318074-v1-Sequence\_listing

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Val Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Ile Ser Gly Ser Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Val Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Phe Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Thr Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Asn Arg Ala Lys Asp Phe Asp Tyr Arg Phe Ile  
405 410 415



CASEDOCS-#2318074-v1-Sequence\_listing

Ser Glu Ala Asp Gly Ser Met Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Ser Arg Ser Asn Val Thr Phe Leu  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Val Pro Trp Asp Ser Gly Asn Phe Asp Pro Ala Thr Lys  
530 535 540

Leu Thr Val Gly Thr Thr Asn Asn Ile Ser Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Thr Ser Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Ser Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Arg Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Val Thr Asp Glu Ser Asn Ile Arg Asn  
625 630 635 640

His Val Asn Gly Met Ser Gly Ala Pro Val Trp Gly Gly Gln Trp Phe  
645 650 655

Trp Gly Glu Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Leu Pro  
675 680 685



CASEDOCS-#2318074-v1-Sequence\_listing

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Ile Tyr Asn Ser Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Asn Ser Arg Glu  
740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ser Asn Pro Thr  
755 760 765

Ala Pro Ser Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Asn  
785 790 795 800

Met Ile Phe Asn Arg Ile Ser Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Asn Leu Gln Asn Gly Ala His Ser Gly Gln  
820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Ser Ile Phe Val Asn Phe  
835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
865 870 875 880

Asn Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly  
885 890 895

Ile Phe Ala Val Leu Asp Asn Ala Ala Pro Ile Ala Thr Val Gln Pro  
900 905 910

Gly Val Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ala Ala  
915 920 925

Asn Tyr Asn Ser Gly Gln Lys Pro Ala Gly Thr Trp Arg Cys Met Gly  
930 935 940

Tyr Val Val Asn Arg Asp Ala Asn Thr Pro Asp Ser Ala Thr Leu Phe  
945 950 955 960



CASEDOCS-#2318074-v1-Sequence\_listing

Gln Arg Val Thr

<210> 48  
 <211> 964  
 <212> PRT  
 <213> bacteriophage C36  
 <400> 48

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
 1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Ser Ser Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Val Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Ile Ser Gly Ser Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
 210 215 220



## CASEDOCS-#2318074-v1-Sequence\_listing

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Pro Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Val Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Phe Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Thr Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Asn Asn Arg Ala Lys Asp Phe Asp Tyr Arg Phe Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Met Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Ser Arg Ser Asn Val Thr Phe Leu  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495



## CASEDOCS-#2318074-v1-Sequence\_listing

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Ile Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Val Pro Trp Asp Ser Gly Asn Phe Asp Pro Ala Thr Lys  
530 535 540

Leu Thr Val Gly Thr Thr Asn Asn Ile Ser Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Thr Ser Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Ser Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Val Gln Ile Phe Gly Arg Gly  
580 585 590

Asp Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Val Thr Asp Glu Ser Asn Ile Arg Phe  
625 630 635 640

His Val Asn Ser Met Ala Gly Thr Pro Val Trp Gly Gly Asn Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Met Pro  
675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Ile Tyr Asn Ser Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Ser Ser Arg Glu  
740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ala Asn Pro Thr  
755 760 765



CASEDOCS-#2318074-v1-Sequence\_listing

Ala Pro Ser Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Asn  
785 790 795 800

Met Val Phe Asn Arg Ile Ser Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Asn Leu Gln Asn Gly Ala His Ser Gly Gln  
820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Ser Ile Phe Val Asn Phe  
835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
865 870 875 880

Asn Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly  
885 890 895

Ile Phe Ala Val Leu Asp Asn Ala Ala Pro Ile Ala Thr Val Gln Pro  
900 905 910

Gly Val Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ser Ala  
915 920 925

Asn Tyr Asn Ser Gly Gln Arg Pro Ala Gly Thr Trp Arg Cys Met Gly  
930 935 940

Tyr Val Val Asn Arg Asp Ala Asn Thr Pro Asp Ser Ala Thr Leu Phe  
945 950 955 960

Gln Arg Val Thr

<210> 49  
<211> 964  
<212> PRT  
<213> bacteriohage LBL3

<400> 49

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
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## CASEDOCS-#2318074-v1-Sequence\_listing

35

40

45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ile Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
 210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
 225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
 245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
 260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Ser Thr  
 275 280 285

Ile Asn Val Ser Gly Phe Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
 290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu



305 310 315 320

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Arg Gly



## CASEDOCS-#2318074-v1-Sequence\_listing

580

585

590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
 595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
 610 615 620

Leu Gly Asn Asn Ser Tyr Val Val Thr Asp Glu Ser Asn Ile Arg Phe  
 625 630 635 640

His Val Asn Ser Met Ala Gly Thr Pro Val Trp Gly Gly Asn Glu Phe  
 645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
 660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Met Pro  
 675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
 690 695 700

Val Tyr Asn Ser Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
 705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
 725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Ser Ser Arg Glu  
 740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ala Asn Pro Thr  
 755 760 765

Ala Pro Thr Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe Asp  
 770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Asn  
 785 790 795 800

Met Ile Phe Asn Arg Ile Ala Gly Thr Gly Ser Gly Ile Ala Ser Ser  
 805 810 815

Asp Arg Val Gly Ala Ile Ser Leu Gln Asn Gly Ala Thr Ala Gly Ala  
 820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Gly Phe Phe Val Asn Phe  
 835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly



## CASEDOCS-#2318074-v1-Sequence\_listing

850

855

860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
 865 870 875 880

Asn Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly  
 885 890 895

Ile Phe Ala Val Leu Asp Tyr Ala Ala Pro Thr Ala Thr Val Gln Pro  
 900 905 910

Gly Val Ile Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ser Ala  
 915 920 925

His Tyr Asn Ser Gly Gln Arg Pro Ala Gly Thr Trp Arg Cys Met Gly  
 930 935 940

Tyr Val Leu Asn Arg Asp Ala Arg Asp Pro Asp Ser Ala Thr Leu Phe  
 945 950 955 960

Gln Arg Val Thr

<210> 50  
 <211> 964  
 <212> PRT  
 <213> bacteriohage Phi33

<400> 50

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
 1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ile Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125



CASEDOCS-#2318074-v1-Sequence\_listing

Trp Ser Val Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Val Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400



CASEDOCS-#2318074-v1-Sequence\_listing

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Ile Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Val Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
530 535 540

Leu Thr Val Asn Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Leu Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ala Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Phe  
625 630 635 640

His Val Asn Ser Met Ala Gly Thr Pro Val Trp Gly Gly Asn Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670



CASEDOCS-#2318074-v1-Sequence\_listing

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Gly Thr Met Pro  
675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Val Tyr Asn Ala Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Ile Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Ser Ser Arg Glu  
740 745 750

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ala Asn Pro Thr  
755 760 765

Ala Pro Ser Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Ala Asn Ala Thr Asn Gly Asn  
785 790 795 800

Met Ile Phe Asn Arg Ile Ala Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Asn Leu Gln Asn Gly Glu His Ser Gly Gln  
820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Ser Ile Phe Val Asn Phe  
835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Asn Tyr Ile  
865 870 875 880

Asn Gln Ala Leu Val Gln Val Gly Leu Glu Gly Val Gly Ser Tyr Gly  
885 890 895

Ile Phe Ala Val Leu Asp Asn Ala Ala Pro Thr Ala Thr Val Gln Pro  
900 905 910

Gly Val Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ala Ala  
915 920 925

Asn Tyr Asn Ser Gly Lys Arg Pro Ala Gly Thr Trp Arg Cys Met Gly  
930 935 940



CASEDOCS-#2318074-v1-Sequence\_listing

Tyr Val Val Asn Arg Asp Ala Asn Thr Pro Asp Ser Ala Thr Leu Phe  
945 950 955 960

Gln Arg Val Thr

<210> 51  
<211> 964  
<212> PRT  
<213> bacteriohage LMA2

<400> 51

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
35 40 45

Gln Ala Lys Val Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
115 120 125

Trp Ser Ala Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ile Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
195 200 205



## CASEDOCS-#2318074-v1-Sequence\_listing

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Thr Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480



CASEDOCS-#2318074-v1-Sequence\_listing

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
530 535 540

Leu Thr Val Asn Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Leu Asn Ile Arg Asn  
625 630 635 640

His Ile Asn Gly Met Ala Ala Arg Pro Val Trp Gly Gly Asn Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Tyr Ser Gly Thr Met Pro  
675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Ile Tyr Asn Ala Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Leu Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Ser Ser Met Glu  
740 745 750



CASEDOCS-#2318074-v1-Sequence\_listing

Ile Ala Asp Ser Ser Asn Ile Met Asn Leu Trp Ala Ala Asn Pro Thr  
755 760 765

Ala Pro Thr Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Pro Asn Ala Thr Asn Gly Asn  
785 790 795 800

Met Ile Phe Asn Arg Ile Ala Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Ser Leu Gln Asn Gly Ala Thr Ala Gly Ala  
820 825 830

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Gly Phe Phe Val Asn Phe  
835 840 845

Gly Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly  
850 855 860

Ala Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Ser Tyr Ile  
865 870 875 880

Asn Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Ala  
885 890 895

Ala Leu Ala Val Tyr Asp Thr Ser Ala Pro Ala Ser Ser Val Gly Pro  
900 905 910

Gly Thr Ile Leu Asp Gly Ser Val Leu Phe Tyr Ser Ser Phe Asn Ala  
915 920 925

Asn Phe Arg Ser Gly Thr Lys Pro Thr Gly Thr Trp Arg Cys Met Gly  
930 935 940

Tyr Ile Leu Asn Arg Asp Gly Thr Asn Pro Asp Ser Ala Thr Leu Phe  
945 950 955 960

Gln Arg Val Thr

<210> 52  
<211> 963  
<212> PRT  
<213> bacteriohage KPP12

<400> 52

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15



## CASEDOCS-#2318074-v1-Sequence\_listing

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Ala Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ile Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Leu Arg Gly Leu Asn  
 210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
 225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
 245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
 260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Ser Thr  
 275 280 285



## CASEDOCS-#2318074-v1-Sequence\_listing

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
 290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
 305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
 325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
 340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
 355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
 370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
 385 390 395 400

Phe His Phe Asn Asn Asn Arg Ala Lys Asp Phe Asp Tyr Arg Phe Ile  
 405 410 415

Ser Glu Ala Asp Gly Ser Met Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
 420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Ser Arg Ser Asn Val Thr Phe Leu  
 435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
 450 455 460

Gly Ser Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
 465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
 485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Ile Met Arg Trp  
 500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
 515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
 530 535 540

Leu Thr Val Asn Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
 545 550 555 560



## CASEDOCS-#2318074-v1-Sequence\_listing

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Ser Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Leu Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Leu Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ala Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Phe  
625 630 635 640

His Val Asn Ser Met Ala Gly Thr Pro Val Trp Gly Gly Asn Glu Phe  
645 650 655

Trp Gly Ser Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Ile Lys Ala  
660 665 670

Gly Thr Gln Glu Thr Ser Ser Thr Ala Ile Phe Ser Glu Thr Met Pro  
675 680 685

Phe Ala Pro Ile Ala Ser Leu Ser Asp Tyr Ser Gln Ala Pro Leu Thr  
690 695 700

Ile Tyr Asn Ala Pro Thr Gly Pro Ser Ala Lys Pro Ala Val Ile Ala  
705 710 715 720

Phe Ile Arg Pro Gly Asn Trp Gly Ala Phe Phe Gly Leu Asp Thr Asp  
725 730 735

Asn Lys Leu Lys Trp Gly Gly Gly Ser Leu Gly Asn Ser Ser Arg Glu  
740 745 750

Ile Ala Asp Ser Arg Asn Ile Met Asn Leu Trp Ala Ala Asn Pro Thr  
755 760 765

Ala Pro Thr Trp Asn Gly Gln Thr Val Trp Arg Ser Gly Asn Phe Asp  
770 775 780

Pro Ala Thr Lys Val Asp Leu Asn Ala Pro Asn Ala Thr Asn Gly Asn  
785 790 795 800

Met Ile Phe Asn Arg Ile Ala Gly Thr Gly Ser Gly Ile Ala Ser Ser  
805 810 815

Gly Arg Val Gly Ala Ile Ser Leu Gln Asn Gly Ala Thr Ala Gly Ala  
820 825 830



## CASEDOCS-#2318074-v1-Sequence\_listing

Ala Ala Ala Val Thr Phe Glu Arg Gly Gly Phe Phe Val Asn Phe Gly  
 835 840 845

Leu Asp Thr Asp Asn Val Leu Lys Val Gly Gly Gly Asn Leu Gly Ala  
 850 855 860

Asn Ala Tyr Pro Val Ile His Ala Gly Asn Tyr Asn Ser Tyr Ile Asn  
 865 870 875 880

Gln Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Ala Ala  
 885 890 895

Leu Ala Val Tyr Asp Thr Ser Ala Pro Ala Ser Ser Val Gly Pro Gly  
 900 905 910

Thr Ile Leu Asp Gly Ser Val Leu Phe Tyr Ser Ser Phe Asp Ala Asn  
 915 920 925

Phe Arg Ser Gly Thr Lys Pro Thr Gly Thr Trp Arg Cys Met Gly Tyr  
 930 935 940

Val Leu Asn Arg Asp Gly Thr Asn Pro Asp Ser Ala Ala Leu Phe Gln  
 945 950 955 960

Arg Val Thr

<210> 53  
 <211> 962  
 <212> PRT  
 <213> bacteriohage JG024

<400> 53

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
 1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
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## CASEDOCS-#2318074-v1-Sequence\_listing

100

105

110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Thr Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Glu  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ala Ile Val Val Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ser Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
 210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
 225 230 235 240

Gln His Gly Arg Val Thr Tyr Gly Thr Ala Ala Gly Pro Ala Asn Ala  
 245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Ile Gln Gly Gly Leu Val Asp Gly  
 260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Thr Thr  
 275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
 290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
 305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
 325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
 340 345 350

Lys Gln Val Lys Asp Tyr Val Glu Ser Gln Lys Leu Thr Glu Val Asp  
 355 360 365

Trp Thr Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr



## CASEDOCS-#2318074-v1-Sequence\_listing

370

375

380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
 385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
 405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
 420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
 435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
 450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
 465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
 485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
 500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
 515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
 530 535 540

Leu Thr Val Ser Ala Thr Asn Gln Ile Ser Gly Pro Thr Gly Ile Arg  
 545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
 565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
 580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
 595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
 610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
 625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Asn Val Glu Phe



## CASEDOCS-#2318074-v1-Sequence\_listing

645

650

655

Trp Gly Pro Trp Asn Phe Asp Pro Asn Leu Lys Leu Thr Leu Asn Ala  
660 665 670

Phe Asn Asp Ser Ser Tyr Thr Arg Met Thr Asn Ser Gly Ala Lys Asp  
675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
690 695 700

Phe Asn Tyr Glu Ala Ser Asn Pro Thr Gly Pro Arg Ala Ala Val Ile  
705 710 715 720

Ser Phe Val Arg Asn Gly Ser Arg Gly Val Leu Phe Gly Leu Asp Ser  
725 730 735

Asp Asn Lys Leu Lys Trp Gly Gly Tyr Ser Leu Gly Ala Val Ala Phe  
740 745 750

Glu Ile Ala Asp Ser Asn Asn Leu Met Ser Leu Trp Ser Ser His Ala  
755 760 765

Ala Ala Pro Asn Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe  
770 775 780

Asn Pro Asp Thr Lys Ala Thr Leu Ala Ala Arg Asn Thr Thr Ser Ser  
785 790 795 800

Pro Thr Ile Phe Ser Tyr Gly Ala Ser Gly Ile Ala Ser Thr Gly Gln  
805 810 815

Val Gly Ala Leu Val Val Glu Asn Asn Ser Val Thr Asn Thr Ala Ala  
820 825 830

Ala Ile Thr Phe His Ser Pro Gln Lys Tyr Gln Val Asn Phe Gly Leu  
835 840 845

Asp Ala Asp Asn Val Val Lys Ile Gly Gly Gly Thr Met Gly Gly Val  
850 855 860

Ala Tyr Pro Ile Ile His Ser Gly Asn Tyr Asn Asn Tyr Ile Asn Gln  
865 870 875 880

Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Ala Ile Leu  
885 890 895

Ala Val Leu Asp Thr Ser Ala Pro Ala Ala Ser Ile Ala Pro Gly Thr  
900 905 910

Ile Met Asp Ser Ser Lys Leu Phe Tyr Ser Ser Cys Asp Ser Thr Tyr



## CASEDOCS-#2318074-v1-Sequence\_listing

915

920

925

Arg Ser Ser Ala Ser Pro Thr Gly Thr Trp Arg Cys Met Gly Tyr Val  
 930 935 940

Tyr Asn Arg Asp Ser Thr Asn Gly Asp Ser Ala Ser Leu Phe Gln Arg  
 945 950 955 960

Val Thr

<210> 54  
 <211> 962  
 <212> PRT  
 <213> bacteriohage PTP92

<400> 54

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
 1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Thr Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Glu  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ala Ile Val Val Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190



CASEDOCS-#2318074-v1-Sequence\_listing

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ser Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln His Gly Arg Val Thr Tyr Gly Thr Ala Ala Gly Pro Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Ile Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Thr Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Glu Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Thr Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460



## CASEDOCS-#2318074-v1-Sequence\_listing

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
530 535 540

Leu Thr Val Ser Ala Thr Asn Gln Ile Ser Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Asn Val Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asp Pro Asn Leu Lys Leu Thr Leu Asn Ala  
660 665 670

Phe Asn Asp Ser Ser Tyr Thr Arg Met Thr Asn Ser Gly Ala Lys Asp  
675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
690 695 700

Phe Asn Tyr Glu Ala Ser Asn Pro Thr Gly Pro Arg Ala Ala Val Ile  
705 710 715 720

Ser Phe Val Arg Asn Gly Ser Arg Gly Val Leu Phe Gly Leu Asp Ser  
725 730 735



CASEDOCS-#2318074-v1-Sequence\_listing

Asp Asn Lys Leu Lys Trp Gly Gly Tyr Ser Leu Gly Ala Val Ala Phe  
740 745 750

Glu Ile Ala Asp Ser Asn Asn Leu Met Ser Leu Trp Ser Ser His Ala  
755 760 765

Ala Ala Pro Asn Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe  
770 775 780

Asn Pro Asp Thr Lys Ala Thr Leu Ala Ala Arg Asn Thr Thr Ser Ser  
785 790 795 800

Pro Thr Ile Phe Ser Tyr Gly Ala Ser Gly Ile Ala Ser Thr Gly Gln  
805 810 815

Val Gly Ala Leu Val Val Glu Asn Asn Ser Val Thr Asn Thr Ala Ala  
820 825 830

Ala Ile Thr Phe His Ser Pro Gln Lys Tyr Gln Val Asn Phe Gly Leu  
835 840 845

Asp Ala Asp Asn Val Val Lys Ile Gly Gly Gly Thr Met Gly Gly Val  
850 855 860

Ala Tyr Pro Ile Ile His Ser Gly Asn Tyr Asn Asn Tyr Ile Asn Gln  
865 870 875 880

Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Ala Ile Leu  
885 890 895

Ala Val Leu Asp Thr Ser Ala Pro Ala Ala Ser Ile Ala Pro Gly Thr  
900 905 910

Ile Met Asp Ser Ser Lys Leu Phe Tyr Ser Ser Cys Asp Ser Thr Tyr  
915 920 925

Arg Ser Ser Ala Ser Pro Thr Gly Thr Trp Arg Cys Met Gly Tyr Val  
930 935 940

Tyr Asn Arg Asp Ser Thr Asn Gly Asp Ser Ala Ser Leu Phe Gln Arg  
945 950 955 960

Val Thr

<210> 55  
<211> 962  
<212> PRT  
<213> bacteriohage NH-4

<400> 55



CASEDOCS-#2318074-v1-Sequence\_listing

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Arg Asn Ala Glu Val Val Arg  
85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
115 120 125

Trp Ser Val Met Arg Thr Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Glu  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ala Ile Val Val Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ser Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln His Gly Arg Val Thr Tyr Gly Thr Ala Ala Gly Pro Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Ile Gln Gly Gly Leu Val Asp Gly  
260 265 270



CASEDOCS-#2318074-v1-Sequence\_listing

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Thr Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Thr Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
530 535 540



CASEDOCS-#2318074-v1-Sequence\_listing

Leu Thr Val Ser Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Asn Val Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Leu Gly Ser  
660 665 670

Phe Asn Asp Ser Gln His Thr Arg Met Val Asn Ser Ala Ala Lys Asp  
675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
690 695 700

Phe Asn Tyr Glu Ala Ser Thr Pro Thr Gly Asn Arg Ala Ala Val Ile  
705 710 715 720

Ser Phe Val Arg Asn Gly Ala Arg Gly Val Leu Phe Gly Leu Asp Thr  
725 730 735

Asp Asn Lys Leu Lys Trp Gly Gly Tyr Ser Leu Gly Ala Val Ala Phe  
740 745 750

Glu Ile Ala Asp Ser Asn Asn Leu Met Ser Leu Trp Ser Ser His Ala  
755 760 765

Ala Ala Pro Asn Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe  
770 775 780

Asn Pro Asp Thr Lys Ala Thr Leu Ala Ala Arg Asn Thr Thr Ser Ser  
785 790 795 800

Pro Thr Ile Phe Ser Tyr Gly Ala Ser Gly Ile Ala Ser Thr Gly Gln  
805 810 815



CASEDOCS-#2318074-v1-Sequence\_listing

Val Gly Ala Leu Val Val Glu Asn Asn Ser Val Thr Asn Thr Ala Ala  
820 825 830

Ala Ile Thr Phe His Ser Pro Gln Lys Tyr Gln Val Asn Phe Gly Leu  
835 840 845

Asp Ala Asp Asn Val Val Lys Ile Gly Gly Gly Thr Met Gly Gly Val  
850 855 860

Ala Tyr Pro Ile Ile His Ser Gly Asn Tyr Asn Asn Tyr Ile Asn Gln  
865 870 875 880

Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Ala Ile Leu  
885 890 895

Ala Val Leu Asp Thr Ser Ala Pro Ala Ala Ser Ile Ala Pro Gly Thr  
900 905 910

Ile Met Asp Ser Ser Lys Leu Phe Tyr Ser Ser Cys Asp Ser Thr Tyr  
915 920 925

Arg Ser Ser Ala Arg Pro Thr Gly Thr Trp Arg Cys Met Gly Tyr Val  
930 935 940

Tyr Asn Arg Asp Ser Thr Asn Gly Asp Ser Ala Ser Leu Phe Gln Arg  
945 950 955 960

Val Thr

<210> 56  
<211> 962  
<212> PRT  
<213> bacteriophage 14-1

<400> 56

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
65 70 75 80



## CASEDOCS-#2318074-v1-Sequence\_listing

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
115 120 125

Trp Ser Val Met Arg Ser Ser Ile Pro Met Pro Ala Gly Gly Pro Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ile Ala  
165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Ile Ser Arg Ser Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Glu Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Pro Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Val Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350



## CASEDOCS-#2318074-v1-Sequence\_listing

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
 355 360 365

Trp Thr Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
 370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
 385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
 405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
 420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
 435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
 450 455 460

Gly Pro Ile Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
 465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
 485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
 500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asp Arg Pro Leu Phe Ala  
 515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
 530 535 540

Leu Thr Val Ser Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
 545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
 565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
 580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
 595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Arg Leu Lys Arg Ala Gly Trp Ser  
 610 615 620



## CASEDOCS-#2318074-v1-Sequence\_listing

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Asn Val Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asp Pro Asn Leu Lys Leu Thr Leu Asn Ala  
660 665 670

Phe Asn Asp Ser Ser Tyr Thr Arg Met Thr Asn Ser Gly Ala Lys Asp  
675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
690 695 700

Phe Asn Tyr Glu Ala Ser Asn Pro Thr Gly Pro Arg Ala Ala Val Ile  
705 710 715 720

Ser Phe Val Arg Asn Gly Ser Arg Gly Val Leu Phe Gly Leu Asp Ser  
725 730 735

Asp Asn Lys Leu Lys Trp Gly Gly Tyr Ser Leu Gly Ala Val Ala Phe  
740 745 750

Glu Ile Ala Asp Ser Asn Asn Leu Met Ser Leu Trp Ser Ser His Ala  
755 760 765

Ala Ala Pro Asn Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe  
770 775 780

Asn Pro Asp Thr Lys Ala Thr Leu Ala Ala Arg Asn Thr Thr Ser Ser  
785 790 795 800

Pro Thr Ile Phe Ser Tyr Gly Ala Ser Gly Ile Ala Ser Thr Gly Gln  
805 810 815

Val Gly Ala Leu Val Val Glu Asn Asn Ser Val Thr Asn Thr Ala Ala  
820 825 830

Ala Ile Thr Phe His Ser Pro Gln Lys Tyr Gln Val Asn Phe Gly Leu  
835 840 845

Asp Ala Asp Asn Val Val Lys Ile Gly Gly Gly Thr Met Gly Gly Val  
850 855 860

Ala Tyr Pro Ile Ile His Ser Gly Asn Tyr Asn Asn Tyr Ile Asn Gln  
865 870 875 880

Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly Ile Phe  
885 890 895



CASEDOCS-#2318074-v1-Sequence\_listing

Ala Val Leu Asp Asn Ala Ala Pro Ile Ala Thr Val Gln Pro Gly Val  
900 905 910

Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ala Ala Asn Tyr  
915 920 925

Asn Ser Gly Gln Arg Pro Ala Gly Thr Trp Arg Cys Met Gly Tyr Val  
930 935 940

Val Asn Arg Asp Ala Asn Thr Pro Asp Ser Ala Thr Leu Phe Gln Arg  
945 950 955 960

Val Thr

<210> 57  
<211> 962  
<212> PRT  
<213> bacteriohage PTP47

<400> 57

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
65 70 75 80

Phe Gln Asp Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
115 120 125

Trp Ser Ala Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Ile Ala



## CASEDOCS-#2318074-v1-Sequence\_listing

165

170

175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
245 250 255

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Thr Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
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## CASEDOCS-#2318074-v1-Sequence\_listing

435

440

445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
 450 455 460

Gly Pro Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
 465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Ala Val Ile Ala Val  
 485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
 500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
 515 520 525

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
 530 535 540

Leu Thr Val Ser Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Arg  
 545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
 565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Arg Ile Phe Gly Lys Gly  
 580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
 595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
 610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
 625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Asn Val Glu Phe  
 645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Leu Gly Ser  
 660 665 670

Phe Asn Asp Gly Gln His Thr Arg Met Val Asn Ser Ala Ala Lys Asp  
 675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
 690 695 700

Phe Asn Tyr Glu Ala Ser Thr Pro Thr Gly Asn Arg Ala Ala Val Ile



705 710 715 720

val Thr



## CASEDOCS-#2318074-v1-Sequence\_listing

&lt;211&gt; 962

&lt;212&gt; PRT

&lt;213&gt; bacteriohage SN

&lt;400&gt; 58

Met Ile Thr Pro Glu Leu Ile Pro Ser Pro Phe Ala Ala Gln Gly Asp  
 1 5 10 15

Lys Asp Pro Ile Pro Gln Thr Ser Ser Thr Gly Phe Ala Asn Leu Arg  
 20 25 30

Asp Gly Tyr Thr Pro Asp Tyr Glu Ile Ser Leu Ala Ser Asn Asn Pro  
 35 40 45

Gln Ala Lys Ala Val Glu Arg Lys Ile Gln Asn Gln Leu Phe Phe Ile  
 50 55 60

Ala Thr Gln Asn Ala Gln Ala Trp Gln Arg Gln Met Ala Pro Pro Trp  
 65 70 75 80

Phe Gln Gly Met Pro Gly Gly Tyr Glu Gln Asn Ala Glu Val Val Arg  
 85 90 95

Val Gly Asn Asp Gly Ile Met Arg Arg Tyr Arg Ser Met Val Asn Ala  
 100 105 110

Asn Ala Ser Asp Pro Leu Ser Ser Thr Thr Trp Glu Glu Gln Pro Ala  
 115 120 125

Trp Ser Val Met Arg Ser Asn Ile Pro Met Pro Ala Gly Gly Pro Gly  
 130 135 140

Leu Ser Ser Gly Gly Glu Val Ile Thr Thr Gly Arg Asn Phe Asn Asp  
 145 150 155 160

Leu Leu Asn Gly Thr Trp Glu Phe Phe Ser Asp Ser Val Val Val Ala  
 165 170 175

Ser Gln Asn Ala Pro Val Tyr Pro Ala Ser Ala Gly Ala Ala Ala Gly  
 180 185 190

Met Leu Glu Ala Lys Ser Trp Val Ser Gly Ala Asn Thr Phe Cys Val  
 195 200 205

Gln Arg Tyr Thr Asp Arg Val Gly Asn Val Ala Val Arg Gly Leu Asn  
 210 215 220

Ala Gly Ala Trp Thr Asn Trp Met Tyr Ala Val Asn Val Met Ala Leu  
 225 230 235 240

Gln Gln Gly Arg Val Thr Tyr Gly Val Ala Ala Gly Ser Ala Asn Ala  
 245 250 255



CASEDOCS-#2318074-v1-Sequence\_listing

Tyr Thr Leu Thr Leu Val Pro Gln Leu Gln Gly Gly Leu Val Asp Gly  
260 265 270

Met Ile Leu Arg Val Lys Phe Asn Thr Met Asn Thr Gly Ala Ser Thr  
275 280 285

Ile Asn Val Ser Gly Leu Gly Ala Lys Ala Ile Val Gly Ala Ala Asn  
290 295 300

Phe Pro Leu Thr Gly Gly Glu Leu Gly Gln Gly Leu Ile Ala Glu Leu  
305 310 315 320

Val Phe Asp Ala Ala Gly Asp Arg Trp Arg Ile Leu Ala Gly Ala Pro  
325 330 335

Arg Ile Gln Val Gly Asn Ala Asp Gln Asp Tyr Gln Ala Pro Ser Trp  
340 345 350

Lys Gln Val Lys Asp Tyr Val Ala Ser Gln Lys Leu Thr Glu Val Asp  
355 360 365

Trp Ala Asp Val Val Asn Lys Pro Asn Val Ala Ile Gln Asp Thr Thr  
370 375 380

Pro Trp Phe Ala Asn Leu Glu Leu Ser Asp Ala Arg Pro Phe Ile Asp  
385 390 395 400

Phe His Phe Asn Ser Asn Arg Ala Lys Asp Phe Asp Tyr Arg Leu Ile  
405 410 415

Ser Glu Ala Asp Gly Ser Leu Ala Phe Tyr Ser Arg Gln Gly Ser Ala  
420 425 430

Gly Pro Thr Gln Asp Ile Leu Phe Asn Arg Asn Ser Val Thr Phe Phe  
435 440 445

Gln Pro Arg Leu Asp Val Ala Lys Asn Leu Ala Tyr Ile Ala Asn Ser  
450 455 460

Gly Ser Leu Trp Gln Asn Thr Thr Ala Asp Gln Pro Gly Trp Lys Phe  
465 470 475 480

Thr Phe Ala Gln Gly Val Asp Ala Asn Asn Asn Ala Val Ile Ala Val  
485 490 495

Asn Thr Thr Asn Pro Asp Gly Ser Tyr Arg Ser Gln Val Met Arg Trp  
500 505 510

Asp Trp Ala Ser Thr Asn Val Ile Phe Asn Asn Arg Pro Leu Phe Ala  
515 520 525



CASEDOCS-#2318074-v1-Sequence\_listing

Gly Gln Tyr Thr Pro Trp Asp Ser Gly Asn Phe Asp Pro Ser Thr Lys  
530 535 540

Leu Thr Val Arg Ala Thr Asn Gln Ile Ala Gly Pro Thr Gly Ile Gln  
545 550 555 560

Asn Thr Asn Gly Asn Thr Gly Asn Met Asn Thr Trp Gly Ser Gly Ser  
565 570 575

Thr Thr Ala Ser Tyr Gly Asn Ala Ala Ile Gln Ile Phe Gly Lys Gly  
580 585 590

Gly Gly Glu Pro Ala Ala Ile Tyr Phe Asp Asn Ser Gln Thr Gly Trp  
595 600 605

Tyr Leu Gly Met Asp Lys Asp Gly Gln Leu Lys Arg Ala Gly Trp Ser  
610 615 620

Leu Gly Asn Asn Ser Tyr Val Ile Thr Asp Glu Ser Asn Ile Arg Thr  
625 630 635 640

His Ile Asn Thr Met Ala Ala Arg Pro Ile Trp Gly Gly Val Glu Phe  
645 650 655

Trp Gly Pro Trp Asn Phe Asn Pro Asn Thr Lys Leu Thr Leu Gly Ser  
660 665 670

Phe Asn Asp Ser Gln His Thr Arg Met Val Asn Ser Ala Ala Lys Asp  
675 680 685

Val Gly Ile Ala Ser Met Thr Ser Tyr Ala Asp Ala Ala Met Ser Phe  
690 695 700

Phe Asn Tyr Glu Ala Ser Thr Pro Thr Gly Asn Arg Ala Ala Val Ile  
705 710 715 720

Ser Phe Val Arg Asn Gly Ala Arg Gly Val Leu Phe Gly Leu Asp Thr  
725 730 735

Asp Asn Lys Leu Lys Trp Gly Gly Tyr Ser Leu Gly Ala Val Ala Phe  
740 745 750

Glu Ile Ala Asp Ser Asn Asn Leu Met Ser Leu Trp Ser Ser His Ala  
755 760 765

Ala Ala Pro Asn Trp Asn Gly Gln Thr Ile Trp Arg Ser Gly Asn Phe  
770 775 780

Asn Pro Asp Thr Lys Ala Thr Leu Ala Ala Arg Asn Thr Thr Ser Ser  
785 790 795 800



CASEDOCS-#2318074-v1-Sequence\_listing

Pro Thr Ile Phe Ser Tyr Gly Ala Ser Gly Ile Ala Ser Thr Gly Gln  
805 810 815

Val Gly Ala Leu Val Val Glu Asn Asn Ser Val Thr Asn Thr Ala Ala  
820 825 830

Ala Ile Thr Phe His Ser Pro Gln Lys Tyr Gln Val Asn Phe Gly Leu  
835 840 845

Asp Ala Asp Asn Val Val Lys Ile Gly Gly Gly Thr Met Gly Gly Val  
850 855 860

Ala Tyr Pro Ile Ile His Ser Gly Asn Tyr Asn Asn Tyr Ile Asn Gln  
865 870 875 880

Ala Leu Val Gln Val Gly Leu Gly Gly Val Gly Ser Tyr Gly Ile Phe  
885 890 895

Ala Val Leu Asp Asn Ala Ala Pro Thr Ala Thr Val Gln Pro Gly Val  
900 905 910

Val Val Asp Gly Ser Ile Leu Ile Tyr Ser Ser Cys Ala Ala Asn Tyr  
915 920 925

Asn Ser Gly Gln Arg Pro Ala Gly Thr Trp Arg Cys Met Gly Tyr Val  
930 935 940

Val Asn Arg Asp Ala Asn Thr Pro Asp Ser Ala Thr Leu Phe Gln Arg  
945 950 955 960

Val Thr