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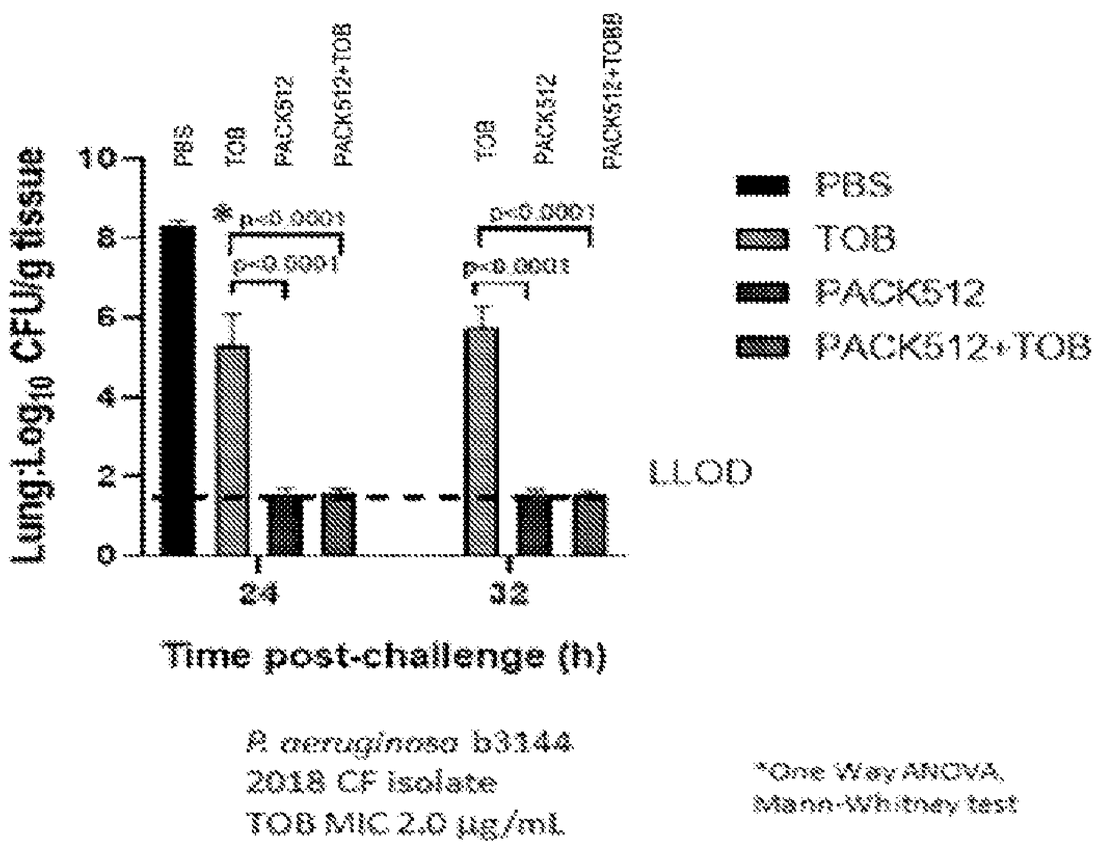


Fig. 18D

(57) Abstract: Disclosed here are phage compositions targeting a Pseudomonas species comprising CRISPR-Cas systems and methods of use thereof.

[Continued on next page]

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PHAGE COMPOSITIONS FOR *PSEUDOMONAS* COMPRISING CRISPR-CAS SYSTEMS AND METHODS OF USE THEREOF

CROSS-REFERENCE

[001] This Application claims the benefit of U.S. Provisional Application No. 63/110,288, filed on November 5, 2020, and U.S. Provisional Application No. 63/184,728, filed on May 5, 2021, both of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 27, 2021, is named 53240-743_601_SL.txt and is 71,774 bytes in size.

SUMMARY

[003] Disclosed herein, in certain embodiments, are phage compositions comprising CRISPR-Cas systems and methods of use thereof.

[004] Disclosed herein, in certain embodiments, are bacteriophages comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequence at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some

embodiments, the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system. In some embodiments, the Cascade complex comprises: (i) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system); (ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system); (iii) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system); (iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system); (v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); (vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system). In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the nucleic acid sequence further comprises a promoter sequence. In some embodiments, the *Pseudomonas* species is killed solely by lytic activity of the bacteriophage. In some embodiments, the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage. In some embodiments, the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage. In some embodiments, the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic. In some embodiments, the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage. In some embodiments, the bacteriophage infects multiple bacterial strains. In some embodiments, the bacteriophage is an obligate lytic bacteriophage. In some embodiments, the bacteriophage is a temperate bacteriophage that is rendered lytic. In some embodiments, the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene. In some embodiments, the bacteriophage comprises a PhiKZvirus, a PhiKMV virus, a Brunyoghevirus, a Samunavirus, a Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus,

Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or a Pbunavirus bacteriophage. In some embodiments, the bacteriophage is engineered from a bacteriophage that infects *Pseudomonas*. In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Pbunavirus phage subtype listed in **Table 5A,** wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., phage p1106 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include an engineered Pbunavirus phage subtype listed in **Table 5A**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., p1106e003 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Samunavirus phage subtype, an engineered Samunavirus phage subtype, a wildtype PhiKZvirus, a wildtype PhiKMVvirus, or a wildtype Bruynoghevirus, e.g., as listed in **Table 5B**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+)**.** As listed in **Table 5A**, the wildtype Pbunavirus phage subtypes can be p1106, p1587, p1835, p2037, p2363, p2421, and/or pb1, while the engineered Pbunavirus phage subtypes can be p1106e003, p1587e002, p1835e002, p2037e002, p2363e003, and/or p2421e002. As listed in **Table 5B**, the wildtype Samunavirus phage subtypes can be p1772, p2131, p2132, and/or p2973, the engineered Samunavirus phage subtypes can be pb1e002, p1772e005, p2131e002, p2132e002, and/or p2973e002, the wildtype PhiKZvirus phage subtypes can be p1194, and/or p4430, the wildtype PhiKMVvirus phage subtype can be p2167, and the wildtype Bruynoghevirus phage subtypes can be p1695, and p3278. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Nankokuvirus. In some embodiments, a bacteriophage that infects *Pseudomonas* kills *Pseudomonas*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the

bacteriophage that kills *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *A. baumanii*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, a combination of bacteriophage infect *Pseudomonas*. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B. In some embodiments, a combination of bacteriophage kill *Pseudomonas*. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B.

[005] In some embodiments, provided is a cocktail system comprising one or more bacteriophage. In some embodiments, the bacteriophage included in the cocktail system includes any one of p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof. In some embodiments, the bacteriophage cocktail system used herein includes, one, two, three, four, five, six or more that are selected from the group consisting of p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, and PB1. In some embodiments, the bacteriophage is a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%

sequence identity to a bacteriophage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, and PB1. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one, two, three, four, five, six, or more from p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p1194, p4430, and p1695. In some embodiments, the nucleic acid sequence is inserted in place of or adjacent to a non-essential bacteriophage gene. In some embodiments, the bacteriophage is selected from a group consisting of p1106e003, p1835e002, p1772e005, and p2131e002. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, and p1194. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, and p4430. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, and p1695. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of e p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the bacteriophage cocktail system comprises the bacteriophage of CK000512 (p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695).

[006] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising: (a) the bacteriophage described herein; and (b) a pharmaceutically acceptable excipient. In some embodiments, the bacteriophage are selected from among a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus

and Pbunavirus. In some embodiments, the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage are selected from among a p1106e003, p1835e002, p1772e005, p2131e002, p1194, and a p1695 phage. In some embodiments, the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the pharmaceutical composition is in the form of a tablet, a liquid, a syrup, an oral formulation, an intravenous formulation, an intranasal formulation, an ocular formulation, an otic formulation, a subcutaneous formulation, an inhalable respiratory formulation, a suppository, a lyophilized formulation, a nebulizable formulation, and any combination thereof. In one embodiment, the pharmaceutical composition comprises p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695 in a nebulizable formulation for pulmonary delivery.

[007] In certain aspects, disclosed herein is a method of killing a *Pseudomonas* species comprising introducing into the target bacterium a nucleic acid sequence encoding a Type I CRISPR-Cas system from a bacteriophage, the nucleic acid comprising: a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in the *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some embodiments, the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas

system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system. In some embodiments, the Cascade complex comprises: (i) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system); (ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system); (iii) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system); (iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system); (v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); (vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system). In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the nucleic acid sequence further comprises a promoter sequence. In some embodiments, the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage. In some embodiments, the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage. In some embodiments, the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic. In some embodiments, the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage. In some embodiments, the bacteriophage infects multiple bacterial strains. In some embodiments, the bacteriophage is an obligate lytic bacteriophage. In some embodiments, the bacteriophage is a temperate bacteriophage that is rendered lytic. In some embodiments, the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene. In some embodiments, the bacteriophage comprises a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus bacteriophage. In some embodiments, the bacteriophage is part of a bacteriophage cocktail. In some embodiments, the bacteriophage or bacteriophage cocktail comprises p1106, p1194, p1587, p1695, p1772, p1835,

p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof. In some embodiments, the bacteriophage is a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a bacteriophage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, and PB1. In some embodiments, the bacteriophage or bacteriophage cocktail comprises p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the bacteriophage or bacteriophage cocktail comprises a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the nucleic acid sequence is inserted in place of or adjacent to a non-essential bacteriophage gene. In some embodiments, a mixed population of bacterial cells comprises the *Pseudomonas* species. In some embodiments, the bacteriophage cocktail comprise p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the bacteriophage cocktail comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

[008] In certain aspects, disclosed herein is a method of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array; a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleic acid sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence

comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some embodiments, the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system. In some embodiments, the Cascade complex comprises: (i) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system); (ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system); (iii) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system); (iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system); (v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); (vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system). In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the nucleic acid sequence further comprises a promoter sequence. In some embodiments, the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage. In some embodiments, the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage. In some embodiments, the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic. In some embodiments, the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage In some embodiments, the bacteriophage infects multiple bacterial strains. In some embodiments, the bacteriophage is an obligate lytic bacteriophage. In some embodiments, the bacteriophage is a temperate bacteriophage that is rendered lytic. In some embodiments, the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene. In some

embodiments, the bacteriophage comprises a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the bacteriophage is part of a bacteriophage cocktail. In some embodiments, the bacteriophage or bacteriophage cocktail comprises p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof. In some embodiments, the bacteriophage is a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a bacteriophage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, and PB1. In some embodiments, the bacteriophage or bacteriophage cocktail comprises p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the bacteriophage or bacteriophage cocktail comprises a bacteriophage having at least 80%, at least 85%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the nucleic acid sequence is inserted in place of or adjacent to a non-essential bacteriophage gene. In some embodiments, the method further comprises administering at least one additional bacteriophage type. In some embodiments, the method further comprises administering 2, 3, 4, 5, 6, 7, 8, 9, or 10 different bacteriophages. In some embodiments, the method further comprises administering at least six different bacteriophages. In some embodiments, the method further comprises administering at least six different bacteriophages, wherein the bacteriophages in a bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the method further comprises administering at least six different bacteriophages, wherein the bacteriophages comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the disease is a bacterial infection. In some embodiments, the bacterial infection is a *Pseudomonas* bacterial infection. In some embodiments, the bacterial infection is associated with cystic fibrosis. In some embodiments the bacterial infection is associated with non-cystic fibrosis bronchiectasis. In some embodiments, the disease or condition is cystic fibrosis. In some embodiments, the disease

or condition is non-cystic fibrosis bronchiectasis. In some embodiments, the bacterial infection is a *Pseudomonas* bacterial infection associated with cystic fibrosis. In some embodiments the bacterial infection is a *Pseudomonas* bacterial infection associated with non-cystic fibrosis bronchiectasis. In some embodiments, the disease or condition is pneumonia. For instance, the pneumonia is hospital acquired pneumonia, ventilator acquired pneumonia, community acquired pneumonia, or health care acquired pneumonia. In some embodiments, the disease or condition is a blood system infection (BSI). In some embodiments, the *Pseudomonas* species causing the disease or condition is a drug resistant *Pseudomonas* species. In some embodiments, the drug resistant *Pseudomonas* species is resistant to at least one antibiotic. In some embodiments, the *Pseudomonas* species causing the disease or condition is a multidrug resistant *Pseudomonas* species. In some embodiments, the multi-drug resistant *Pseudomonas* species is resistant to at least one antibiotic. In some embodiments, the antibiotic comprises a cephalosporin, a fluoroquinolone, a carbapenem, a colistin, an aminoglycoside, vancomycin, streptomycin, or methicillin. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa.* In some embodiments, the administering is intra-arterial, intravenous, intraurethral, intramuscular, oral, subcutaneous, inhalation, topical, cutaneous, transdermal, transmucosal, implantation, sublingual, buccal, rectal, vaginal, ocular, otic, or nasal administration or any combination thereof. In some embodiments, the method further comprises administering an additional therapeutic. In some embodiments, the additional therapeutic comprises tobramycin. In some embodiments, the individual is a mammal. In some embodiments, the additional therapeutic comprises a drug for improving airway function. In some embodiments, the additional therapeutic comprises a drug for reducing airway responsiveness. In some embodiments, the additional therapeutic comprises a drug for reducing airway inflammation. In some embodiments, the additional therapeutic comprises a bronchodilator. In some embodiments, the additional therapeutic comprises a drug for improving oxygen availability. In some embodiments, the additional therapeutic comprises a drug for reducing airway mucogenesis. In some embodiments, the additional therapeutic comprises a DNAse. In some embodiments, the additional therapeutic is saline. In some embodiments, the additional therapeutic is a therapeutic method comprising coughing practices, e.g., as used for treating cystic fibrosis.

[009] In certain aspects, disclosed herein is a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide comprising Cas5, Cas8c and Cas7; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-

120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some embodiments, the nucleic acid sequence further comprises a promoter sequence. In some embodiments, the *Pseudomonas* species is killed solely by lytic activity of the bacteriophage. In some embodiments, the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage. In some embodiments, the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage. In some embodiments, the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic. In some embodiments, the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage. In some embodiments, the bacteriophage infects multiple bacterial strains. In some embodiments, the bacteriophage is an obligate lytic bacteriophage. In some embodiments, the bacteriophage is a temperate bacteriophage that is rendered lytic. In some embodiments, the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene. In some embodiments, the bacteriophage is one from a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the

bacteriophage used herein includes any one or more of p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof. In some embodiments, the bacteriophage is a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a bacteriophage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, and PB1. In some embodiments, the bacteriophage in the used herein includes any one or more of p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the bacteriophage used herein includes any one or more of a bacteriophage having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, the bacteriophage used herein is selected from a group consisting of p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the bacteriophage in the bacteriophage cocktail system used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the nucleic acid sequence is inserted into a non-essential bacteriophage gene. In some embodiments, disclosed herein is a pharmaceutical composition comprising: (a) the bacteriophage disclosed herein; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises at least two different bacteriophages. In some embodiments, the pharmaceutical composition comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 different bacteriophages. In some embodiments, the pharmaceutical composition comprises at least six different bacteriophages. In some embodiments, the pharmaceutical composition comprises at least six different bacteriophages, wherein the bacteriophage used herein includes any one or more of p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the pharmaceutical composition comprises at least six different bacteriophages, wherein the bacteriophage used herein includes p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the pharmaceutical composition is in the form of a tablet, a capsule, a liquid, a syrup, an oral formulation, an intravenous formulation, an intranasal formulation, an ocular formulation, an otic formulation, a subcutaneous formulation, a topical formulation, a transdermal formulation, a transmucosal formulation, an inhalable respiratory formulation, a suppository, a lyophilized formulation, a nebulizable formulation, and any combination thereof. In some embodiments, the

pharmaceutical composition comprises p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695 in a nebulizable formulation for pulmonary delivery.

[0010] In certain aspects, disclosed herein is a method of sanitizing a surface in need thereof, the method comprising administering to the surface a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array; a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and a Cas3 polypeptide. In some embodiments, the surface is a hospital surface, a vehicle surface, an equipment surface, or an industrial surface.

[0011] In certain aspects, disclosed herein is a method of preventing contamination in a food product or a nutritional supplement, the method comprising contacting the food product or the nutritional supplement a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array; a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and a Cas3 polypeptide. In some embodiments, the food product or nutritional supplement comprises milk, yoghurt, curd, cheese, fermented milks, milk based fermented products, ice-creams, fermented cereal based products, milk based powders, infant formulae or tablets, liquid suspensions, dried oral supplement, wet oral supplement, or dry-tube-feeding.

[0012] In certain aspects, disclosed herein is a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: a CRISPR array comprising spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species, wherein the spacer sequences comprise SEQ ID NOs: 12, 16, and 20; a Cascade polypeptide; and a Cas3 polypeptide.

[0013] In certain aspects, disclosed herein is a bacteriophage comprising at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to a phage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the bacteriophage used herein includes any one or more of a bacteriophage having at least 80%,85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof. In some embodiments, provided is a bacteriophage cocktail system comprising two more bacteriophage. In some embodiments, the bacteriophage cocktail system comprises the bacteriophage of CK000512 (p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695). In some embodiments, the bacteriophage further comprises a CRISPR array; a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and a Cas3 polypeptide. In some embodiments, the one or

more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

[0014] In certain aspects, disclosed herein is a composition comprising at least four bacteriophage, comprising: a first bacteriophage comprising p1106e003 or having at least 80% sequence identity to p1106e003; a second bacteriophage comprising p1835e002 or having at least 80% sequence identity to p1835e002; a third bacteriophage comprising p1772e005 or having at least 80% sequence identity to p1772e005; and a fourth bacteriophage comprising p2131e002 or having at least 80% sequence identity to p2131e002. In some embodiments, the composition further comprises a fifth bacteriophage comprising p1194 or having at least 80% sequence identity to p1194. In some embodiments, the composition further comprises a fifth bacteriophage comprising p1695 or having at least 80% sequence identity to p1695. In some embodiments, the composition further comprises a fifth bacteriophage comprising p4430 or having at least 80% sequence identity to p4430. In some embodiments, the composition further comprises a sixth bacteriophage comprising p1695 or having at least 80% sequence identity to p1695. In some embodiments, the composition comprises the bacteriophage of CK000512 (p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695).

[0015] In any of the methods embodiments herein, the bacteriophage of the method is engineered from a bacteriophage that infects *Pseudomonas*. In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Pbunavirus phage subtype listed in **Table 5A,** wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., phage p1106 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include an engineered Pbunavirus phage subtype listed in **Table 5A**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., p1106e003 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Samunavirus phage subtype, an engineered Samunavirus phage subtype, a wildtype PhiKZvirus, a wildtype PhiKMVvirus, or a

wildtype Bruynoghevirus, e.g., as listed in **Table 5B**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+)**.** As listed in **Table 5A**, the wildtype Pbunavirus phage subtypes can be p1106, p1587, p1835, p2037, p2363, p2421, and/or pb1, while the engineered Pbunavirus phage subtypes can be p1106e003, p1587e002, p1835e002, p2037e002, p2363e003, and/or p2421e002. As listed in **Table 5B**, the wildtype Samunavirus phage subtypes can be p1772, p2131, p2132, and/or p2973, the engineered Samunavirus phage subtypes can be pb1e002, p1772e005, p2131e002, p2132e002, and/or p2973e002, the wildtype PhiKZvirus phage subtypes can be p1194, and/or p4430, the wildtype PhiKMVvirus phage subtype can be p2167, and the wildtype Bruynoghevirus phage subtypes can be p1695 and/or p3278. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Nankokuvirus, PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, a bacteriophage that infects *Pseudomonas* kills *Pseudomonas*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *A. baumanii*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that kills

Pseudomonas does not kill *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, a combination of bacteriophage infect *Pseudomonas*. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B. In some embodiments, a combination of bacteriophage kill *Pseudomonas*. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosures will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosures are utilized, and the accompanying drawings of which:

[0017] Fig. 1A depicts the sequence and arrangement of crArray1 (SEQ ID NO: 83). **Fig. 1B** depicts the sequence and arrangement of crArray2 (SEQ ID NO: 84). **Fig. 1C** depicts the sequence and arrangement of crArray3 (SEQ ID NO: 85). **Fig. 1D** depicts the sequence and arrangement of crArray4 (SEQ ID NO: 86). **Fig. 1E** depicts the sequence and arrangement of crArray 5 (SEQ ID NO: 87). **Figs. 1F-1K** depicts the arrangement of crArray1 and the PaIC insert (SEQ ID NO: 25). **Figs. 1L-1Q** depicts the arrangement of crArray3 and the PaIC insert (SEQ ID NO: 24).

[0018] Fig. 2A (top panel) depicts the effects of transforming two *P. aeruginosa* strains with a plasmid containing crRNA using endogenous CRISPR-Cas3 system as measured by the number

of transformants in colony forming units (CFU). The bottom panel shows the effects of transforming *P. aeruginosa* with a plasmid containing both a crRNA containing 3 spacers and an exogenous Type I-C Cas operon, which results in fewer transformants than the limit of detection. **Fig. 2B** depicts the number of bacterial transformants obtained per mL of transformation into a Cas operon null mutant of *P. aeruginosa* strain b1121. Array 1 targets the bacterial genome while array 2 is a non-targeting control. The different plasmids were normalized by molarity to the empty vector control plasmid. **Fig. 2C** depicts the effects of transforming individual spacers targeting rpoB or ftsA or 3-spacer arrays Array 3 or Array 4 into *P. aeruginosa* strains with (b1121) or without (b1121 cas KO) an endogenous Type I-C Cas operon.

[0019] Fig. 3A depicts a schematic representation of the genome of wild type phage p1772 and its engineered variants. The bar below the genome axis indicates the region of the genome that was removed and replaced. The schematics below the phage genome illustrate the DNA that was used to replace WT phage genes in the deleted region. Array 1, Array 3, and Array 4 target the bacterial genome and will kill bacteria in the presence of a Type I-C Cas operon. The spacers in Array 2 are non-targeting, but the array is structurally the same as the three targeting arrays. **Fig. 3B** compares the sequences of p1772e005 (targeting crArray1 + Cas system) after it had been passaged 5 or 10 times at 37 degrees Celsius. No difference was observed in the insert at the nucleotide level indicating the stability of engineered phages expressing CRISPR-Cas3.

[0020] Fig. 4 exemplifies that phage engineered with CRISPR-Cas3 does not exhibit structural changes. There were no gross morphological differences between p1772wt (wild type), p1772e004 (Cas system only), and p1772e005 (targeting crArray + Cas system) when imaged by TEM.

[0021] Fig. 5A-Fig. 5C exemplify full construct phage amplifies similarly to the wild type parent phage in variants of different Cas types and retains a similar host range. **Fig. 5A** depict the *in vitro* amplification titers of p1772wt (wild type), p1772e004 (Cas system), and p1772e005 (targeting crArray1 + Cas system) in *P. aeruginosa* strains containing Type I-F Cas systems. **Fig 5B** depicts the *in vitro* amplification titers of p1772wt and p1772e005 in *P. aeruginosa* strains containing Type I-C Cas systems. **Fig. 5C** depicts the host range of p1772wt, p1772e004 and p1772e005 on 44 strains of *P. aeruginosa.* The phage is considered to infect a given strain if (AUC in the presence of phage)/(AUC in the absence of phage) is less than 0.65.

[0022] Fig. 6A-Fig. 6E exemplify exogenous CRISPR-Cas3 system is efficiently expressed from the phage genome. **Fig. 6A** depicts a schematic of the spacer array and Cas operon inserted into engineered variants of p1772. **Fig. 6B-6D** depict the expression of the crArray, Cas3 and Cas8 in *P. aeruginosa* strain b1121 infected with p1772wt (wild type) or p1772e005 (targeting crArray1 + Cas system) over 1600 minutes. **Fig. 6E** depicts the expression of Cas3 1 and 24 hours after

infection with p1772e005, p2131e002 (targeting crArray1 + Cas system) and p2132e002 (targeting crArray1 + Cas system).

[0023] Fig. 7 depicts plaques resulting from plating p1772wt (wild type) or p1772e005 (targeting crArray1 + Cas system) onto *P. aeruginosa.*

[0024] Fig. 8A exemplifies the results of a plate-based kill assay. p1772wt (wild type), p1772e004 (Cas system only), p1772e006 (targeting crArray1 only) and p1772e005 (targeting crArray1 + Cas system) were mixed with *P. aeruginosa* at multiplicities of infection (MOIs) from 100 to 0.0000954. **Fig. 8B** depicts a portion of a plate set up as in Fig. 8A at greater magnification. **Fig. 8C** shows a quantification of the relative fluorescent units of *P. aeruginosa* infected with p1772wt, p1772e008 (non-targeting crArray2 + Cas system), p1772e006 and p1772e005 at a MOI of 1.5

[0025] Fig. 9A depicts the growth of p1772wt (wild type), p1772e004 (Cas system only), p1772e005 (targeting crArray1 + Cas system) and p1772e006 (targeting crArray1 only) in the *P. aeruginosa* strain b1121 over 24 hours when inoculated at an MOI of 1. **Fig. 9B** depicts the growth of p1772wt, p1772e004, p1772e005 and p1772e006 in the *P. aeruginosa* strain b1121 over 24 hours when inoculated at an MOI of 10. **Fig. 9C** depicts the growth of p1772wt, p1772e004, p1772e005 and p1772e006 in the *P. aeruginosa* strain b1121 over 24 hours when inoculated at an MOI of 100.

[0026] Fig. 10A depicts the growth on an agar plate of *P. aeruginosa* cultures mixed with p1772wt (wild type), p1772e008 (non-targeting crArray2 + Cas system), p1772e006 (targeting crArray 1 only), and pArray3 (targeting crArray3 + Cas system) at MOIs from 100 to 0.0001. **Fig. 10B** depicts the growth on an agar plate of *P. aeruginosa* cultures mixed with p1772wt, p1772e008, p1772e006, and pArray4 (targeting crArray4 + Cas system) at MOIs from 100 to 0.0001. **Fig. 10C** is an inset of Fig. 10A and depicts a magnification of p1772e006 compared to pArray3 at an MOI of 0.0244 (top row) and 0.00610 (bottom row). **Fig. 10D** is a quantification of the fluorescence signal from the bacteria following infection with phage at a MOI of about 1.5 in **Fig. 10A**. **Fig. 10E** is a quantification of fluorescence signal from the bacteria following infection with phage at a MOI of about 1.5 in **Fig. 10B**.

[0027] Fig. 11 depicts the growth on an agar plate of *P. aeruginosa* cultures mixed with p1772 variants with different promoters. **Fig. 11A** shows the growth on an agar plate of *P. aeruginosa* cultures mixed with p1772wt (wild type) and variants containing the same crArray 1 and Cas system, where the Cas system was driven by a different promoter, at an MOI of 100 to 0.00001. **Fig. 11B** shows a quantification of the fluorescence of the cells at MOI 1.5 from Fig. 11A.

[0028] Fig. 12A depicts a quantification of the fluorescence the growth on an agar plate of *P. aeruginosa* cultures mixed with p2132wt (wild type) and p2132e002 (targeting crArray1 + Cas system) at an MOI of 1.5. **Fig. 12B** depicts a quantification of the fluorescence from the growth

on an agar plate of *P. aeruginosa* cultures mixed with p2973wt (wild type) and p2973e002 (targeting crArray1 + Cas system) at an MOI of 1.5.

[0029] Fig. 13 depicts the growth on an agar plate of different strains of *P. aeruginosa* cultures mixed different phage variants. p4209wt (wild type) and p4209e002 (targeting crArray1 + Cas system) were mixed with b2550 (Type I-E Cas), b2631 (Type I-F Cas), b2816 (Type I-E/I-F Cas), and b2825 (no active Type I Cas) strains of *P. aeruginosa* and plated after 0 hours, 3 hours or 24 hours of incubation.

[0030] Fig. 14 depicts the efficacy of the crArray/Cas insert in multiple *P. aeruginosa* strains. p4209wt (wild type), p4209e001 (Cas system only) and p4209e002 (targeting crArray1 + Cas system) were plaqued on b2550 (Type I-E Cas), b2631 (Type I-F Cas), b2816 (Type I-E/I-F Cas), and b2825 (no active Type I Cas) strains of *P. aeruginosa.*

[0031] Fig. 15A-Fig. 15D exemplify *in vivo* efficacy results comparing p1772wt (wild type) to p1772e005 (targeting crArray1 + Cas system). **Fig. 15A** is a schematic depicting the experimental set-up for Figs. 15B-15D. **Fig. 15B** depicts the efficacy of the phage when injected into mouse thigh muscle. The left panel depicts the number of colony forming units (CFU) recovered at 6 hours post-infection. The right panel depicts the number of plaque forming units (PFU) recovered at 6 hours post-infection. **Fig. 15C** depicts the efficacy of the phage when injected into mouse thigh muscle and depicts the number of CFU (top) and PFU (bottom) recovered at 8 and 24 hours post-infection. **Fig. 15D** depicts the efficacy of the phage when administered intravenously and depicts the number of CFU (top) and PFU (bottom) recovered 9, 12, 15 and 24 hours post infection. **Fig. 15E** depicts the experimental set-up for Fig. 15F. **Fig. 15F** depicts the dose response for treatment with p1772wt and p1772e005 and depicts the amount of CFU (top) and PFU (bottom) recovered 8 and 24 hours post-infection. Data shown as mean ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. One- way ANOVA with multiple comparisons or Two-way ANOVA with Tukey's test.

[0032] Fig. 16 exemplifies CRISPR-Cas3 engineered reference phage PB1e002 (crArray1 + Cas system) acts cooperatively with p1772e005 (crArray1 + Cas system).

[0033] Fig. 17 depicts the number of transformants produced after transfecting the *Pseudomonas* with inserts containing different spacer sequences.

[0034] Fig. 18A depicts the assay used to test efficiency of CRISPR-engineered phage alone or in a cocktail. **Fig. 18B** depicts the effects of treatment with the cocktail in mice infected with *P. aeruginosa* b2631. **Fig. 18C** depicts the effects of treatment with the cocktail in mice infected with *P. aeruginosa* b1121. **Fig. 18D** depicts the effects of treatment with the cocktail in mice infected with *P. aeruginosa* b3144. **Fig. 18E** depicts the effects of treatment with CRISPR-engineered phage as compared to wild-type phage. **Fig. 18F** depicts a graphical representation of the assay

used to test cocktail efficacy in comparison to treatment with individual phage. **Fig. 18G** depicts the effects of treatment with the individual phages or the phage cocktail (as shown in the figure) in mice infected with *P. aeruginosa* b2631. **Fig. 18H** depicts the effects of treatment with the cocktail or individual phages in mice infected with *P. aeruginosa* b3144. **Fig. 18I** depicts the effects of treatment with the cocktail or individual phages in mice infected with *P. aeruginosa*.

[0035] Fig. 19A depicts the assay used to test a cocktail efficacy. **FIG. 19B** depicts the effects of treatment with the phage cocktail CK125 in mice infected with *P. aeruginosa* b2631. **Fig. 19C** depicts the effects of treatment with the cocktail in mice infected with *P. aeruginosa* b1121. **Fig. 19D** depicts the effects of treatment with the cocktail in mice infected with *P. aeruginosa* b3144. TOB = tobramycin.

[0036] Fig. 20A shows a graphical representation of the experimental setup to test anti-biofilm activity of the phage cocktail CK125 against preformed biofilms from key *P. aeruginosa* strains b1121 and b2631, using minimum biofilm eradication concentration (MBEC) assay. **Fig. 20B** Left, % inhibition at 24 h, Middle, % inhibition at 48 h. Right, Table showing comparative data depicting MBEC IC50 with phage cocktail or Ciprofloxacin.

[0037] Fig. 21 (Top panel) shows experimental setup and results of testing anti-biofilm activity of the phage cocktail PACK512 against biofilms from respiratory/clinical isolates of *P. aeruginosa* strains b1121, b2631 and b2631, using minimum biofilm eradication concentration (MBEC) method. **Fig. 22** (Bottom panel) Left, % inhibition at 24 h, Right, % inhibition at 48 h.

[0038] Fig. 22A shows assay setup for testing bactericidal activity of the cocktail in the presence of human mucin. **Fig. 22B** shows results from the assay, bacterial load in the different treatments, Left, results for *P. aeruginosa* strains b1121 inhibition from respiratory isolate; Right, results for *P. aeruginosa* strains b2631 inhibition from CF isolates.

[0039] Fig. 23A shows assay setup to test bactericidal efficacy of cocktail in presence of mucin, and comparison with Tobramycin. **Fig. 23B** shows bacterial load in presence of cocktail, or in presence of Tobramycin treatment, in comparison to no treatment control.

[0040] Fig. 24 shows data from testing phage levels after bacterial clearance in an low respiratory tract infection model with *P. aeruginosa*.

DETAILED DESCRIPTION

[0041] Disclosed herein, in certain embodiments, are bacteriophages comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: (a) a CRISPR array (also referred to as "crArray"); (b) a Cascade polypeptide; and (c) a Cas3 polypeptide. Also disclosed herein, in certain embodiments, are pharmaceutical compositions comprising the bacteriophages disclosed herein. Further disclosed herein, in certain embodiments, are methods of killing a *Pseudomonas*

species comprising introducing into the *Pseudomonas* species a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: (a) a CRISPR array; (b) a Cascade polypeptide; and (c) a Cas3 polypeptide. Further disclosed herein, in certain embodiments, are methods of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual a bacteriophage a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: (a) a CRISPR array; (b) a Cascade polypeptide; and (c) a Cas3 polypeptide

Certain terminology

[0042] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The terminology used in the description of the disclosure herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the disclosure.

[0043] Unless the context indicates otherwise, it is specifically intended that the various features of the disclosure described herein are able of being used in any combination. Moreover, the present disclosure also contemplates that in some embodiments, any feature or combination of features set forth herein are excluded or omitted. To illustrate, if the specification states that a composition comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, are omitted and disclaimed singularly or in any combination.

[0044] One of skill in the art will understand the interchangeability of terms designating the various CRISPR-Cas systems and their components due to a lack of consistency in the literature and an ongoing effort in the art to unify such terminology.

[0045] As used in the description and the appended claims, the singular forms “a,” “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also as used herein, “and/or” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

[0046] The term “about” as used herein when referring to a measurable value such as a dosage or time period and the like refers to variations of ± 20%, ± 10%, ± 5%, ± 1%, + 0.5%, or even ± 0.1% of the specified amount. As used herein, phrases such as “between X and Y” and “between about X and Y” should be interpreted to include X and Y. As used herein, phrases such as “between about X and Y” mean “between about X and about Y” and phrases such as “from about X to Y” mean “from about X to about Y.”

[0047] The term “comprise”, “comprises”, and “comprising”, “includes”, “including”, “have” and “having”, as used herein, specify the presence of the stated features, steps, operations, elements,

and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof.

[0048] As used herein, the transitional phrase "consisting essentially of" means that the scope of a claim is to be interpreted to encompass the specified materials or steps recited in the claim and those that do not materially affect the basic and novel characteristic(s) of the claimed disclosure. Thus, the term "consisting essentially of" when used in a claim of this disclosure is not intended to be interpreted to be equivalent to "comprising."

[0049] The term "consists of" and "consisting of", as used herein, excludes any features, steps, operations, elements, and/or components not otherwise directly stated. The use of "consisting of" limits only the features, steps, operations, elements, and/or components set forth in that clause and does exclude other features, steps, operations, elements, and/or components from the claim as a whole.

[0050] The terms "complementary" or "complementarity", as used herein, refer to the natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing. For example, the sequence "A-G-T" binds to the complementary sequence "T-C-A." Complementarity between two single-stranded molecules is "partial," in which only some of the nucleotides bind, or it is complete when total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands.

[0051] "Complement" as used herein means 100% complementarity or identity with the comparator nucleotide sequence or it means less than 100% complementarity (e.g., about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and the like, complementarity). Complement or complementable may also be used in terms of a "complement" to or "complementing" a mutation.

[0052] As used herein, the term "CRISPR phage", "CRISPR enhanced phage", and "crPhage" refers to a bacteriophage particle comprising bacteriophage DNA comprising at least one heterologous polynucleotide that encodes at least one component of a CRISPR-Cas system (e.g., CRISPR array, crRNA; e.g., P1 bacteriophage comprising an insertion of a targeting crRNA). In some embodiments, the polynucleotide encodes at least one transcriptional activator of a CRISPR-Cas system. In some embodiments, the polynucleotide encodes at least one component of an anti-CRISPR polypeptide of a CRISPR-Cas system.

[0053] As used herein, the phrase "substantially identical," or "substantial identity" in the context of two nucleic acid molecules, nucleotide sequences or protein sequences, refers to two or more sequences or subsequences that have at least about 50%, 51 %, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61 %, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71 %, 72%, 73%, 74%,

75%, 76%, 77%, 78%, 79%, 80%, 81 %, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and/or 100% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection. In some embodiments, substantial identity refers to two or more sequences or subsequences that have at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95, 96, 96, 97, 98, or 99% identity. For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0054] Optimal alignment of sequences for aligning a comparison window are conducted by tools such as the local homology algorithm of Smith and Waterman, the homology alignment algorithm of Needleman and Wunsch, the search for similarity method of Pearson and Lipman, and optionally by computerized implementations of these algorithms such as GAP, BESTFIT, FASTA, and TFASTA available as part of the GCG® Wisconsin Package® (Accelrys Inc., San Diego, CA). An "identity fraction" for aligned segments of a test sequence and a reference sequence is the number of identical components which are shared by the two aligned sequences divided by the total number of components in the reference sequence segment, i.e., the entire reference sequence or a smaller defined part of the reference sequence. Percent sequence identity is represented as the identity fraction multiplied by 100. The comparison of one or more polynucleotide sequences is to a full-length polynucleotide sequence or to a portion thereof, or to a longer polynucleotide sequence. In some instances, "Percent identity" is determined using BLASTX version 2.0 for translated nucleotide sequences and BLASTN version 2.0 for polynucleotide sequences.

[0055] As used herein, a "target nucleotide sequence" refers to the portion of a target gene (i.e., target region in the genome or the "protospacer sequence," which is adjacent to a protospacer adjacent motif (PAM) sequence) that is fully complementary or substantially complementary (e.g., at least 70% complementary (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more)) to a spacer sequence in a CRISPR array.

[0056] As used herein, the term "protospacer adjacent motif" or "PAM" refers to a DNA sequence present on the target DNA molecule adjacent to the nucleotide sequence matching the spacer sequence. This motif is found in the target gene next to the region to which a spacer sequence binds as a result of being complementary to that region and identifies the point at which base pairing

with the spacer nucleotide sequence begins. The exact PAM sequence that is required varies between each different CRISPR-Cas system. Non-limiting examples of PAMs include CCA, CCT, CCG, TTC, AAG, AGG, ATG, GAG, and/or CC. In some instances, in Type I systems, the PAM is located immediately 5' to the sequence that matches the spacer, and thus is 3' to the sequence that base pairs with the spacer nucleotide sequence, and is directly recognized by Cascade. In some instances, for *B. halodurans* Type I-C systems, the PAM is YYC, where Y can be either T or C. In some instances, for the *P. aeruginosa* Type I-C system, the PAM is TTC. Once a cognate protospacer and PAM are recognized, Cas3is recruited, which then cleaves and degrades the target DNA. For Type II systems, the PAM is required for a Cas9/sgRNA to form an R-loop to interrogate a specific DNA sequence through Watson-Crick pairing of its guide RNA with the genome. The PAM specificity is a function of the DNA-binding specificity of the Cas9 protein (e.g., a —protospacer adjacent motif recognition domain at the C-terminus of Cas9).

[0057] As used herein, the term “gene” refers to a nucleic acid molecule capable of being used to produce mRNA, tRNA, rRNA, miRNA, anti-microRNA, regulatory RNA, and the like. Genes may or may not be capable of being used to produce a functional protein or gene product. Genes include both coding and non-coding regions (e.g., introns, regulatory elements, promoters, enhancers, termination sequences and/or 5' and 3' untranslated regions). A gene is "isolated" by which is meant a nucleic acid that is substantially or essentially free from components normally found in association with the nucleic acid in its natural state. Such components include other cellular material, culture medium from recombinant production, and/or various chemicals used in chemically synthesizing the nucleic acid.

[0058] By the terms "treat," "treating," or "treatment," it is intended that the severity of the subject's condition is reduced or at least partially improved or modified and that some alleviation, mitigation or decrease in at least one clinical symptom is achieved, and/or there is a delay in the progression of the disease or condition, and/or delay of the onset of a disease or illness. With respect to an infection, a disease or a condition, the term refers to a decrease in the symptoms or other manifestations of the infection, disease or condition. In some embodiments, treatment provides a reduction in symptoms or other manifestations of the infection, disease or condition by at least about 5%, e.g., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more.

[0059] The terms “prevent,” “preventing,” and “prevention” (and grammatical variations thereof) refer to prevention and/or delay of the onset of an infection, disease, condition and/or a clinical symptom(s) in a subject and/or a reduction in the severity of the onset of the infection, disease, condition and/or clinical symptom(s) relative to what would occur in the absence of carrying out the methods disclosed herein prior to the onset of the disease, disorder and/or clinical symptom(s).

Thus, in some embodiments, to prevent infection, food, surfaces, medical tools and devices are treated with compositions and by methods disclosed herein.

[0060] The terms with respect to an "infection", "a disease", or "a condition", used herein, refer to any adverse, negative, or harmful physiological condition in a subject due to the presence of a target bacterium in the subject. The terms are used interchangeably.

[0061] The terms "individual", or "subject" as used herein includes any animal that has or is susceptible to an infection, disease or condition involving bacteria. Thus, in some embodiments, subjects are mammals, avians, reptiles, amphibians, fish, crustaceans, or mollusks. Mammalian subjects include but are not limited to humans, non-human primates (e.g., gorilla, monkey, baboon, and chimpanzee, etc.), dogs, cats, goats, horses, pigs, cattle, sheep, and the like, and laboratory animals (e.g., rats, guinea pigs, mice, gerbils, hamsters, and the like). Avian subjects include but are not limited to chickens, ducks, turkeys, geese, quail, pheasants, and birds kept as pets (e.g., parakeets, parrots, macaws, cockatoos, canaries, and the like). Fish subjects include but are not limited to species used in aquaculture (e.g., tuna, salmon, tilapia, catfish, carp, trout, cod, bass, perch, snapper, and the like). Crustacean subjects include but are not limited to species used in aquaculture (e.g., shrimp, prawn, lobster, crayfish, crab and the like). Mollusk subjects include but are not limited to species used in aquaculture (e.g., abalone, mussel, oyster, clams, scallop and the like). In some embodiments, suitable subjects include both males and females and subjects of any age, including embryonic (e.g., in-utero or in-ovo), infant, juvenile, adolescent, adult and geriatric subjects. In some embodiments, a subject is a human.

[0062] As used here the term "isolated" in context of a nucleic acid sequence is a nucleic acid sequence that exists apart from its native environment.

[0063] As used herein, "expression cassette" means a recombinant nucleic acid molecule comprising a nucleotide sequence of interest (e.g., the recombinant nucleic acid molecules and CRISPR arrays disclosed herein), wherein the nucleotide sequence is operably associated with at least a control sequence (e.g., a promoter).

[0064] As used herein, "chimeric" refers to a nucleic acid molecule or a polypeptide in which at least two components are derived from different sources (e.g., different organisms, different coding regions).

[0065] As used herein, "selectable marker" means a nucleotide sequence that when expressed imparts a distinct phenotype to the host cell expressing the marker and thus allows such transformed cells to be distinguished from those that do not have the marker.

[0066] As used herein, "vector" refers to a composition for transferring, delivering or introducing a nucleic acid (or nucleic acids) into a cell.

[0067] As used herein, "pharmaceutically acceptable" means a material that is not biologically or otherwise undesirable, i.e., the material are administered to a subject without causing any undesirable biological effects such as toxicity.

[0068] As used herein the term "biofilm" means an accumulation of microorganisms embedded in a matrix of polysaccharide. Biofilms form on solid biological or non-biological surfaces and are medically important, accounting for over 80 percent of microbial infections in the body.

[0069] As used herein, the term "in vivo" is used to describe an event that takes place in a subject's body.

[0070] As used herein, the term "in vitro" is used to describe an event that takes places contained in a container for holding laboratory reagent such that it is separated from the biological source from which the material is obtained. In vitro assays can encompass cell-based assays in which living or dead cells are employed. In vitro assays can also encompass a cell-free assay in which no intact cells are employed.

CRISPR/CAS Systems

[0071] CRISPR-Cas systems are naturally adaptive immune systems found in bacteria and archaea. The CRISPR system is a nuclease system involved in defense against invading phages and plasmids that provides a form of acquired immunity. There is a diversity of CRISPR-Cas systems based on the set of *cas* genes and their phylogenetic relationship. There are at least six different types (I through VI) where Type I represents over 50% of all identified systems in both bacteria and archaea. In some embodiments, a Type I, Type II, Type II, Type IV, Type V, or Type VI CRISPR-Cas system is used herein.

[0072] Type I systems are divided into seven subtypes including: Type I-A, Type I-B, Type I-C, Type I-D, Type I-E, Type I-F, and Type I-U. Type I CRISPR-Cas systems include a multi-subunit complex called Cascade (for complex associated with antiviral defense), Cas3 (a protein with nuclease, helicase, and exonuclease activity that is responsible for degradation of the target DNA), and CRISPR array encoding crRNA (stabilizes Cascade complex and directs Cascade and Cas3 to DNA target). Cascade forms a complex with the crRNA, and the protein-RNA pair recognizes its genomic target by complementary base pairing between the 5' end of the crRNA sequence and a predefined protospacer. This complex is directed to homologous loci of pathogen DNA via regions encoded within the crRNA and protospacer-adjacent motifs (PAMs) within the pathogen genome. Base pairing occurs between the crRNA and the target DNA sequence leading to a conformational change. In the Type I-E system, the PAM is recognized by the CasA protein within Cascade, which then unwinds the flanking DNA to evaluate the extent of base pairing between the target

and the spacer portion of the crRNA. Sufficient recognition leads Cascade to recruit and activate Cas3. Cas3 then nicks the non-target strand and begins degrading the strand in a 3'-to-5' direction.

[0073] In the Type I-C system, the proteins Cas5, Cas8c, and Cas7 form the Cascade effector complex. Cas5 processes the pre-crRNA (which can take the form of a multi-spacer array, or a single spacer between two repeats) to produce individual crRNA(s) made up of a hairpin structure formed from the remaining repeat sequence and a linear spacer. The effector complex then binds to the processed crRNA and scans DNA to identify PAM sites. In the Type I-C system, the PAM is recognized by the Cas8c protein, which then acts to unwind the DNA duplex. If the sequence 3' of the PAM matches the crRNA spacer that is bound to effector complex, a conformational change in the complex occurs and Cas3 is recruited to the site. Cas3 then nicks the non-target strand and begins degrading the DNA. In some cases, Cas5 includes Cas5, Cas5c, Cas5d, and a sequence at least 90% identical to SEQ ID NO: 76. In some cases, Cas7 includes Cas7, Cas7c, and a sequence at least 90% identical to SEQ ID NO: 78. In some cases, Cas8 includes Cas8, Cas8c, and a sequence at least 90% identical to SEQ ID NO: 77.

[0074] In some embodiments, the CRISPR-Cas system is endogenous to a *Pseudomonas* species. In some embodiments, the CRISPR-Cas system is exogenous to the *Pseudomonas* species. In some embodiments, the CRISPR-Cas system is a Type I CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-A CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-B CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-C CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-C CRISPR-Cas system derived from *Pseudomonas aeruginosa.* In some embodiments, the CRISPR-Cas system is a Type I-D CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-E CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-F CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type I-U CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type II CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is a Type III CRISPR-Cas system.

[0075] In some embodiments, processing of a CRISPR-array disclosed herein includes, but is not limited to, the following processes: 1) transcription of the nucleic acid encoding a pre-crRNA; 2) recognition of the pre-crRNA by Cascade and/ or specific members of Cascade, such as Cas6, and (3) processing of the pre-crRNA by Cascade or members of Cascade, such as Cas6, into mature crRNAs. In some embodiments, the mode of action for a Type I CRISPR system includes, but is not limited to, the following processes: 4) mature crRNA complexation with Cascade; 5) target recognition by the complexed mature crRNA/Cascade complex; and 6) nuclease activity at the target leading to DNA degradation.

[0076] In some embodiments, provided herein are components of a CRISPR-Cas system and bacteriophage comprising CRISPR-Cas system components. As an example, provided herein is a nucleic acid sequence comprising at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to any one of SEQ ID NOS: 83-87. In some cases, the nucleic acid sequence comprises at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 83. In some cases, the nucleic acid sequence comprises at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 84. In some cases, the nucleic acid sequence comprises at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 85. In some cases, the nucleic acid sequence comprises at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 86. In some cases, the nucleic acid sequence comprises at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 87. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 83. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 84. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 85. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 86. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 87. In any of these embodiments, the nucleic acid sequence may comprise a sequence at least 90% identical to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In a non-limiting example, the nucleic acid sequence comprises one or more of: SEQ ID NO: 12, SEQ ID NO: 16, and SEQ ID NO: 20.

[0077] Further provided herein are CRISPR-Cas system components comprising a nucleic acid sequence at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 24. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 24. In any of these embodiments, the nucleic acid sequence may comprise a sequence at least 90% identical to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In a non-limiting example, the nucleic acid sequence comprises one or more of: SEQ ID NO: 12, SEQ ID NO: 16, and SEQ ID NO: 20.

[0078] Provided herein are CRISPR-Cas system components comprising at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 25. In some cases, the nucleic acid sequence comprises at least about 90% identity to SEQ ID NO: 25. In any of these embodiments, the nucleic acid sequence

may comprise a sequence at least 90% identical to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In a non-limiting example, the nucleic acid sequence comprises one or more of: SEQ ID NO: 12, SEQ ID NO: 16, and SEQ ID NO: 20.

CRISPR Phages

[0079] Disclosed herein, in certain embodiments, are bacteriophage compositions comprising CRISPR-Cas systems and methods of use thereof.

[0080] Bacteriophages or "phages" represent a group of bacterial viruses and are engineered or sourced from environmental sources. Individual bacteriophage host ranges are usually narrow, meaning, phages are highly specific to one strain or few strains of a bacterial species and this specificity makes them unique in their antibacterial action. Bacteriophages are bacterial viruses that rely on the host's cellular machinery to replicate. Bacteriophages are generally classified as virulent or temperate phages depending on their lifestyle. Virulent bacteriophages, also known as lytic bacteriophages, can only undergo lytic replication. Lytic bacteriophages infect a host cell, undergo numerous rounds of replication, and trigger cell lysis to release newly made bacteriophage particles. In some embodiments, the lytic bacteriophages disclosed herein retain their replicative ability. In some embodiments, the lytic bacteriophages disclosed herein retain their ability to trigger cell lysis. In some embodiments, the lytic bacteriophages disclosed herein retain both they replicative ability and the ability to trigger cell lysis. In some embodiments, the bacteriophages disclosed herein comprise a CRISPR array. In some embodiments, the CRISPR array does not affect the bacteriophages ability to replicate and/or trigger cell lysis. Temperate or lysogenic bacteriophages can undergo lysogeny in which the phage stops replicating and stably resides within the host cell, either integrating into the bacterial genome or being maintained as an extrachromosomal plasmid. Temperate phages can also undergo lytic replication similar to their lytic bacteriophage counterparts. Whether a temperate phage replicates lytically or undergoes lysogeny upon infection depends on a variety of factors including growth conditions and the physiological state of the cell. A bacterial cell that has a lysogenic phage integrated into its genome is referred to as a lysogenic bacterium or lysogen. Exposure to adverse conditions may trigger reactivation of the lysogenic phage, termination of the lysogenic state and resumption of lytic replication by the phage. This process is called induction. Adverse conditions which favor the termination of the lysogenic state include desiccation, exposure to UV or ionizing radiation, and exposure to mutagenic chemicals. This leads to the expression of the phage genes, reversal of the integration process, and lytic multiplication. In some embodiments, the temperate bacteriophages disclosed herein are rendered lytic. The term "lysogeny gene" refers to any gene whose gene product promotes lysogeny of a temperate phage. Lysogeny genes can directly promote, as in the

case of integrase proteins that facilitate integration of the bacteriophage into the host genome. Lysogeny genes can also indirectly promote lysogeny as in the case of CI transcriptional regulators which prevent transcription of genes required for lytic replication and thus favor maintenance of lysogeny.

[0081] Bacteriophages package and deliver synthetic DNA using three general approaches. Under the first approach, the synthetic DNA is recombined into the bacteriophage genome in a targeted manner, which usually involves a selectable marker. Under the second approach, restriction sites within the phage are used to introduce synthetic DNA *in-vitro*. Under the third approach, a plasmid generally encoding the phage packaging sites and lytic origin of replication is packaged as part of the assembly of the bacteriophage particle. The resulting plasmids have been coined "phagemids."

[0082] Phages are limited to a given bacterial strain for evolutionary reasons. In some cases, injecting their genetic material into an incompatible strain is counterproductive. Phages have therefore evolved to specifically infect a limited cross-section of bacterial strains. However, some phages have been discovered that inject their genetic material into a wide range of bacteria. The classic example is the P1 phage, which has been shown to inject DNA in a range of gram-negative bacteria.

[0083] Phage capsids have a limited capacity, meaning that their genome size must stay within a tight range in order to be properly packaged. Since DNA encoding the Cas operon + CRISPR array is rather large (total ~6000 bp), other DNA must be removed from the phage genome in order to make room for the Cas system. Exemplary phage engineered herein comprise a Cas operon and CRISPR array inserted into a phage such that the phage retains viability.

[0084] Disclosed herein, in some embodiments, are bacteriophages comprising a first nucleic acid sequence encoding a first spacer sequence or a crRNA transcribed therefrom, wherein the first spacer sequence is complementary to a target nucleotide sequence from a target gene in a *Pseudomonas* species. In some embodiments, the bacteriophage comprises a first nucleic acid sequence encoding a first spacer sequence or a crRNA transcribed therefrom, wherein the first spacer sequence is complementary to a target nucleotide sequence from a target gene in *Pseudomonas aeruginosa*, provided that the bacteriophage is rendered lytic. In some embodiments, the bacteriophage is a temperate bacteriophage. In some embodiments, the bacteriophage is rendered lytic by removal, replacement, or inactivation of a lysogenic gene. In some embodiments, the lysogenic gene plays a role in the maintenance of lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene plays a role in establishing the lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene plays a role in both establishing the lysogenic cycle and in the maintenance of the lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene is a repressor gene. In some embodiments, the lysogenic gene is

*c*I repressor gene. In some embodiments, the bacteriophage is rendered lytic by the removal of a regulatory element of a lysogeny gene. In some embodiments, the bacteriophage is rendered lytic by the removal of a promoter of a lysogeny gene. In some embodiments, the bacteriophage is rendered lytic by the removal of a functional element of a lysogeny gene. In some embodiments, the lysogenic gene is an activator gene. In some embodiments, the lysogenic gene is *c*II gene. In some embodiments, the lysogenic gene is *lexA* gene. In some embodiments, the lysogenic gene is *int* (integrase) gene. In some embodiments, two or more lysogeny genes are removed, replaced, or inactivated to cause arrest of a bacteriophage lysogeny cycle and/or induction of a lytic cycle. In some embodiments, the bacteriophage is rendered lytic via a second CRISPR array comprising a second spacer directed to a lysogenic gene. In some embodiments, the bacteriophage is rendered lytic by the insertion of one or more lytic genes. In some embodiments, the bacteriophage is rendered lytic by the insertion of one or more genes that contribute to the induction of a lytic cycle. In some embodiments, the bacteriophage is rendered lytic by altering the expression of one or more genes that contribute to the induction of a lytic cycle. In some embodiments, the bacteriophage phenotypically changes from a lysogenic bacteriophage to a lytic bacteriophage. In some embodiments, the phenotypic change is via a self-targeting CRISPR-Cas system to render a bacteriophage lytic since it is incapable of lysogeny. In some embodiments, the self-targeting CRISPR-Cas comprises a self-targeting crRNA from the prophage genome and kills lysogens. In some embodiments, the bacteriophage is rendered lytic by environmental alterations. In some embodiments, environmental alterations include, but are not limited to, alterations in temperature, pH, or nutrients, exposure to antibiotics, hydrogen peroxide, foreign DNA, or DNA damaging agents, presence of organic carbon, and presence of heavy metal (e.g., in the form of chromium (VI)). In some embodiments, the bacteriophage that is rendered lytic is prevented from reverting to lysogenic state. In some embodiments, the bacteriophage that is rendered lytic is prevented from reverting back to lysogenic state by way of introducing an additional CRIPSR array. In some embodiments, the bacteriophage does not confer any new properties onto the *Pseudomonas* species beyond cellular death cause by lytic activity of the bacteriophage and/or the activity of the CRISPR array.

[0085] Further disclosed herein, in some embodiments, are temperate bacteriophages comprising a first nucleic acid sequence encoding a first spacer sequence or a crRNA transcribed therefrom, wherein the first spacer sequence is complementary to a target nucleotide sequence from a target gene in a *Pseudomonas* species, provided the bacteriophage is rendered lytic. In some embodiments, the bacteriophage infects multiple bacterial strains. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence for the target gene. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence

located on a coding strand of a transcribed region of the target gene. In some embodiments, the target nucleotide sequence comprises at least a portion of an essential gene that is needed for survival of the *Pseudomonas* species. In some embodiments, the target nucleotide sequence comprises a highly-conserved non-coding or intergenic sequence. In some embodiments, the target sequence is an intergenic sequence that sits between the essential gene *rpmF* and a conserved hypothetical protein. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some embodiments, the essential gene is *dnaA, ftsA, gyrB, dnaN, glnS,* or *rpoB*. In some embodiments, the target sequence is PA4325 (hypothetical protein), PA1310 (phnW, pyruvate aminotransferase), or the boundary between PA2970 (rpmF, 50S ribosomal protein L32) and PA2971 (conserved hypothetical protein). In some embodiments, the target nucleotide sequence is in a non-essential gene. In some embodiments, the target nucleotide sequence is a noncoding sequence. In some embodiments, the noncoding sequence is an intergenic sequence. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence of a highly conserved sequence in a *Pseudomonas* species. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence of a sequence present in the *Pseudomonas* species. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence that comprises all or a part of a promoter sequence of the essential gene. In some embodiments, the first nucleic acid sequence comprises a first CRISPR array comprising at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the first spacer sequence at either its 5' end or its 3' end.

[0086] In some embodiments, the bacteriophage DNA is from a lysogenic or temperate bacteriophage. In some embodiments, the bacteriophage includes, but is not limited to, p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4209, p4430, or PB1, or two or more phage thereof.

[0087] In some embodiments, bacteriophages of interest are obtained from environmental sources. or commercial research vendors. In some embodiments, obtained bacteriophages are screened for lytic activity against a library of bacteria and their associated strains. In some embodiments, the bacteriophages are screened against a library of bacteria and their associated strains for their ability to generate primary resistance in the screened bacteria.

[0088] In some embodiments, a nucleic acid is inserted into the bacteriophage genome. In some embodiments, the nucleic acid comprises a crArray, a Cas system, or a combination thereof. In some embodiments, the nucleic acid is inserted into the bacteriophage genome at a transcription terminator site at the end of an operon of interest. In some embodiments, the nucleic acid is inserted

into the bacteriophage genome as a replacement for one or more removed non-essential genes. In some embodiments, the nucleic acid is inserted into the bacteriophage genome as a replacement for one or more removed lysogenic genes. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid enhances the lytic activity of the bacteriophage. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid renders a lysogenic bacteriophage lytic.

[0089] In some embodiments, a nucleic acid is introduced into the bacteriophage genome at a first location while one or more non-essential and/or lysogenic genes are separately removed and/or inactivated from the bacteriophage genome at a separate location. In some embodiments, the removal of one or more non-essential and/or lysogenic genes renders a lysogenic bacteriophage into a lytic bacteriophage. Similarly, in some embodiments, one or more lytic genes are introduced into the bacteriophage so as to render a non-lytic, lysogenic bacteriophage into a lytic bacteriophage.

[0090] In some embodiments, the replacement, removal, inactivation, or any combination thereof, of one or more non-essential and/or lysogenic genes is achieved by chemical, biochemical, and/or any suitable method. In some embodiments, the insertion of one or more lytic genes is achieved by any suitable chemical, biochemical, and/or physical method by homologous recombination.

[0091] In some embodiments, the non-essential gene to be removed and/or replaced from the bacteriophage is a gene that is non-essential for the survival of the bacteriophage. In some embodiments, the non-essential gene to be removed and/or replaced from the bacteriophage is a gene that is non-essential for the induction and/or maintenance of lytic cycle.

[0092] Disclosed herein, in certain embodiments, are bacteriophages comprising a complete exogenous CRISPR-Cas system. In some embodiments, the CRISPR-Cas system is Type I CRISPR-Cas system, Type II CRISPR-Cas system, Type III CRISPR-Cas system, Type IV CRISPR-Cas system, Type V CRISPR-Cas system, or Type VI CRISPR-Cas system. Disclosed herein, in certain embodiments, are bacteriophages comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising: (a) a CRISPR array; (b) a Cascade polypeptide; and (c) a Cas3 polypeptide. In some embodiments, the CRISPR-Cas system comprises at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 24. In some embodiments, the CRISPR-Cas system comprises at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 25.

[0093] In some embodiments, the bacteriophage is p1106 (ATCC Accession No. PTA-127024), wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p1587 (ATCC Accession No. PTA-127027) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p1772

(ATCC Accession No. PTA-127030), wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p1835 (ATCC Accession No. PTA-127032), wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2037 (ATCC Accession No. PTA-127034) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2131 (ATCC Accession No. PTA-127036) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2132 (ATCC Accession No. PTA-127038) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2363 (ATCC Accession No. PTA-127041) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2421 (ATCC Accession No. PTA-127043) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is p2973 (ATCC Accession No. PTA-127045), wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage is PB1 (ATCC Accession No. PTA-127049) , wherein the bacteriophage comprises a Type I CRISPR-Cas system. In some embodiments, the bacteriophage comprises a phage listed in **Table 1A.**

[0094] In some embodiments, the bacteriophage comprises a CRISPR-system having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 25.

[0095] In some embodiments, the bacteriophage is p1106e003 (ATCC Accession No. PTA-127023) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p1106e003. In some embodiments, the bacteriophage is p1587e002 (ATCC Accession No. PTA-127026) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p1587e002. In some embodiments, the bacteriophage is p1772e005 (ATCC Accession No. PTA-127029) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p1772e005. In some embodiments, the bacteriophage is p1835e002 (ATCC Accession No. PTA-127031) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p1835e002. In some embodiments, the bacteriophage is p2037e002 (ATCC Accession No. PTA-127033) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2037e002. In some embodiments, the bacteriophage is p2131e002 (ATCC Accession No. PTA-127035) or is at

least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2131e002. In some embodiments, the bacteriophage is p2132e002 (ATCC Accession No. PTA-127037) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2132e002. In some embodiments, the bacteriophage is p2363e003 (ATCC Accession No. PTA-127040) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2363e003. In some embodiments, the bacteriophage is p2421e002 (ATCC Accession No. PTA-127042) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2421e002. In some embodiments, the bacteriophage is p2973e002 (ATCC Accession No. PTA-127044) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to p2973e002. In some embodiments, the bacteriophage is PB1e002 (ATCC Accession No. PTA-127048) or is at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to PB1e002. In some embodiments, the bacteriophage comprises a phage listed in **Table 1A.** In some embodiments, provided is a bacteriophage cocktail system comprising one or more engineered bacteriophage, and a wild-type phage. In some embodiments, the wild-type phage is a phage of Table 5A, Table 5B, or Table 6A. In some embodiments, the wild-type phage is a wildtype Pbunavirus. Non-limiting example wild-type Pbunavirus include p1106, p1587, p1835, p2037, p2363, p2421, and pb1. In some embodiments, the wild-type phage is a wild-type Samunavirus. Non-limiting example wild-type Samunavirus include p1772, p2121, p2132, and p2973. In some embodiments, the wild-type phage is a wild-type a Nankokuvirus. In some embodiments, the wild-type phage is a wild-type PhiKZ-virus. Non-limiting examples of wild-type PhiKZ-virus include p1194p.b008 and p4430. In some embodiments, the wild-type phage is wild-type PhiKMV-virus. A non-limiting example of a wild-type PhiKMV-virus is p2167. In some embodiments, the wild-type phage is wild-type Bruynoghevirus. Non-limiting examples of a wild-type Bruynoghevirus include p1695 and p3278. In some embodiments, the wild-type phage is p1194. In some embodiments, the wild-type phage is p4430. In some embodiments, the wild-type phage is p1695. In some embodiments, the wild-type phage is PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus.

[0096] In some embodiments, the bacteriophage cocktail system comprises CK000512 (p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695).

[0097] In some embodiments, a plurality of bacteriophages are used together. In some embodiments, the plurality of bacteriophages used together targets the same or different bacteria within a sample or subject. In some embodiments, a cocktail comprising a plurality of bacteriophages is used together. In some embodiments, the cocktail comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 phages selected from Table 1A. In some embodiments, the cocktail comprises 2 phages selected from Table 1A. In some embodiments, the cocktail comprises 3 phages selected from Table 1A. In some embodiments, the cocktail comprises 3 phages selected from Table 1A. In some embodiments, the cocktail comprises 4 phages selected from Table 1A. In some embodiments, the cocktail comprises 5 phages selected from Table 1A. In some embodiments, the cocktail comprises 6 phages selected from Table 1A. In some embodiments, the cocktail comprises a cocktail selected from Table 6A. In some embodiments, at least one bacteriophage in the cocktail comprises a CRISPR array. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 bacteriophages present in the cocktail comprise a CRISPR array. In some embodiments, at least one bacteriophage in the cocktail comprises a nucleic acid sequence encoding a Cascade polypeptide. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 bacteriophages present in the cocktail comprise a nucleic acid sequence encoding a Cascade polypeptide. In some embodiments, at least one bacteriophage in the cocktail comprises a nucleic acid sequence encoding a Cas3 polypeptide. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 bacteriophages present in the cocktail comprise a nucleic acid sequence encoding a Cas3 polypeptide. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, and p2131e002. In some embodiments, the cocktail further comprises p1194. In some embodiments, the cocktail further comprises p1695. In some embodiments, the cocktail further comprises p4430. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

[0098] In some embodiments, provided herein is a PhiKZvirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the PhiKZvirus is p1194 or p4430. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-

23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[0099] In some embodiments, provided herein is a PhiKMV virus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[00100] In some embodiments, provided herein is a Brunyoghevirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g.,

selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[00101] In some embodiments, provided herein is a Samunavirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[00102] In some embodiments, provided herein is a Pbunavirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d

polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[00103] In some embodiments, provided herein is a Nankokuvirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

[00104] In some embodiments, provided herein is an Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, or Zicotriavirus bacteriophage comprising a Type I CRISPR-Cas system. In some embodiments, the CRISPR-Cas system comprises one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array comprises at least one repeat sequence comprising at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the nucleic acid sequence further comprises a promoter sequence, e.g., selected from SEQ ID NOS: 1-11. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In

some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 24. In some embodiments, the bacteriophage comprises a CRISPR-system having at least 90% identity to SEQ ID NO: 25.

CRISPR Array

[00105] In some embodiments, the CRISPR array (crArray) comprises a spacer sequence and at least one repeat sequence. In some embodiments, the CRISPR array encodes a processed, mature crRNA. In some embodiments, the mature crRNA is introduced into a phage or a *Pseudomonas* species. In some embodiments, an endogenous or exogenous Cas6 processes the CRISPR array into mature crRNA. In some embodiments, an exogenous Cas6 is introduced into the phage. In some embodiments, the phage comprises an exogenous Cas6. In some embodiments, an exogenous Cas6 is introduced into a *Pseudomonas* species.

[00106] In some embodiments, the CRISPR array comprises a spacer sequence. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the spacer sequence at either its 5' end or its 3' end. In some embodiments, the CRISPR array is of any length and comprises any number of spacer nucleotide sequences alternating with repeat nucleotide sequences necessary to achieve the desired level of killing of a *Pseudomonas* species by targeting one or more essential genes. In some embodiments, the CRISPR array comprises, consists essentially of, or consists of 1 to about 100 spacer nucleotide sequences, each linked on its 5' end and its 3' end to a repeat nucleotide sequence. In some embodiments, the CRISPR array comprises, consists essentially of, or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 , 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41 , 42, 43, 44, 45, 46, 47, 48, 49, 50, 51 , 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 , 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or more, spacer nucleotide sequences.

[00107] In some embodiments, the CRISPR array comprises a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 83. In some embodiments, the CRISPR array comprises a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 84. In some embodiments, the CRISPR array comprises a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 85. In some embodiments, the CRISPR array comprises a sequence at least 80%, 81%, 82%, 83%, 84%,

85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 86. In some embodiments, the CRISPR array comprises a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 87. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

Spacer Sequence

[00108] In some embodiments, the spacer sequence is complementary to a target nucleotide sequence in a *Pseudomonas* species. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence in *Pseudomonas* aeruginosa. the In some embodiments, the target

nucleotide sequence is a coding region. In some embodiments, the coding region is an essential gene. In some embodiments, the coding region is a nonessential gene. In some embodiments, the target nucleotide sequence is a noncoding sequence. In some embodiments, the noncoding sequence is an intergenic sequence. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence of a highly conserved sequence in a *Pseudomonas* species. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence of a sequence present in the *Pseudomonas* species. In some embodiments, the spacer sequence is complementary to a target nucleotide sequence that comprises all or a part of a promoter sequence of the essential gene. In some embodiments, the spacer sequence comprises one, two, three, four, or five mismatches as compared to the target nucleotide sequence. In some embodiments, the mismatches are contiguous. In some embodiments, the mismatches are noncontiguous. In some embodiments, the spacer sequence has 70% complementarity to a target nucleotide sequence. In some embodiments, the spacer sequence has 80% complementarity to a target nucleotide sequence. In some embodiments, the spacer sequence is 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% complementarity to a target nucleotide sequence. In some embodiments, the spacer sequence has 100% complementarity to the target nucleotide sequence. In some embodiments, the spacer sequence has complete complementarity or substantial complementarity over a region of a target nucleotide sequence that are at least about 8 nucleotides to about 150 nucleotides in length. In some embodiments, a spacer sequence has complete complementarity or substantial complementarity over a region of a target nucleotide sequence that is at least about 20 nucleotides to about 100 nucleotides in length. In some embodiments, the 5 ' region of the spacer sequence is 100% complementary to a target nucleotide sequence while the 3' region of the spacer is substantially complementary to the target nucleotide sequence and therefore the overall complementarity of the spacer sequence to the target nucleotide sequence is less than 100%. For example, in some embodiments, the first 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 nucleotides in the 3' region of a 20 nucleotide spacer sequence (seed region) is 100% complementary to the target nucleotide sequence, while the remaining nucleotides in the 5' region of the spacer sequence are substantially complementary (e.g., at least about 70% complementary) to the target nucleotide sequence. In some embodiments, the first 7 to 12 nucleotides of the 3' end of the spacer sequence is 100% complementary to the target nucleotide sequence, while the remaining nucleotides in the 5' region of the spacer sequence are substantially complementary (e.g., at least about 50% complementary (e.g., 50%, 55%, 60%, 65%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more)) to the target nucleotide sequence. In some embodiments, the first 7 to 10 nucleotides in the 3' end of the spacer sequence is 75%-99% complementary to the target nucleotide

sequence, while the remaining nucleotides in the 5' region of the spacer sequence are at least about 50% to about 99% complementary to the target nucleotide sequence. In some embodiments, the first 7 to 10 nucleotides in the 3' end of the spacer sequence is 100% complementary to the target nucleotide sequence, while the remaining nucleotides in the 5' region of the spacer sequence are substantially complementary (e.g., at least about 70% complementary) to the target nucleotide sequence. In some embodiments, the first 10 nucleotides (within the seed region) of the spacer sequence is 100% complementary to the target nucleotide sequence, while the remaining nucleotides in the 5' region of the spacer sequence are substantially complementary (e.g., at least about 70% complementary) to the target nucleotide sequence. In some embodiment, the 5' region of a spacer sequence (e.g., the first 8 nucleotides at the 5' end, the first 10 nucleotides at the 5' end, the first 15 nucleotides at the 5' end, the first 20 nucleotides at the 5' end) have about 75% complementarity or more (75% to about 100% complementarity) to the target nucleotide sequence, while the remainder of the spacer sequence have about 50% or more complementarity to the target nucleotide sequence. In some embodiments, the first 8 nucleotides at the 5' end of the spacer sequence have 100% complementarity to the target nucleotide sequence or have one or two mutations and therefore is about 88% complementary or about 75% complementary to the target nucleotide sequence, respectively, while the remainder of the spacer nucleotide sequence is at least about 50% or more complementary to the target nucleotide sequence.

[00109] In some embodiments, the spacer sequence is about 15 nucleotides to about 150 nucleotides in length. In some embodiments, the spacer nucleotide sequence is about 15 nucleotides to about 100 nucleotides in length (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 nucleotides or more). In some embodiments, the spacer nucleotide sequence is a length of about 8 to about 150 nucleotides, about 8 to about 100 nucleotides, about 8 to about 50 nucleotides, about 8 to about 40 nucleotides, about 8 to about 30 nucleotides, about 8 to about 25 nucleotides, about 8 to about 20 nucleotides, about 10 to about 150 nucleotides, about 10 to about 100 nucleotides, about 10 to about 80 nucleotides, about 10 to about 50 nucleotides, about 10 to about 40, about 10 to about 30, about 10 to about 25, about 10 to about 20, about 15 to about 150, about 15 to about 100, about 15 to about 50, about 15 to about 40, about 15 to about 30, about 20 to about 150 nucleotides, about 20 to about 100 nucleotides, about 20 to about 80 nucleotides, about 20 to about 50 nucleotides, about 20 to about 40, about 20 to about 30, about 20 to about 25, at least about 8, at least about 10, at least about 15, at least about 20, at least about 25, at least about 30, at least about 32, at least about 35, at least about 40, at least about 44, at least about 50, at least about 60,

at least about 70, at least about 80, at least about 90, at least about 100, at least about 110, at least about 120, at least about 130, at least about 140, at least about 150 nucleotides in length, or more, and any value or range therein. In some embodiments, the *P. aeruginosa* Type I-C Cas system has a spacer length of about 30 to 39 nucleotides, about 31 to about 38 nucleotides, about 32 to about 37 nucleotides, about 33 to about 36 nucleotides, about 34 to about 35 nucleotides, or about 35 nucleotides In some embodiments, the *P. aeruginosa* Type I-C Cas system has a spacer length of about 34 nucleotides. In some embodiments, the *P. aeruginosa* Type I-C Cas system has a spacer length of at least about 10, at least about 15, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 29, at least about 29, at least about 30, at least about 31, at least about 32, at least about 33, at least about 34, at least about, at least about 35, at least about 36, at least about 37, at least about 38, at least about 39, at least about 20, at least about 41, at least about 42, at least about 43, at least about 44, at least about 45, or more than about 45 nucleotides.

[00110] In some embodiments, the spacer sequence comprises at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some instances, the spacer sequence comprises at least or about 95% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the spacer sequence comprises at least or about 97% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the spacer sequence comprises at least or about 99% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the spacer sequence comprises 100% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the spacer sequence comprises at least a portion having at least or about 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or more than 34 nucleotides of any one of SEQ ID NOS: 12-23, 31-74, or 88-120.

[00111] The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity.

[00112] The term "homology" or "similarity" between two proteins is determined by comparing the amino acid sequence and its conserved amino acid substitutes of one protein sequence to the second protein sequence. Similarity may be determined by procedures which are well-known in

the art, for example, a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information).

[00113] In some embodiments, the identity of two or more spacer sequences of the CRISPR array is the same. In some embodiments, the identity of two or more spacer sequences of the CRISPR array is different. In some embodiments, the identity of two or more spacer sequences of the CRISPR array is different but are complementary to one or more target nucleotide sequences. In some embodiments, the identity of two or more spacer sequences of the CRISPR array is different and are complementary to one or more target nucleotide sequences that are overlapping sequences. In some embodiments, the identity of two or more spacer sequences of the CRISPR array is different and are complementary to one or more target nucleotide sequences that are not overlapping sequences. In some embodiments, the target nucleotide sequence is about 10 to about 40 consecutive nucleotides in length located immediately adjacent to a PAM sequence (PAM sequence located immediately 3' of the target region) in the genome of the organism. In some embodiments, a target nucleotide sequence is located adjacent to or flanked by a PAM (protospacer adjacent motif). In some embodiments, the two or more sequences of the CRISPR array comprises at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some instances, the two or more sequences of the CRISPR array comprises at least or about 95% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the two or more sequences of the CRISPR array comprises at least or about 97% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the two or more sequences of the CRISPR array comprises at least or about 99% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the two or more sequences of the CRISPR array comprises 100% homology to any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some instances, the two or more sequences of the CRISPR array comprises at least a portion having at least or about 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or more than 34 nucleotides of any one of SEQ ID NOS: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a

Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00114] In some embodiments, the CRISPR array comprises a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 12-15; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 16-19; a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 20-23, wherein said first spacer sequence, second spacer sequence, and third spacer sequence comprise from 0-8 nucleotide modifications. In some instances, the first spacer sequence comprises at least or about 97% homology to any one of SEQ ID NOS: 12-15; the second spacer sequence comprises at least or about 97% homology to any one of SEQ ID NOS: 16-19; and the third spacer sequence comprises at least or about 97% homology to any one of SEQ ID NOS: 20-23. In some instances, the first spacer sequence comprises at least or about 99% homology to any one of SEQ ID NOS: 12-15; the second spacer sequence comprises at least or about 99% homology to any one of SEQ ID NOS: 16-19; and the third spacer sequence comprises at least or about 99% homology to any one of SEQ ID NOS: 20-23. In some instances, the first spacer sequence comprises at least or about 100% homology to any one of SEQ ID NOS:

12-15; the second spacer sequence comprises at least or about 100% homology to any one of SEQ ID NOS: 16-19; and the third spacer sequence comprises at least or about 100% homology to any one of SEQ ID NOS: 20-23. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00115] In some embodiments, the CRISPR array comprises a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 12; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16; a third spacer sequence comprising at least or about 70%, 80%, 85%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 20, wherein said first spacer sequence, second spacer sequence, and third spacer sequence comprise from 0-8 nucleotide modifications. In some instances, the first spacer sequence comprises at least or about 97% homology to SEQ ID NO: 12; the second spacer sequence comprises at least or about 97% homology to SEQ ID NO: 16; and the third spacer sequence comprises at least or about 97% homology to SEQ ID NO: 20. In some instances, the first spacer sequence comprises at least or about 99% homology to SEQ ID NO: 12; the second spacer sequence comprises at least or about 99% homology to SEQ ID NO: 16; and the third spacer sequence comprises at least or about 99% homology to SEQ ID NO: 20. In some instances, the first spacer sequence comprises at least or about 100% homology to SEQ ID NO: 12; the second spacer sequence comprises at least or about 100% homology to SEQ ID NO: 16; and the third spacer sequence comprises at least or about 100% homology to SEQ ID NO: 20. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some

embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00116] In some embodiments, the CRISPR array comprises a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 13; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 17; a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 21, wherein said first spacer sequence, second spacer sequence, and third spacer sequence comprise from 0-8 nucleotide modifications. In some instances, the first spacer sequence comprises at least or about 97% homology to SEQ ID NO: 13; the second spacer sequence comprises at least or about 97% homology to SEQ ID NO: 17; and the third spacer sequence comprises at least or about 97% homology to SEQ ID NO: 21. In some instances, the first spacer sequence comprises at least or about 99% homology to SEQ ID NO: 13; the second spacer sequence comprises at least or about 99% homology to SEQ ID NO: 17; and the third spacer sequence comprises at least or about 99% homology to SEQ ID NO: 21. In some instances, the first spacer sequence comprises at least or about 100% homology to SEQ ID NO: 13; the second spacer sequence comprises at least or about 100% homology to SEQ ID NO: 17; and the third spacer sequence comprises at least or about 100% homology to SEQ ID NO: 21. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a

Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00117] In some embodiments, the CRISPR array comprises a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 14; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 18; a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 22, wherein said first spacer sequence, second spacer sequence, and third spacer sequence comprise from 0-8 nucleotide modifications. In some instances, the first spacer sequence comprises at least or about 97% homology to SEQ ID NO: 14; the second spacer sequence comprises at least or about 97% homology to SEQ ID NO: 18; and the third spacer sequence comprises at least or about 97% homology to SEQ ID NO: 22. In some instances, the first spacer sequence comprises at least or about 99% homology to SEQ ID NO: 14; the second spacer sequence comprises at least or about 99% homology to SEQ ID NO: 18; and the third spacer sequence comprises at least or about 99% homology to SEQ ID NO: 22. In some instances, the first spacer sequence comprises at least or about 100% homology to SEQ ID NO: 14; the second spacer sequence comprises at least or about 100% homology to SEQ ID NO: 18; and the third spacer sequence comprises at least or about 100% homology to SEQ ID NO: 22. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a

Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00118] In some embodiments, the CRISPR array comprises a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 15; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 19; a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 23, wherein said first spacer sequence, second spacer sequence, and third spacer sequence comprise from 0-8 nucleotide modifications. In some instances, the first spacer sequence comprises at least or about 97% homology to SEQ ID NO: 15; the second spacer sequence comprises at least or about 97% homology to SEQ ID NO: 19; and the third spacer sequence comprises at least or about 97% homology to SEQ ID NO: 23. In some instances, the first spacer sequence comprises at least or about 99% homology to SEQ ID NO: 15; the second spacer sequence comprises at least or about 99% homology to SEQ ID NO: 19; and the third spacer

sequence comprises at least or about 99% homology to SEQ ID NO: 23. In some instances, the first spacer sequence comprises at least or about 100% homology to SEQ ID NO: 15; the second spacer sequence comprises at least or about 100% homology to SEQ ID NO: 19; and the third spacer sequence comprises at least or about 100% homology to SEQ ID NO: 23. In some embodiments, the CRISPR array is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the CRISPR array is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the CRISPR array is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the CRISPR array is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the CRISPR array is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the CRISPR array is engineered into a Nankokuvirus. In some embodiments, the CRISPR array is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the CRISPR array is engineered into a Beetrevirus. In some embodiments, the CRISPR array is engineered into a Casadabanvirus. In some embodiments, the CRISPR array is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the CRISPR array is engineered into a Detrevirus. In some embodiments, the CRISPR array is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the CRISPR array is engineered into a Kochitakasuvirus. In some embodiments, the CRISPR array is engineered into a Litunavirus. In some embodiments, the CRISPR array is engineered into a Luzseptimavirus. In some embodiments, the CRISPR array is engineered into a Nipunavirus. In some embodiments, the CRISPR array is engineered into a Pakpunavirus. In some embodiments, the CRISPR array is engineered into a Pamexvirus. In some embodiments, the CRISPR array is engineered into a Paundecimvirus. In some embodiments, the CRISPR array is engineered into a Phitrevirus. In some embodiments, the CRISPR array is engineered into a Primolicivirus. In some embodiments, the CRISPR array is engineered into a Septimatrevirus. In some embodiments, the CRISPR array is engineered into a Stubburvirus. In some embodiments, the CRISPR array is engineered into a Tertilicivirus. In some embodiments, the CRISPR array is engineered into a Yuavirus. In some embodiments, the CRISPR array is engineered into a Zicotriavirus.

[00119] In some embodiments, the spacers are combined in plurality, in clusters within one or more bacteriophages, e.g. engineered bacteriophages. A bacteriophage or a bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence

identity to any one of SEQ ID NOs: 12-15; a second spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 16-19; a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 20-23. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 12; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 23. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 13; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 22. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 14; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 21. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 15; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 20. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 19. In some embodiments, the bacteriophage cocktail may comprise one or more arrays with a first spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 17; a second or a third spacer sequence comprising at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 18. In some embodiments, a plurality of bacteriophages are used together. In some embodiments, the plurality of bacteriophages used together targets the same or different bacteria within a sample or subject. In some embodiments, a cocktail comprising a

plurality of bacteriophages is used together. In some embodiments, the cocktail comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 phages selected from Table 1A. In some embodiments, the cocktail comprises 2 phages selected from Table 1A. In some embodiments, cocktail comprises a wild-type or engineered PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, cocktail comprises a wild-type or engineered PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, cocktail comprises a wild-type or engineered Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, cocktail comprises a wild-type or engineered Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, cocktail comprises a wild-type or engineered Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, cocktail comprises a wild-type or engineered Nankokuvirus. In some embodiments, cocktail comprises a wild-type or engineered Abidjanvirus. In some embodiments, cocktail comprises a wild-type or engineered Baikalvirus. In some embodiments, cocktail comprises a wild-type or engineered Beetrevirus. In some embodiments, cocktail comprises a wild-type or engineered Casadabanvirus. In some embodiments, cocktail comprises a wild-type or engineered Citexvirus. In some embodiments, cocktail comprises a wild-type or engineered Cystovirus. In some embodiments, cocktail comprises a wild-type or engineered Detrevirus. In some embodiments, cocktail comprises a wild-type or engineered Elvirus. In some embodiments, cocktail comprises a wild-type or engineered Hollowayvirus. In some embodiments, cocktail comprises a wild-type or engineered Kochitakasuvirus. In some embodiments, cocktail comprises a wild-type or engineered Litunavirus. In some embodiments, cocktail comprises a wild-type or engineered Luzseptimavirus. In some embodiments, cocktail comprises a wild-type or engineered Nipunavirus. In some embodiments, cocktail comprises a wild-type or engineered Pakpunavirus. In some embodiments, cocktail comprises a wild-type or engineered Pamexvirus. In some embodiments, cocktail comprises a wild-type or engineered Paundecimvirus. In some embodiments, cocktail comprises a wild-type or engineered Phitrevirus. In some embodiments, cocktail comprises a wild-type or engineered Primolicivirus. In some embodiments, cocktail comprises a wild-type or engineered Septimatrevirus. In some embodiments, cocktail comprises a wild-type or engineered Stubburvirus. In some embodiments, cocktail comprises a wild-type or engineered Tertilicivirus. In some embodiments, cocktail comprises a wild-type or engineered Yuavirus. In some embodiments, cocktail comprises a wild-type or engineered Zicotriavirus.

[00120] In some embodiments, the cocktail comprises a cocktail selected from Table 6A. In some embodiments, at least one bacteriophage in the cocktail comprises a CRISPR array. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,

25, 26, or 27 bacteriophages present in the cocktail comprise a CRISPR array. In some embodiments, at least one bacteriophage in the cocktail comprises a nucleic acid sequence encoding a Cascade polypeptide. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 bacteriophages present in the cocktail comprise a nucleic acid sequence encoding a Cascade polypeptide. In some embodiments, at least one bacteriophage in the cocktail comprises a nucleic acid sequence encoding a Cas3 polypeptide. In some embodiments, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 bacteriophages present in the cocktail comprise a nucleic acid sequence encoding a Cas3 polypeptide. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, and p2131e002. In some embodiments, the cocktail further comprises p1194. In some embodiments, the cocktail further comprises p1695. In some embodiments, the cocktail further comprises p4430. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, p2131e002, p1194, and p1695. In some embodiments, the cocktail comprises p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

[00121] The PAM sequence is found in the target gene next to the region to which a spacer sequence binds as a result of being complementary to that region and identifies the point at which base pairing with the spacer nucleotide sequence begins. The exact PAM sequence that is required varies between each different CRISPR-Cas system and is identified through established bioinformatics and experimental procedures. Non-limiting examples of PAMs include CCA, CCT, CCG, TTC, AAG, AGG, ATG, GAG, and/or CC. For Type I systems, the PAM is located immediately 5' to the sequence that matches the spacer, and thus is 3' to the sequence that base pairs with the spacer nucleotide sequence, and is directly recognized by Cascade. Once a protospacer is recognized, Cascade generally recruits the endonuclease Cas3, which cleaves and degrades the target DNA. For Type II systems, the PAM is required for a Cas9/sgRNA to form an R-loop to interrogate a specific DNA sequence through Watson-Crick pairing of its guide RNA with the genome. The PAM specificity is a function of the DNA-binding specificity of the Cas9 protein (e.g., a —protospacer adjacent motif recognition domain at the C-terminus of Cas9)

[00122] In some embodiments, the target nucleotide sequence in the bacterium to be killed is any essential target nucleotide sequence of interest. In some embodiments, the target nucleotide sequence is a non-essential sequence. In some embodiments, a target nucleotide sequence comprises, consists essentially of or consist of all or a part of a nucleotide sequence encoding a promoter, or a complement thereof, of the essential gene. In some embodiments, the spacer nucleotide sequence is complementary to a promoter, or a part thereof, of the essential gene. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding or a non-coding strand of the essential gene. In some embodiments, the target

nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding of a transcribed region of the essential gene.

[00123] In some embodiments, the essential gene is any gene of an organism that is critical for its survival. However, being essential is highly dependent on the circumstances in which an organism lives. For instance, a gene required to digest starch is only essential if starch is the only source of energy. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence for the target gene. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of the target gene. In some embodiments, the target nucleotide sequence comprises at least a portion of an essential gene that is needed for survival of the *Pseudomonas* species. In some embodiments, the target nucleotide sequence comprises a highly-conserved non-coding or intergenic sequence. In some embodiments, the target sequence is an intergenic sequence that sits between the essential gene rpmF and a conserved hypothetical protein. In some embodiments, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*. In some embodiments, the essential gene is *dnaA, ftsA, gyrB, dnaN, glnS,* or *rpoB*. In some embodiments, the target sequence is PA4325 (hypothetical protein), PA1310 (phnW, pyruvate aminotransferase), or the boundary between PA2970 (rpmF, 50S ribosomal protein L32) and PA2971 (conserved hypothetical protein). In some embodiments, a non-essential gene is any gene of an organism that is not critical for survival. However, being non-essential is highly dependent on the circumstances in which an organism lives.

[00124] In some embodiments, non-limiting examples of the target nucleotide sequence of interest includes a target nucleotide sequence encoding a transcriptional regulator, a translational regulator, a polymerase gene, a metabolic enzyme, a transporter, an RNase, a protease, a DNA replication enzyme, a DNA modifying or degrading enzyme, a regulatory RNA, a transfer RNA, or a ribosomal RNA. In some embodiments, the target nucleotide sequence is from a gene involved in cell-division, cell structure, metabolism, motility, pathogenicity, virulence, or antibiotic resistance. In some embodiments, the target nucleotide sequence is from a hypothetical gene whose function is not yet characterized. Thus, for example, these genes are any genes from any bacterium.

[00125] In some embodiments, the appropriate spacer sequences for a full-construct phage is identified by locating a search set of representative genomes, searching the genomes with relevant parameters, and determining the quality of a spacer for use in a CRISPR engineered phage.

[00126] First, a suitable search set of representative genomes is located and acquired for the organism/species/target of interest. The set of representative genomes, in some embodiments, is

found in a variety of databases, including without limitations the NCBI GenBank or the PATRIC database. NCBI GenBank is one of the largest databases available and contains a mixture of reference and submitted genomes for nearly every organism sequenced to date. Specifically, for pathogenic prokaryotes, the PATRIC (Pathosystems Resource Integration Center) database provides an additional comprehensive resource of genomes and provides a focus on clinically relevant strains and genomes relevant to a drug product. Both of the above databases allow for bulk downloading of genomes via FTP (File Transfer Protocol) servers, enabling rapid and programmatic dataset acquisition

[00127] Next, the genomes are searched with relevant parameters to locate suitable spacer sequences. In some embodiments, genomes are read from start to end, in both the forward and reverse complement orientations, to locate contiguous stretches of DNA that contain a PAM (Protospacer Adjacent Motif) site. The spacer sequence will be the N-length DNA sequence 3' or 5' adjacent to the PAM site (depending on the CRISPR system type), where N is specific to the Cas system of interest and is generally known ahead of time. Characterizing the PAM sequence and spacer sequences, in some embodiments, is performed during the discovery and initial research of a Cas system. In some embodiments, every observed PAM-adjacent spacer is saved to a file and/or database for downstream use. The exact PAM sequence that is required varies between each different CRISPR-Cas system and is identified through established bioinformatics and experimental procedures.

[00128] Next, the quality of a spacer for use in a CRISPR engineered phage is determined. Each observed spacer, in some embodiments, is evaluated to determine how many of the evaluated genomes they are present in. In some embodiments, the observed spacers are evaluated to see how many times they may occur in each given genome. Spacers that occur in more than one location per genome, in some embodiments, are advantageous because the Cas system may not be able to recognize the target site if a mutation occurs, and each additional "backup" site increases the likelihood that a suitable, non-mutated target location will be present. In some embodiments, the observed spacers are evaluated to determine whether they occur in functionally annotated regions of the genome. If such information is available, the functional annotations may be further evaluated to determine whether those regions of the genome are "essential" for the survival and function of the organism. By focusing on spacers that occur in all, or nearly all, evaluated genomes of interest (>= 99%), the spacer selection may be broadly applicable to many targeted genomes. Provided a large selection pool of conserved spacers exists, preference may be given to spacers that occur in regions of the genome that have known function, with higher preference given if those genomic regions are "essential" for survival and occur more than 1 time per genome.

[00129] The spacer sequences for a full construct phage, in some embodiments, are validated. In some embodiments, a first step comprises identifying a plasmid that replicates in the organism, species, or target of interest. In some embodiments, the plasmid has a selectable marker. In some embodiments, the selectable marker is an antibiotic-resistance gene. In some embodiments, an expression cassette includes a nucleotide sequence for a selectable marker. In some embodiments, the selectable marker is adenine deaminase (*ada*), blasticidin S deaminases (*Bsr, BSD*), bleomycin-binding protein (*Ble*), Neomycin phosphotransferase (*neo*), histidinol dehydrogenase (*hisD*), glutamine synthetase (*GS*), dihydrofolate reductase (*dhfr*), cytosine deaminase (*codA*), puromycin N-acetyltransferase (*Pac*), or hygromycin B phosphotransferase (*Hph*), ampicillin, chloramphenicol, kanamycin, tetracycline, polymyxin B, erythromycin, carbenicillin, streptomycin, spectinomycin, puromycin N-acetyltransferase (*Pac*), or zeocin (*Sh bla*). In some embodiments, the selectable marker is a gene involved in thymidylate synthase, thymidine kinase, dihydrofolate reductase, or glutamine synthetase. In some embodiments, the selectable marker is a gene encoding a fluorescent protein.

[00130] In some embodiments, a second step comprises inserting the genes encoding the Cas system into the plasmid such that they will be expressed in the organism, species, or target of interest. In some embodiments, a promoter is provided upstream of the Cas system. In some embodiments, the promoter is recognized by the organism, species, or target of interest to drive the expression of the Cas system. Exemplary promoters include, but are not limited to, L-arabinose inducible (*araBAD, P_{BAD}*) promoter, any *lac* promoter, L-rhamnose inducible (rhaPBAD) promoter, T7 RNA polymerase promoter, *trc* promoter, *tac* promoter, lambda phage promoter (p_Lp_L-9G-50), anhydrotetracycline-inducible (*tetA*) promoter, *trp*, *Ipp, phoA*, *recA*, *proU*, *cst*-1, *cadA*, *nar*, *Ipp-lac*, *cspA*, *11-lac* operator, T3-*lac* operator, T4 gene *32*, T5-*lac* operator, *nprM*- lac operator, Vhb, Protein A, corynebacterial-*E. coli* like promoters, *thr*, *horn*, diphtheria toxin promoter, *sig* A, *sig* B, *nusG*, *SoxS*, *katb*, *a-amylase* (*Pamy*), *Ptms*, *P43* (comprised of two overlapping RNA polymerase σ factor recognition sites, σA, σB), *Ptms*, *P43*, *rplK-rplA*, ferredoxin promoter, and/or xylose promoter. In some embodiments, the promoter is a BBa_J23102, BBa_J23104, or BBa_J23109. In some embodiments the promoter is derived from the organism, species, or target bacterium, such as endogenous CRISPR promoter, endogenous *Cas* operon promoter, p16, plpp, or ptat. In some embodiments, the promoter is a phage promoter, such as the promoter for gp105 or gp245. In some embodiments, a ribosomal binding site (RBS) is provided between the promoter and the Cas system. In some embodiments, the RBS is recognized by the organism, species, or target of interest.

[00131] In some embodiments, a third step comprises providing genome-targeting spacers into the plasmid. In some embodiments, the genome-targeting spacers are identified using

bioinformatics. In some embodiments, the genome-targeting spacers are provided upstream of the repeat-spacer-repeat. In some embodiments, a promoter is provided. In some embodiments, the promoter is recognized by the organism, species, or target of interest to drive the expression of the crRNA. In some embodiments, the cloning for the third step comprises using an organism or species that is not targeted by the spacer being cloned.

[00132] In some embodiments, a fourth step comprises providing a non-target spacer into the plasmid that expresses the Cas system. In some embodiments, the non-target spacer comprises a sequence is random. In some embodiments, the non-target spacer comprises a sequence that does not comprise targeting sites in the genome of the organism, species, or target of interest. In some embodiments, the non-target spacer sequence is determined using bioinformatics to not comprise targeting sites in the genome of the organism, species, or target of interest. In some embodiments, the non-target spacer sequence is provided upstream of the repeat-spacer-repeat. In some embodiments, a promoter is provided. In some embodiments, the promoter is recognized by the organism, species, or target of interest to drive the expression of the crRNA.

[00133] In some embodiments, a fifth step comprises determining an efficacy of each spacer generated. In some embodiments, the killing efficacy is determined. In some embodiments, the efficacy of each spacer at targeting the bacterial genome is determined. In some embodiments, the plasmids comprising the spacer comprises about 0.5-fold, about 1-fold, 5-fold, 10-fold, 20-fold, 40-fold, 60-fold, 80-fold, or up to about 100 fold reduction in transfer rate as compared to a plasmid that comprises the non-targeting spacer.

Repeat Nucleotide Sequences

[00134] In some embodiments, a repeat nucleotide sequence of the CRISPR array comprises a nucleotide sequence of any known repeat nucleotide sequence of a CRISPR-Cas system. In some embodiments, a repeat nucleotide sequence is of a synthetic sequence comprising the secondary structure of a native repeat from a CRISPR-Cas system (e.g., an internal hairpin). In some embodiments, the repeat nucleotide sequences are distinct from one another based on the known repeat nucleotide sequences of a CRISPR-Cas system. In some embodiments, the repeat nucleotide sequences are each composed of distinct secondary structures of a native repeat from a CRISPR-Cas system (e.g., an internal hairpin). In some embodiments, the repeat nucleotide sequences are a combination of distinct repeat nucleotide sequences operable with a CRISPR-Cas system.

[00135] In some embodiments, the spacer sequence is linked at its 5' end to the 3’ end of a repeat sequence. In some embodiments, the spacer sequence is linked at its 5’ end to about 1 to about 8, about 1 to about 10, or about 1 to about 15 nucleotides of the 3’ end of a repeat sequence. In some embodiments, the about 1 to about 8, about 1 to about 10, about 1 to about 15 nucleotides

of the repeat sequence are a portion of the 3’ end of a repeat sequence. In some embodiments, the spacer nucleotide sequence is linked at its 3' end to the 5’ end of a repeat sequence. In some embodiments, the spacer is linked at its 3’ end to about 1 to about 8, about 1 to about 10, or about 1 to about 15 nucleotides of the 5’ end of a repeat sequence. In some embodiments, the about 1 to about 8, about 1 to about 10, about 1 to about 15 nucleotides of the repeat sequence are a portion of the 5’ end of a repeat sequence.

[00136] In some embodiments, the spacer nucleotide sequence is linked at its 5' end to a first repeat sequence and linked at its 3' end to a second repeat sequence to form a repeat-spacer-repeat sequence. In some embodiments, the spacer sequence is linked at its 5' end to the 3’ end of a first repeat sequence and is linked at its 3' end to the 5’ of a second repeat sequence where the spacer sequence and the second repeat sequence are repeated to form a repeat-(spacer-repeat)n sequence such that n is any integer from 1 to 100. In some embodiments, a repeat-(spacer-repeat)n sequence comprises, consists essentially of, or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 , 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41 , 42, 43, 44, 45, 46, 47, 48, 49, 50, 51 , 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 , 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81 , 82, 83, 84, 85, 86, 87, 88, 89, 90, 91 , 92, 93, 94, 95, 96, 97, 98, 99, 100, or more, spacer nucleotide sequences.

[00137] In some embodiments, the repeat sequence is identical to or substantially identical to a repeat sequence from a wild-type CRISPR loci. In some embodiments, the repeat sequence is a repeat sequence found in Table 3. In some embodiments, the repeat sequence is a sequence described herein. In some embodiments, the repeat sequence comprises a portion of a wild type repeat sequence (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous nucleotides of a wild type repeat sequence). In some embodiments, the repeat sequence comprises, consists essentially of, or consists of at least one nucleotide (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, or more nucleotides, or any range therein). In some embodiments, the repeat sequence comprises, consists essentially of, or consists of no more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 nucleotides. In some embodiments, the repeat sequence comprises about 20 to 40, 21 to 40, 22 to 40 23 to 40, 24 to 40, 25 to 40, 26 to 40, 27 to 40, 28 to 40, 29 to 40, 30 to 30, 31 to 40, 32 to 40, 33 to 40, 34 to 40, 35 to 40, 36 to 40, 37 to 40, 38 to 40, 39 to 40, 20 to 39, 20 to 38, 20 to 37, 20 to 36, 20 to 35, 20 to 34, 20 to 33, 20 to 32, 20 to 31, 20 to 30, 20 to 29, 20 to 28, 20 to 26, 20 to 25, 20 to 24, 20 to 23, 20 to 22, or 20 to 21 nucleotides. In some embodiments, the repeat sequence comprises about 20 to 35, 21 to 35, 22 to 35 23 to 35, 24 to 35, 25 to 35, 26 to 35, 27 to 35, 28 to

35, 29 to 35, 30 to 30, 31 to 35, 32 to 35, 33 to 35, 34 to 35, 25 to 40, 25 to 39, 25 to 38, 25 to 37, 25 to 36, 25 to 35, 25 to 34, 25 to 33, 25 to 32, 25 to 31, 25 to 30, 25 to 29, 25 to 28, 25 to 26 nucleotides. In some embodiments, the system is a *P. aeruginosa* Type I-C Cas system. In some embodiments, the *P. aeruginosa* Type I-C Cas system has a repeat length of about 25 to 38 nucleotides.

[00138] In some embodiments, the repeat sequence comprises at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 26-30. In some instances, the repeat sequence comprises at least or about 95% homology to any one of SEQ ID NOS: 26-30. In some instances, the repeat sequence comprises at least or about 97% homology to any one of SEQ ID NOS: 26-30. In some instances, the repeat sequence comprises at least or about 99% homology to any one of SEQ ID NOS: 26-30. In some instances, the repeat sequence comprises 100% homology to any one of SEQ ID NOS: 26-30. In some instances, the repeat sequence comprises at least a portion having at least or about 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or more than 32 nucleotides of any one of SEQ ID NOS: 26-30. In some embodiments, the repeat is engineered into a PhiKZ virus. In some embodiments, the PhiKZ virus is p1194 or p4430. In some embodiments, the repeat is engineered into a PhiKMV virus. In some embodiments, the PhiKMV virus is p2167. In some embodiments, the repeat is engineered into a Brunyoghevirus virus. In some embodiments, the Brunyoghevirus is p1695 or p3278. In some embodiments, the repeat is engineered into a Samunavirus virus. In some embodiments, the Samunavirus is p1772, p2131, p2132, or p2973. In some embodiments, the repeat is engineered into a Pbunavirus. In some embodiments, the Pbunavirus is p1106, p1587, p1835, p2037, p2363, p2421, or pb1. In some embodiments, the repeat is engineered into a Nankokuvirus. In some embodiments, the repeat is engineered into a Abidjanvirus. In some embodiments, the CRISPR array is engineered into a Baikalvirus. In some embodiments, the repeat is engineered into a Beetrevirus. In some embodiments, the repeat is engineered into a Casadabanvirus. In some embodiments, the repeat is engineered into a Citexvirus. In some embodiments, the CRISPR array is engineered into a Cystovirus. In some embodiments, the repeat is engineered into a Detrevirus. In some embodiments, the repeat is engineered into a Elvirus. In some embodiments, the CRISPR array is engineered into a Hollowayvirus. In some embodiments, the repeat is engineered into a Kochitakasuvirus. In some embodiments, the repeat is engineered into a Litunavirus. In some embodiments, the repeat is engineered into a Luzseptimavirus. In some embodiments, the repeat is engineered into a Nipunavirus. In some embodiments, the repeat is engineered into a Pakpunavirus. In some embodiments, the repeat is engineered into a Pamexvirus. In some embodiments, the repeat is engineered into a Paundecimvirus. In some embodiments, the repeat is

engineered into a Phitrevirus. In some embodiments, the repeat is engineered into a Primolicivirus. In some embodiments, the repeat is engineered into a Septimatrevirus. In some embodiments, the repeat is engineered into a Stubburvirus. In some embodiments, the repeat is engineered into a Tertilicivirus. In some embodiments, the repeat is engineered into a Yuavirus. In some embodiments, the repeat is engineered into a Zicotriavirus. In some embodiments, the repeat is part of a CRISPR array engineered into the bacteriophage.

Type I CRISPR-Cas System

[00139] In some embodiments, the Type I CRISPR-Cas system is a Type I-A system, Type I-B system, Type I-C system, Type I-D system, Type I-E system, or Type I-F system. In some embodiments, the Type I CRISPR-Cas system is a Type I-A system. In some embodiments, the Type I CRISPR-Cas system is a Type I-B system. In some embodiments, the Type I CRISPR-Cas system is a Type I-C system. In some embodiments, the Type I CRISPR-Cas system is a Type I-D system. In some embodiments, the Type I CRISPR-Cas system is a Type I-E system. In some embodiments, the Type I CRISPR-Cas system is a Type I-F system. In some embodiments, the Type I CRISPR-Cas system comprises Cascade polypeptides. Type I Cascade polypeptides process CRISPR arrays to produce a processed RNA that is then used to bind the complex to a target sequence that is complementary to the spacer in the processed RNA. In some embodiments, the Type I Cascade complex is a Type I-A Cascade polypeptides, a Type I-B Cascade polypeptides, a Type I-C Cascade polypeptides, a Type I-D Cascade polypeptides, a Type I-E Cascade polypeptides, a Type I-F Cascade polypeptides, or a Type I-U Cascade polypeptides.

[00140] In some embodiments, the Type I Cascade complex comprises: (a) a nucleotide sequence encoding a Cas7 (Csa2) polypeptide, a nucleotide sequence encoding a Cas8a1 (Csx13) polypeptide or a Cas8a2 (Csx9) polypeptide, a nucleotide sequence encoding a Cas5 polypeptide, a nucleotide sequence encoding a Csa5 polypeptide, a nucleotide sequence encoding a Cas6a polypeptide, a nucleotide sequence encoding a Cas3' polypeptide, and a nucleotide sequence encoding a Cas3" polypeptide having no nuclease activity (Type I-A); (b) a nucleotide sequence encoding a Cas6b polypeptide, a nucleotide sequence encoding a Cas8b (Csh1) polypeptide, a nucleotide sequence encoding a Cas7 (Csh2) polypeptide, and a nucleotide sequence encoding a Cas5 polypeptide (Type I-B); (c) a nucleotide sequence encoding a Cas5d polypeptide, a nucleotide sequence encoding a Cas8c (Csd1) polypeptide, and a nucleotide sequence encoding a Cas7 (Csd2) polypeptide (Type I-C); (d) a nucleotide sequence encoding a Casl Od (Csc3) polypeptide, a nucleotide sequence encoding a Csc2 polypeptide, a nucleotide sequence encoding a Csc1 polypeptide, and a nucleotide sequence encoding a Cas6d polypeptide (Type I-D); (e) a nucleotide sequence encoding a Cse1 (CasA) polypeptide, a nucleotide sequence encoding a Cse2 (CasB) polypeptide, a nucleotide sequence encoding a Cas7 (CasC) polypeptide, a nucleotide sequence

encoding a Cas5 (CasD) polypeptide, and a nucleotide sequence encoding a Cas6e (CasE) polypeptide (Type I-E); and/or (f) a nucleotide sequence encoding a Cys1 polypeptide, a nucleotide sequence encoding a Cys2 polypeptide, a nucleotide sequence encoding a Cas7 (Cys3) polypeptide, and a nucleotide sequence encoding a Cas6f polypeptide (Type I-F).

[00141] In some embodiments, the Type I CRISPR-Cas system is exogenous to the target bacterium. In some embodiments, the exogenous Type I CRISPR-Cas system comprises (a) a nucleotide sequence encoding a Cas7 (Csa2) polypeptide, a nucleotide sequence encoding a Cas8a1 (Csx13) polypeptide or a Cas8a2 (Csx9) polypeptide, a nucleotide sequence encoding a Cas5 polypeptide, a nucleotide sequence encoding a Csa5 polypeptide, a nucleotide sequence encoding a Cas6a polypeptide, a nucleotide sequence encoding a Cas3' polypeptide, and a nucleotide sequence encoding a Cas3" polypeptide having no nuclease activity (Type I-A); (b) a nucleotide sequence encoding a Cas6b polypeptide, a nucleotide sequence encoding a Cas8b (Csh1) polypeptide, a nucleotide sequence encoding a Cas7 (Csh2) polypeptide, and a nucleotide sequence encoding a Cas5 polypeptide (Type I-B); (c) a nucleotide sequence encoding a Cas5d polypeptide, a nucleotide sequence encoding a Cas8c (Csd1) polypeptide, and a nucleotide sequence encoding a Cas7 (Csd2) polypeptide (Type I-C); (d) a nucleotide sequence encoding a Casl Od (Csc3) polypeptide, a nucleotide sequence encoding a Csc2 polypeptide, a nucleotide sequence encoding a Csc1 polypeptide, and a nucleotide sequence encoding a Cas6d polypeptide (Type I-D); (e) a nucleotide sequence encoding a Cse1 (CasA) polypeptide, a nucleotide sequence encoding a Cse2 (CasB) polypeptide, a nucleotide sequence encoding a Cas7 (CasC) polypeptide, a nucleotide sequence encoding a Cas5 (CasD) polypeptide, and a nucleotide sequence encoding a Cas6e (CasE) polypeptide (Type I-E); and/or (f) a nucleotide sequence encoding a Cys1 polypeptide, a nucleotide sequence encoding a Cys2 polypeptide, a nucleotide sequence encoding a Cas7 (Cys3) polypeptide, and a nucleotide sequence encoding a Cas6f polypeptide (Type I-F).

[00142] In some embodiments, the Type I CRISPR-Cas system exogenous to the target bacterium comprises a nucleotide sequence encoding a Cas5d polypeptide, a nucleotide sequence encoding a Cas8c (Csd1) polypeptide, and a nucleotide sequence encoding a Cas7 (Csd2) polypeptide (Type I-C).

Bacteriophage

[00143] In some embodiments, the bacteriophage is an obligate lytic bacteriophage. In some embodiments, the bacteriophage is a temperate bacteriophage with retained lysogeny genes. In some embodiments, the bacteriophage is a temperate bacteriophage with some lysogeny genes removed, replaced, or inactivated. In some embodiments, the bacteriophage is a temperate bacteriophage with a lysogeny gene removed, replaced, or inactivated, thereby rendering the bacteriophage lytic.

[00144] In some embodiments, the bacteriophage targets *Pseudomonas spp.* In some embodiments, the bacteriophage targets *Pseudomonas aeruginosa.* In some embodiments, the bacteriophage specifically targets *Pseudomonas spp.* over other bacterial species. In some embodiments, the bacteriophage targets *Pseudomonas spp.* in the absence of a CRISPR-Cas system. In some embodiments, the bacteriophage binds to lipopolysaccharide. In some embodiments, the bacteriophage binds to the Type IV pili. In some embodiments, the bacteriophage binds to outer membrane porin OprM. In some embodiments, targets refers to a bacteriophage that infects a bacteria. In some embodiments, targets refers to a bacteriophage that kills a bacteria. In some embodiments, specifically targets refers to a bacteriophage that infects a first bacterial species, but not a second bacterial species. In some embodiments, specifically targets refers to a bacteriophage that kills a first bacterial species, but not a second bacterial species.

[00145] In some embodiments, a bacteriophage herein is or is engineered from a bacteriophage that infects *Pseudomonas*. In some embodiments, the bacteriophage that infects *Pseudomonas* is PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Pbunavirus phage subtype listed in **Table 5A,** wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., phage p1106 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include an engineered Pbunavirus phage subtype listed in **Table 5A**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+) (e.g., p1106e003 infects b002548). In some embodiments, bacteriophages that infect *Pseudomonas* include a wildtype Samunavirus phage subtype, an engineered Samunavirus phage subtype, a wildtype PhiKZvirus, a wildtype PhiKMVvirus, or a wildtype Bruynoghevirus, e.g., as listed in **Table 5B**, wherein the phage infects a target *Pseudomonas* as marked with a positive sign (+)**.** As listed in **Table 5A**, the wildtype Pbunavirus phage subtypes can be p1106, p1587, p1835, p2037, p2363, p2421, and/or pb1, while the engineered Pbunavirus phage subtypes can be p1106e003, p1587e002, p1835e002, p2037e002, p2363e003, and/or p2421e002. As listed in **Table 5B**, the wildtype Samunavirus phage subtypes can be p1772, p2131, p2132, and/or p2973, the engineered Samunavirus phage subtypes can be pb1e002, p1772e005, p2131e002, p2132e002, and/or p2973e002, the wildtype PhiKZvirus phage subtypes can be p1194, and/or p4430, the wildtype PhiKMVvirus phage subtype can be p2167, and the wildtype Bruynoghevirus phage subtypes can be p1695, and p3278. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Nankokuvirus. In some embodiments, the

bacteriophage that infects *Pseudomonas* is an Abidjanvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Baikalvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Beetrevirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Casadabanvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Citexvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Cystovirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Detrevirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is an Elvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Hollowayvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Kochitakasuvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Litunavirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Luzseptimavirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Nipunavirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Pakpunavirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Pamexvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Paundecimvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Phitrevirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Primolicivirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Septimatrevirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Stubburvirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Tertilicivirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Yuavirus. In some embodiments, the bacteriophage that infects *Pseudomonas* is a Zicotriavirus. In some embodiments, a bacteriophage that infects *Pseudomonas* kills *Pseudomonas*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. aureus*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. aureus*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *K. pneumoniae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *K. pneumoniae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *E. faecium*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. faecium*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the

bacteriophage that infects *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *E. cloacae*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *E. cloacae*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *A. baumanii*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *A. baumanii*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *A. baumanii*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that infects *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not infect *S. epidermidis*. In some embodiments, the bacteriophage that kills *Pseudomonas* does not kill *S. epidermidis*. In some embodiments, a combination of bacteriophage infect *Pseudomonas*. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination infects at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B. In some embodiments, a combination of bacteriophage kill *Pseudomonas*. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5A. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 5B. As a non-limiting example, the combination kills at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the Pseudomonas in Table 6B.

[00146] In some embodiments, the bacteriophage is present in a cocktail comprising other bacteriophage, wherein each of the bacteriophage do not disrupt the function of the other bacteriophage in the cocktail.

[00147] In some embodiments, the bacteriophage is a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus,

Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the bacteriophage is a PhiKZvirus. In some embodiments, the bacteriophage is a PhiKMV virus. In some embodiments, the bacteriophage is a Brunyoghevirus. In some embodiments, the bacteriophage is a Samunavirus. In some embodiments, the bacteriophage is a Pbunavirus. In some embodiments, the bacteriophage comprises a CRISPR-Cas3 system. In some embodiments, the bacteriophage includes, but is not limited to, p1106 (ATCC Accession No PTA-127024), p1194(ATCC Accession No PTA-127025), p1587(ATCC Accession No PTA-127027), p1695(ATCC Accession No PTA-127028), p1772(ATCC Accession No PTA-127030), p1835(ATCC Accession No PTA-127032), p2037(ATCC Accession No PTA-127034), p2131(ATCC Accession No PTA-127036), p2132(ATCC Accession No PTA-127038), p2167(ATCC Accession No PTA-127039), p2363(ATCC Accession No PTA-127041), p2421(ATCC Accession No PTA-127043), p2973(ATCC Accession No PTA-127045), p3278(ATCC Accession No PTA-127046), p4430(ATCC Accession No PTA-127047), or PB1(ATCC Accession No PTA-127049), which target *Pseudomonas sp.*

[00148] In some embodiments, the bacteriophage is p1106, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1106. In some embodiments, the bacteriophage is a p1106 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p1106e003(ATCC Accession No. PTA-127023). In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1106e003.

[00149] In some embodiments, the bacteriophage is p1194, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1194. In some embodiments, the bacteriophage is a p1194 bacteriophage comprising a CRISPR-Cas system.

[00150] In some embodiments, the bacteriophage is p1587, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1587. In some embodiments, the bacteriophage is a p1587 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p1587e002 (ATCC Accession No. PTA-127026). In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of 01587e002.

[00151] In some embodiments, the bacteriophage is p1695, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1695. In some embodiments, the bacteriophage is a p1695 bacteriophage comprising a CRISPR-Cas system.

[00152] In some embodiments, the bacteriophage is p1772, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1772. In some embodiments, the bacteriophage is a p1772 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p1772e005 (ATCC Accession No. PTA-127029). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with that of p1772e005.

[00153] In some embodiments, the bacteriophage is p1835, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1835. In some embodiments, the bacteriophage is a p1835 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p1835e002 (ATCC Accession No. PTA-127026). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1835e002.

[00154] In some embodiments, the bacteriophage is p2037, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2037. In some embodiments, the bacteriophage is a p2037 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2037e002 (ATCC Accession No. PTA-127033). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2037e002.

[00155] In some embodiments, the bacteriophage is p2131, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2131. In some embodiments, the bacteriophage is a p2131 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2131 (ATCC Accession No. PTA-127035). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2131.

[00156] In some embodiments, the bacteriophage is p2132, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least

70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2132. In some embodiments, the bacteriophage is a p2132 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2132e002 (ATCC Accession No. PTA-127037). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2132e002.

[00157] In some embodiments, the bacteriophage is p2167, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2167. In some embodiments, the bacteriophage is a p2167 bacteriophage comprising a CRISPR-Cas system.

[00158] In some embodiments, the bacteriophage is p2163, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2163. In some embodiments, the bacteriophage is a p2163 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2163e003 (ATCC Accession No. PTA-127040). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2163e003.

[00159] In some embodiments, the bacteriophage is p2421, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2421. In some embodiments, the bacteriophage is a p2421 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2141e002 (ATCC Accession No. PTA-127042). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2141e0002.

[00160] In some embodiments, the bacteriophage is p2973, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2973. In some embodiments, the bacteriophage is a p2973 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is p2973e002 (ATCC Accession No. PTA-127044). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2973e002.

[00161] In some embodiments, the bacteriophage is p3278, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with

p3278. In some embodiments, the bacteriophage is a p3278 bacteriophage comprising a CRISPR-Cas system.

[00162] In some embodiments, the bacteriophage is p4430, or a mutant thereof which retains the ability to target *Pseudomonas sp*. I In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p4430. In some embodiments, the bacteriophage is a p1106 bacteriophage comprising a CRISPR-Cas system. n some embodiments, the bacteriophage is PB1, or a mutant thereof which retains the ability to target *Pseudomonas sp*. In some embodiments, the bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with PB1. In some embodiments, the bacteriophage is a PB1 bacteriophage comprising a CRISPR-Cas system. In some embodiments, the bacteriophage is PB1e002 (ATCC Accession No. PTA-127049). In some embodiments, the bacteriophage comprises at least 70%, 775%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with PB1e002.

[00163] In some embodiments, the bacteriophage comprises a phage listed in **Table 1A** , or a mutant thereof which retains the ability to target *Pseudomonas sp*.

[00164] Also disclosed herein is a cocktail comprising two or more bacteriophage. In some embodiments, the two or more bacteriophages are selected from the lineage consisting of a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the cocktail comprises at least six bacteriophages, wherein the bacteriophages comprise a PhiKZvirus, a PhiKMV virus, a Brunyoghevirus, a Samunavirus, and a Pbunavirus. In some embodiments, the cocktail comprises at least one Pbunavirus, at least one Samunavirus, at least one PhiKZvirus, and at least one Bruynoghevirus. In some embodiments, at least one bacteriophage of the cocktail comprises a CRISPR-Cas system. In some embodiments, at least two bacteriophages of the cocktail comprise a CRISPR-Cas system. In some embodiments, at least three bacteriophages of the cocktail comprise a CRISPR-Cas system. In some embodiments, at least four bacteriophages of the cocktail comprise a CRISPR-Cas system. In some embodiments, at least one bacteriophages of the cocktail does not comprise a CRISPR-Cas system. In some embodiments, at least two bacteriophages of the cocktail do not comprise a CRISPR-Cas system.

[00165] In some embodiments, the cocktail comprises at least two bacteriophages, wherein the bacteriophages comprise p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof. In some

embodiments, the cocktail comprises a first bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1106e003. In some embodiments, the cocktail comprises a second bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1835e002. In some embodiments, the cocktail comprises a third bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1772e005. In some embodiments, the cocktail comprises a fourth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2131e002. In some embodiments, the cocktail comprises a fifth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1194. In some embodiments, the cocktail comprises a fifth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p4430. In some embodiments, the cocktail comprises a fifth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1695. In some embodiments, the cocktail comprises a sixth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p4430. In some embodiments, the cocktail comprises a sixth bacteriophage comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1695.

[00166] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1106. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037,

p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00167] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1106. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1106, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1106, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1106, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1106, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1106, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00168] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1587. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1106, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1106, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1106, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth

bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1106, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1106, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00169] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1695. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1106, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1106, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1106, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1106, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1106, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophage comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophage do not comprise a CRISPR Cas system.

[00170] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1772. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1106, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100%

with p1194, p1587, p1695, p1106, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1106, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1106, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1106, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00171] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p1835. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1106, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1106, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1106, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1106, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1106, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00172] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2037. In some

embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p1106, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p1106, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p1106, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p1106, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p1106, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00173] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2131. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p1106, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p1106, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p1106, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p1106, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037,

p1106, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00174] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2132. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p1106, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p1106, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p1106, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p1106, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p1106, p2167, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00175] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2167. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p1106, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p1106, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p1106, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth

bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p1106, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p1106, p2363, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00176] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2363. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p1106, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p1106, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p1106, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p1106, p2421, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p1106, p2421, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00177] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2421. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p1106, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100%

with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p1106, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p1106, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p1106, p2973, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p1106, p2973, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00178] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p2973. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p1106, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p1106, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p1106, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p1106, p3278, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p1106, p3278, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00179] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p3278. In some

embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p1106, p4430, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p1106, p4430, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p1106, p4430, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p1106, p4430, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p1106, p4430, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00180] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with p4430. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p1106, or PB1. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p1106, or PB1. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p1106, or PB1. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p1106, or PB1. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037,

p2131, p2132, p2167, p2363, p2421, p2973, p3278, p1106, or PB1. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00181] In some embodiments, the first bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with PB1. In some embodiments, the cocktail comprises a second bacteriophage, wherein the second bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or p1106. In some embodiments, the cocktail comprises a third bacteriophage, wherein the third bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or p1106. In some embodiments, the cocktail comprises a fourth bacteriophage, wherein the fourth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or p1106. In some embodiments, the cocktail comprises a fifth bacteriophage, wherein the fifth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or p1106. In some embodiments, the cocktail comprises a sixth bacteriophage, wherein the sixth bacteriophage comprises at least 70%, 75%, 80%, 85%, 90% 95%, 96%, 97%, 98%, 99%, or 100% with p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or p1106. In some embodiments, at least one, two, three, or four bacteriophages comprise a CRISPR-Cas system. In some embodiments, at least one or two bacteriophages do not comprise a CRISPR Cas system.

[00182] In some embodiments, bacteriophages of interest are obtained from environmental sources or from commercial research vendors. In some embodiments, obtained bacteriophages are screened for lytic activity against a library of bacteria and their associated strains. In some embodiments, the bacteriophages are screened against a library of bacteria and their associated strains for their ability to generate primary resistance in the screened bacteria.

***Pseudomonas* species**

[00183] In some embodiments, the bacterium is *Pseudomonas*. In some embodiments, the bacterium is *Pseudomonas aeruginosa*.

[00184] In some embodiments, the *Pseudomonas* species causes, contributes to and/or causes complications to an infection, disease, or condition, and the compositions and methods described herein are used to treat the infection, disease, or condition. In some embodiments, the infection, disease or condition is acute or chronic. In some embodiments, the infection, disease or

condition is localized or systemic. In some embodiments, infection, disease or condition is idiopathic. In some embodiments, the infection, disease or condition is acquired through means including, but not limited to, respiratory inhalation, ingestion, skin and wound infections, blood stream infections, middle-ear infections, gastrointestinal tract infections, peritoneal membrane infections, urinary tract infections, urogenital tract infections, oral soft tissue infections, intra-abdominal infections, epidermal or mucosal absorption, eye infections (including contact lens contamination), endocarditis, infections in cystic fibrosis, infections of indwelling medical devices such as joint prostheses, dental implants, catheters and cardiac implants, sexual contact, and/or hospital-acquired and ventilator-associated bacterial pneumonias. In some embodiments, the *Pseudomonas* species causes urinary tract infection. In some embodiments, the *Pseudomonas* speciescauses and/or exacerbates an inflammatory disease. In some embodiments, the *Pseudomonas* species causes and/or exacerbates an autoimmune disease. In some embodiments, the *Pseudomonas* species causes and/or exacerbates inflammatory bowel disease (IBD). In some embodiments, the *Pseudomonas* species causes and/or exacerbates psoriasis. In some embodiments, the *Pseudomonas* species causes and/or exacerbates psoriatic arthritis (PA). In some embodiments, the *Pseudomonas* species causes and/or exacerbates rheumatoid arthritis (RA). In some embodiments, the *Pseudomonas* species causes and/or exacerbates systemic lupus erythematosus (SLE). In some embodiments, the *Pseudomonas* species causes and/or exacerbates multiple sclerosis (MS). In some embodiments, the *Pseudomonas* species causes and/or exacerbates Graves' disease. In some embodiments, the *Pseudomonas* species causes and/or exacerbates Hashimoto's thyroiditis. In some embodiments, the *Pseudomonas* species causes and/or exacerbates Myasthenia gravis. In some embodiments, the *Pseudomonas* species causes and/or exacerbates vasculitis. In some embodiments, the *Pseudomonas* species causes and/or exacerbates cancer. In some embodiments, the *Pseudomonas* species causes and/or exacerbates cancer progression. In some embodiments, the *Pseudomonas* species causes and/or exacerbates cancer metastasis. In some embodiments, the *Pseudomonas* species causes and/or exacerbates resistance to cancer therapy. In some embodiments, the therapy used to address cancer includes, but is not limited to, chemotherapy, immunotherapy, hormone therapy, targeted drug therapy, and/or radiation therapy. In some embodiments, the cancer develops in organs including, but not limited to the, anus, bladder, blood and blood components, bone, bone marrow, brain, breast, cervix uteri, colon and rectum, esophagus, kidney, larynx, lymphatic system, muscle (i.e., soft tissue), oral cavity and pharynx, ovary, pancreas, prostate, skin, small intestine, stomach, testis, thyroid, uterus, and/or vulva. In some embodiments, the *Pseudomonas* species causes and/or exacerbates disorders of the central nervous system (CNS). In some embodiments, the *Pseudomonas* species causes and/or exacerbates attention deficit/hyperactivity disorder (ADHD). In some embodiments,

the *Pseudomonas* species causes and/or exacerbates autism. In some embodiments, the *Pseudomonas* species causes and/or exacerbates bipolar disorder. In some embodiments, the *Pseudomonas* species causes and/or exacerbates major depressive disorder. In some embodiments, the *Pseudomonas* species causes and/or exacerbates epilepsy. In some embodiments, the *Pseudomonas* species causes and/or exacerbates neurodegenerative disorders including, but not limited to, Alzheimer's disease, Huntington's disease, and/or Parkinson's disease. In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat any one of the disease or condition or a symptom associated with a disease or condition described above. In some embodiments the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat a disease or condition described above, or a symptom associated with a disease described above, in combination with one or more other drugs for treatment or alleviating one or more conditions associated with the disease.

[00185] Cystic fibrosis and cystic fibrosis-associated bronchiectasis is associated with infection by *Pseudomonas aeruginosa*. See, e.g., P. Farrell, et al, Radiology, Vol. 252, No. 2, pp. 534-543 (2009). In some embodiments, one or more bacteriophages are administered to a patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis. In some embodiments, a combination of two or more bacteriophages are administered to a patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis. In some embodiments, administration of the bacteriophage to a patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis results in a reduction in bacterial load in the patient. In some embodiments, the reduction in bacterial load results in a clinical improvement in the patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis.

[00186] Non-cystic fibrosis bronchiectasis is associated with infection by *Pseudomonas aeruginosa*. See, e.g., R. Wilson, et al, Respiratory Medicine, Vol. 117, pp. 179-189 (2016). In some embodiments, one or more bacteriophages are administered to a patient with non-cystic fibrosis bronchiectasis. In some embodiments, a combination of two or more bacteriophages are administered to a patient with non-cystic fibrosis bronchiectasis. In some embodiments, administration of the bacteriophage to a patient with non-cystic fibrosis bronchiectasis results in a reduction in bacterial load in the patient. In some embodiments, the reduction in bacterial load results in a clinical improvement in the patient with non-cystic fibrosis bronchiectasis.

[00187] In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein are administered to a subject having an infection by *Pseudomonas aeruginosa* or a disease caused directly or indirectly by *Pseudomonas aeruginosa*. In some embodiments, the compositions

disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat a blood stream infection by *Pseudomonas aeruginosa.* In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is suitable for treating a respiratory inhalation, ingestion, skin and wound infections by *Pseudomonas aeruginosa.* In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat a middle-ear infections, gastrointestinal tract infections, peritoneal membrane infections, urinary tract infections, urogenital tract infections, oral soft tissue infections, intra-abdominal infections, epidermal or mucosal absorption, eye infections (including contact lens contamination), urinary tract infection endocarditis, infections in cystic fibrosis, infections of indwelling medical devices such as joint prostheses, dental implants, catheters and cardiac implants, sexual contact, and/or hospital-acquired and ventilator-associated bacterial pneumonias that is associated with an infection by *Pseudomonas aeruginosa.* In some embodiments, the *Pseudomonas* species causes and/or exacerbates an inflammatory disease and the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the inflammatory disease. In some embodiments, the *Pseudomonas* species causes and/or exacerbates an autoimmune disease and the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the autoimmune disease. In some embodiments, the *Pseudomonas* species causes and/or exacerbates inflammatory bowel disease (IBD) and the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the IBD. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B. In some embodiments the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the disease reduce the bacterial burden. In some embodiments the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the disease reduce the inflammation. In some embodiments the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat the disease reduce one or more symptoms associated with the bacterial infection, or one or more sequela of the bacterial infection.

[00188] In some embodiments, the treatment is administered as an intravenous or intramuscular drug. In some embodiments, the treatment is administered via oral route. In some embodiments, the treatment is administered via a nebulizer. In some embodiments, the treatment

is administered via a patient-operable nebulizer. In some embodiments, the treatment is administered via a metered dose nebulizer. In some embodiments, the treatment is administered in combination with one or more other drugs or therapeutics.

[00189] In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat cancer. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B.

[00190] In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat pneumonia. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B.

[00191] In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat cystic fibrosis bronchiectasis. In some embodiments, administration of the bacteriophage to a patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis results in a reduction in bacterial load in the patient. In some embodiments, the reduction in bacterial load results in a clinical improvement in the patient with cystic fibrosis bronchiectasis. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B. In some embodiments, the treatment is administered as an intravenous or intramuscular drug. In some embodiments, the treatment is administered via oral route. In some embodiments, the treatment is administered via a nebulizer. In some embodiments, the treatment is administered via a patient-operable nebulizer. In some embodiments, the treatment is administered via a metered dose nebulizer. In some embodiments, the treatment is administered in combination with one or more other drugs or therapeutics.

[00192] In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat non-cystic fibrosis bronchiectasis. In some embodiments, administration of the bacteriophage to a patient with non-cystic fibrosis bronchiectasis or fibrosis-associated bronchiectasis results in a reduction in bacterial load in the patient. In some embodiments, the reduction in bacterial load results in a clinical improvement in the patient with non-cystic fibrosis bronchiectasis fibrosis-associated bronchiectasis. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B. In some embodiments, the treatment is administered as an intravenous or intramuscular drug. In some embodiments, the treatment is administered via oral route. In some embodiments, the treatment is administered via a nebulizer. In some embodiments, the treatment is administered via a patient-operable nebulizer. In some embodiments, the treatment

is administered via a metered dose nebulizer. In some embodiments, the treatment is administered in combination with one or more other drugs or therapeutics.

[00193] In some embodiments, the treatment comprises a composition, e.g. a pharmaceutical composition comprising one or more bacteriophages, e.g., a bacteriophage cocktail, wherein the bacteriophage in the composition e.g., the bacteriophage cocktail are from the lineage consisting of a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the composition comprises the bacteriophage cocktail 511. In some embodiments, the composition comprises the bacteriophage cocktail PACK512. In some embodiments, provided herein is a pharmaceutical composition wherein the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage are from a group consisting of p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

Insertion Sites

[00194] In some embodiments, the insertion of the nucleic acid sequence into a bacteriophage preserves the lytic activity of the bacteriophage. In some embodiments, the nucleic acid sequence is inserted into the bacteriophage genome. In some embodiments, the nucleic acid sequence is inserted into the bacteriophage genome at a transcription terminator site at the end of an operon of interest. In some embodiments, the nucleic acid sequence is inserted into the bacteriophage genome as a replacement for one or more removed non-essential genes. In some embodiments, the nucleic acid sequence is inserted into the bacteriophage genome as a replacement for one or more removed lysogenic genes. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid sequence does not affect the lytic activity of the bacteriophage. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid sequence preserves the lytic activity of the bacteriophage. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid sequence enhances the lytic activity of the bacteriophage. In some embodiments, the replacement of non-essential and/or lysogenic genes with the nucleic acid sequence renders a lysogenic bacteriophage lytic.

[00195] In some embodiments, the nucleic acid sequence is introduced into the bacteriophage genome at a first location while one or more non-essential and/or lysogenic genes are separately removed and/or inactivated from the bacteriophage genome at a separate location. In some embodiments, the nucleic acid sequence is introduced into the bacteriophage at a first

location while one or more non-essential and/or lysogenic genes are separately removed and/or inactivated from the bacteriophage genome at multiple separate locations. In some embodiments, the removal and/or inactivation of one or more non-essential and/or lysogenic genes does not affect the lytic activity of the bacteriophage. In some embodiments, the removal and/or inactivation of one or more non-essential and/or lysogenic genes preserves the lytic activity of the bacteriophage. In some embodiments, the removal of one or more non-essential and/or lysogenic genes renders a lysogenic bacteriophage into a lytic bacteriophage.

[00196] In some embodiments, the bacteriophage is a temperate bacteriophage which has been rendered lytic by any of the aforementioned means. In some embodiments, a temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of one or more lysogenic genes. In some embodiments, the lytic activity of the bacteriophage is due to the removal, replacement, or inactivation of at least one lysogeny gene. In some embodiments, the lysogenic gene plays a role in the maintenance of lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene plays a role in establishing the lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene plays a role in both establishing the lysogenic cycle and in the maintenance of the lysogenic cycle in the bacteriophage. In some embodiments, the lysogenic gene is a repressor gene. In some embodiments, the lysogenic gene is *c*I repressor gene. In some embodiments, the lysogenic gene is an activator gene. In some embodiments, the lysogenic gene is *c*II gene. In some embodiments, the lysogenic gene is *lexA* gene. In some embodiments, the lysogenic gene is *int* (integrase) gene. In some embodiments, two or more lysogeny genes are removed, replaced, or inactivated to cause arrest of a bacteriophage lysogeny cycle and/or induction of a lytic cycle. In some embodiments, a temperate bacteriophage is rendered lytic by the insertion of one or more lytic genes. In some embodiments, a temperate bacteriophage is rendered lytic by the insertion of one or more genes that contribute to the induction of a lytic cycle. In some embodiments, a temperate bacteriophage is rendered lytic by altering the expression of one or more genes that contribute to the induction of a lytic cycle. In some embodiments, a temperate bacteriophage phenotypically changes from a lysogenic bacteriophage to a lytic bacteriophage. In some embodiments, a temperate bacteriophage is rendered lytic by environmental alterations. In some embodiments, environmental alterations include, but are not limited to, alterations in temperature, pH, or nutrients, exposure to antibiotics, hydrogen peroxide, foreign DNA, or DNA damaging agents, presence of organic carbon, and presence of heavy metal (e.g., in the form of chromium (VI). In some embodiments, a temperate bacteriophage that is rendered lytic is prevented from reverting to lysogenic state. In some embodiments, a temperate bacteriophage that is rendered lytic is prevented from reverting back to lysogenic state by way the self-targeting activity of the first introduced CRISPR array. In some embodiments, a temperate

bacteriophage that is rendered lytic is prevented from reverting back to lysogenic state by way of introducing an additional CRISPR array. In some embodiments, the bacteriophage does not confer any new properties onto the *Pseudomonas* species beyond cellular death cause by lytic activity of the bacteriophage and/or the activity of the first or second CRISPR array.

[00197] In some embodiments, the replacement, removal, inactivation, or any combination thereof, of one or more non-essential and/or lysogenic genes is achieved by chemical, biochemical, and/or any suitable method. In some embodiments, the insertion of one or more lytic genes is achieved by any suitable chemical, biochemical, and/or physical method by homologous recombination.

Non-Essential Gene

[00198] In some embodiments, the non-essential gene to be removed and/or replaced from the bacteriophage is a gene that is non-essential for the survival of the bacteriophage. In some embodiments, the non-essential gene to be removed and/or replaced from the bacteriophage is a gene that is non-essential for the induction and/or maintenance of lytic cycle.

Transcriptional Activators

[00199] In some embodiments, the nucleic acid sequence further comprises a transcriptional activator. In some embodiments, the transcriptional activator encoded regulates the expression of genes of interest within the *Pseudomonas* species. In some embodiments, the transcriptional activator activates the expression of genes of interest within the *Pseudomonas* species whether exogenous or endogenous. In some embodiments, the transcriptional activator activates the expression genes of interest within the target bacterium by disrupting the activity of one or more inhibitory elements within the target bacterium. In some embodiments, the inhibitory element comprises a transcriptional repressor. In some embodiments, the inhibitory element comprises a global transcriptional repressor. In some embodiments the inhibitory element is a histone-like nucleoid-structuring (H-NS) protein or homologue or functional fragment thereof. In some embodiments, the inhibitory element is a leucine responsive regulatory protein (LRP). In some embodiments, the inhibitory element is a CodY protein.

[00200] In some bacteria, the CRISPR-Cas system is poorly expressed and considered silent under most environmental conditions. In these bacteria, the regulation of the CRISPR-Cas system is the result of the activity of transcriptional regulators, for example histone-like nucleoid-structuring (H-NS) protein which is widely involved in transcriptional regulation of the host genome. H-NS exerts control over host transcriptional regulation by multimerization along AT-rich sites resulting in DNA bending. In some bacteria, the regulation of the CRISPR-Cas3 operon is regulated by H-NS.

[00201] Similarly, in some bacteria, the repression of the CRISPR-Cas system is controlled by an inhibitory element, for example the leucine responsive regulatory protein (LRP). LRP has been implicated in binding to upstream and downstream regions of the transcriptional start sites. Notably, the activity of LRP in regulating expression of the CRISPR-Cas system varies from bacteria to bacteria. Unlike, H-NS which has broad inter-species repression activity, LRP has been shown to differentially regulate the expression of the host CRISPR-Cas system. As such, in some instances, LRP reflects a host-specific means of regulating CRISPR-Cas system expression in different bacteria.

[00202] In some instances, the repression of CRISPR-Cas system is also controlled by inhibitory element CodY. CodY is a GTP-sensing transcriptional repressor that acts through DNA binding. The intracellular concentration of GTP acts as an indicator for the environmental nutritional status. Under normal culture conditions, GTP is abundant and binds with CodY to repress transcriptional activity. However, as GTP concentrations decreases, CodY becomes less active in binding DNA, thereby allowing transcription of the formerly repressed genes to occur. As such, CodY acts as a stringent global transcriptional repressor.

[00203] In some embodiments, the transcriptional activator is a LeuO polypeptide, any homolog or functional fragment thereof, a *leuO* coding sequence, or an agent that upregulates LeuO. In some embodiments, the transcriptional activator comprises any ortholog or functional equivalent of LeuO. In some bacteria, LeuO acts in opposition to H-NS by acting as a global transcriptional regulator that responds to environmental nutritional status of a bacterium. Under normal conditions, LeuO is poorly expressed. However, under amino acid starvation and/or reaching of the stationary phase in the bacterial life cycle, LeuO is upregulated. Increased expression of LeuO leads to it antagonizing H-NS at overlapping promoter regions to effect gene expression. Overexpression of LeuO upregulates the expression of the CRISPR-Cas system.

[00204] In some embodiments, the expression of LeuO leads to disruption of an inhibitory element. In some embodiments, the disruption of an inhibitory element due to expression of LeuO removes the transcriptional repression of a CRISPR-Cas system. In some embodiments, the expression of LeuO removes transcriptional repression of a CRISPR-Cas system due to activity of H-NS. In some embodiments, the disruption of an inhibitory element due to the expression of LeuO causes an increase in the expression of a CRISPR-Cas system. In some embodiments, the increase in the expression of a CRISPR-Cas system due to the disruption of an inhibitory element caused by the expression of LeuO causes an increase in the CRISPR-Cas processing of a nucleic acid sequence comprising a CRISPR array. In some embodiments, the increase in the expression of a CRISPR-Cas system due to the disruption of an inhibitory element by the expression of LeuO causes an increase in the CRISPR-Cas processing of a nucleic acid sequence comprising a CRISPR

array so as to increase the level of lethality of the CRISPR array against a bacterium. In some embodiments, transcriptional activator causes increase activity of a bacteriophage and/or the CRISPR-Cas system.

Regulatory Elements

[00205] In some embodiments, the nucleic acid sequences are operatively associated with a variety of promoters, terminators and other regulatory elements for expression in various organisms or cells. In some embodiments, the nucleic acid sequence further comprises a leader sequence. In some embodiments, the nucleic acid sequence further comprises a promoter sequence. In some embodiments, at least one promoter and/or terminator is operably linked the CRISPR array. Any promoter useful with this disclosure is used and includes, for example, promoters functional with the organism of interest as well as constitutive, inducible, developmental regulated, tissue-specific/preferred- promoters, and the like, as disclosed herein. A regulatory element as used herein is endogenous or heterologous. In some embodiments, an endogenous regulatory element derived from the subject organism is inserted into a genetic context in which it does not naturally occur (e.g. a different position in the genome than as found in nature), thereby producing a recombinant or non-native nucleic acid.

[00206] In some embodiments, expression of the nucleic acid sequence is constitutive, inducible, temporally regulated, developmentally regulated, or chemically regulated. In some embodiments, the expression of the nucleic acid sequence is made constitutive, inducible, temporally regulated, developmentally regulated, or chemically regulated by operatively linking the nucleic acid sequence to a promoter functional in an organism of interest. In some embodiments, repression is made reversible by operatively linking the nucleic acid sequence to an inducible promoter that is functional in an organism of interest. The choice of promoter disclosed herein varies depending on the quantitative, temporal and spatial requirements for expression, and also depending on the host cell to be transformed.

[00207] Exemplary promoters for use with the methods, bacteriophages and compositions disclosed herein include promoters that are functional in bacteria. For example, L-arabinose inducible (*araBAD*, P_{BAD}) promoter, any *lac* promoter, L-rhamnose inducible (rhaPBAD) promoter, T7 RNA polymerase promoter, *trc* promoter, *tac* promoter, lambda phage promoter (p_Lp_L-9G-50), anhydrotetracycline-inducible (*tetA*) promoter, *trp*, *Ipp*, *phoA*, *recA*, *proU*, *cst*-1, *cadA*, *nar*, *Ipp-lac*, *cspA*, *11-lac* operator, T3-*lac* operator, T4 gene *32*, T5-*lac* operator, *nprM*- lac operator, Vhb, Protein A, corynebacterial-*E. coli* like promoters, *thr*, *horn*, diphtheria toxin promoter, *sig* A, *sig* B, *nusG*, *SoxS*, *katb*, *a-amylase* (*Pamy*), *Ptms*, *P43* (comprised of two overlapping RNA polymerase σ factor recognition sites, σA, σB), *Ptms*, *P43*, *rplK-rplA*, ferredoxin promoter, and/or xylose promoter. In some embodiments, the promoter is a BBa_J23102 promoter.

In some embodiments, the promoter works in a broad range of bacteria, such as BBa_J23104, BBa_J23109. In some embodiments the promoter is derived from the target bacterium, such as endogenous CRISPR promoter, endogenous *Cas* operon promoter, p16, plpp, or ptat. In some embodiments, the promoter is a phage promoter, such as the promoter for gp105 or gp245.

[00208] In some embodiments, the promoter comprises at least or about 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 1-11. In some instances, the promoter comprises at least or about 95% homology to any one of SEQ ID NOS: 1-11. In some instances, the promoter comprises at least or about 97% homology to any one of SEQ ID NOS: 1-11. In some instances, the promoter comprises at least or about 99% homology to any one of SEQ ID NOS: 1-11. In some instances, the promoter comprises 100% homology to any one of SEQ ID NOS: 1-11. In some instances, the promoter comprises at least a portion having at least or about 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 or more than 50 nucleotides of any one of SEQ ID NOS: 1-11. In some instances, the promoter comprises at least a portion having at least or about 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, or more than 215 nucleotides of any one of SEQ ID NOS: 1-11.

[00209] In some embodiments, inducible promoters are used. In some embodiments, chemical-regulated promoters are used to modulate the expression of a gene in an organism through the application of an exogenous chemical regulator. The use of chemically regulated promoters enables RNAs and/or the polypeptides encoded by the nucleic acid sequence to be synthesized only when, for example, an organism is treated with the inducing chemicals. In some embodiments where a chemical-inducible promoter is used, the application of a chemical induces gene expression. In some embodiments wherein a chemical-repressible promoter is used, the application of the chemical represses gene expression. In some embodiments, the promoter is a light-inducible promoter, where application of specific wavelengths of light induces gene expression. In some embodiments, a promoter is a light- repressible promoter, where application of specific wavelengths of light represses gene expression.

Expression Cassette

[00210] In some embodiments, the nucleic acid sequence is an expression cassette or in an expression cassette. In some embodiments, the expression cassettes are designed to express the nucleic acid sequence disclosed herein. In some embodiments, the nucleic acid sequence is an expression cassette encoding components of a CRISPR-Cas system. In some embodiments, the nucleic acid sequence is an expression cassette encoding components of a Type I CRISPR-Cas system. In some embodiments, the nucleic acid sequence is an expression cassette encoding an

operable CRISPR-Cas system. In some embodiments, the nucleic acid sequence is an expression cassette encoding the operable components of a Type I CRISPR-Cas system, including Cascade and Cas3. In some embodiments, the nucleic acid sequence is an expression cassette encoding the operable components of a Type I CRISPR-Cas system, including a crRNA, Cascade and Cas3.

[00211] In some embodiments, an expression cassette comprising a nucleic acid sequence of interest is chimeric, meaning that at least one of its components is heterologous with respect to at least one of its other components. In some embodiments, an expression cassette is naturally occurring but has been obtained in a recombinant form useful for heterologous expression.

[00212] In some embodiments, an expression cassette includes a transcriptional and/or translational termination region (i.e. termination region) that is functional in the selected host cell. In some embodiments, termination regions are responsible for the termination of transcription beyond the heterologous nucleic acid sequence of interest and for correct mRNA polyadenylation. In some embodiments, the termination region is native to the transcriptional initiation region, is native to the operably linked nucleic acid sequence of interest, is native to the host cell, or is derived from another source (i.e., foreign or heterologous to the promoter, to the nucleic acid sequence of interest, to the host, or any combination thereof). In some embodiments, terminators are operably linked to the nucleic acid sequence disclosed herein.

[00213] In some embodiments, an expression cassette includes a nucleotide sequence for a selectable marker. In some embodiments, the nucleotide sequence encodes either a selectable or a screenable marker, depending on whether the marker confers a trait that is selected for by chemical means, such as by using a selective agent (e.g. an antibiotic), or on whether the marker is simply a trait that one identifies through observation or testing, such as by screening (e.g., fluorescence).

Vectors

[00214] In addition to expression cassettes, the nucleic acid sequences disclosed herein (e.g. nucleic acid sequence comprising a CRISPR array) are used in connection with vectors. A vector comprises a nucleic acid molecule comprising the nucleotide sequence(s) to be transferred, delivered or introduced. Non-limiting examples of general classes of vectors include, but are not limited to, a viral vector, a plasmid vector, a phage vector, a phagemid vector, a cosmid vector, a fosmid vector, a bacteriophage, an artificial chromosome, or an agrobacterium binary vector in double or single stranded linear or circular form which may or may not be self-transmissible or mobilizable. A vector transforms prokaryotic or eukaryotic host either by integration into the cellular genome or exist extrachromosomally (e.g. autonomous replicating plasmid with an origin of replication). Additionally, included are shuttle vectors by which is meant a DNA vehicle capable, naturally or by design, of replication in two different host organisms. In some embodiments, a shuttle vector replicates in actinomycetes and bacteria and/or eukaryotes. In some

embodiments, the nucleic acid in the vector are under the control of, and operably linked to, an appropriate promoter or other regulatory elements for transcription in a host cell. In some embodiments, the vector is a bi-functional expression vector which functions in multiple hosts.

Codon Optimization

[00215] In some embodiments, the nucleic acid sequence is codon optimized for expression in any species of interest. Codon optimization involves modification of a nucleotide sequence for codon usage bias using species-specific codon usage tables. The codon usage tables are generated based on a sequence analysis of the most highly expressed genes for the species of interest. When the nucleotide sequences are to be expressed in the nucleus, the codon usage tables are generated based on a sequence analysis of highly expressed nuclear genes for the species of interest. The modifications of the nucleotide sequences are determined by comparing the species-specific codon usage table with the codons present in the native polynucleotide sequences. Codon optimization of a nucleotide sequence results in a nucleotide sequence having less than 100% identity (e.g., 50%, 60%, 70%, 71 %, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81 %, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and the like) to the native nucleotide sequence but which still encodes a polypeptide having the same function as that encoded by the original nucleotide sequence. In some embodiments, the nucleic acid sequences of this disclosure are codon optimized for expression in the organism/species of interest.

Transformation

[00216] In some embodiments, the nucleic acid sequence, and/or expression cassettes disclosed herein are expressed transiently and/or stably incorporated into the genome of a host organism. In some embodiments, a the nucleic acid sequence and/or expression cassettes disclosed herein is introduced into a cell by any method known to those of skill in the art. Exemplary methods of transformation include transformation via electroporation of competent cells, passive uptake by competent cells, chemical transformation of competent cells, as well as any other electrical, chemical, physical (mechanical) and/or biological mechanism that results in the introduction of nucleic acid into a cell, including any combination thereof. In some embodiments, transformation of a cell comprises nuclear transformation. In some embodiments, transformation of a cell comprises plasmid transformation and conjugation.

[00217] In some embodiments, when more than one nucleic acid sequence is introduced, the nucleotide sequences are assembled as part of a single nucleic acid construct, or as separate nucleic acid constructs, and are located on the same or different nucleic acid constructs. In some embodiments, nucleotide sequences are introduced into the cell of interest in a single transformation event, or in separate transformation events.

Antimicrobial Agents and Peptides

[00218] In some embodiments, a bacteriophage disclosed herein is further genetically modified to express an antibacterial peptide, a functional fragment of an antibacterial peptide or a lytic gene. In some embodiments, a bacteriophage disclosed herein express at least one antimicrobial agent or peptide disclosed herein. In some embodiments, a bacteriophage disclosed herein comprises a nucleic acid sequence that encodes an enzybiotic where the protein product of the nucleic acid sequence targets phage resistant bacteria. In some embodiments, the bacteriophage comprises nucleic acids which encode enzymes which assist in breaking down or degrading biofilm matrix. In some embodiments, a bacteriophage disclosed herein comprises nucleic acids encoding Dispersin D aminopeptidase, amylase, carbohydrase, carboxypeptidase, catalase, cellulase, chitinase, cutinase, cyclodextrin glycosyltransferase, deoxyribonuclease, esterase, alpha-galactosidase, beta-galactosidase, glucoamylase, alpha-glucosidase, beta-glucosidase, haloperoxidase, invertase, laccase, lipase, mannosidase, oxidase, pectinolytic enzyme, peptidoglutaminase, peroxidase, phytase, polyphenoloxidase, proteolytic enzyme, ribonuclease, transglutaminase, xylanase or lyase. In some embodiments, the enzyme is selected from the group consisting of cellulases, such as glycosyl hydroxylase family of cellulases, such as glycosyl hydroxylase 5 family of enzymes also called cellulase A; polyglucosamine (PGA) depolymerases; and colonic acid depolymerases, such as 1,4-L-fucodise hydrolase, colanic acid, depolymerazing alginase, DNase I, or combinations thereof. In some embodiments, a bacteriophage disclosed herein secretes an enzyme disclosed herein.

[00219] In some embodiments, an antimicrobial agent or peptide is expressed and/or secreted by a bacteriophage disclosed herein. In some embodiments, a bacteriophage disclosed herein secretes and expresses an antibiotic such as ampicillin, penicillin, penicillin derivatives, cephalosporins, monobactams, carbapenems, ofloxacin, ciproflaxacin, levofloxacin, gatifloxacin, norfloxacin, lomefloxacin, trovafloxacin, moxifloxacin, sparfloxacin, gemifloxacin, pazufloxacin or any antibiotic disclosed herein. In some embodiments, a bacteriophage disclosed herein comprises a nucleic acid sequence encoding an antibacterial peptide, expresses an antibacterial peptide, or secretes a peptide that aids or enhances killing of a *Pseudomonas* species. In some embodiments, a bacteriophage disclosed herein comprises a nucleic acid sequence encoding a peptide, a nucleic acid sequence encoding an antibacterial peptide, expresses an antibacterial peptide, or secretes a peptide that aids or enhances the activity of the first and/or the second Type I CRISPR-Cas system.

Methods of Use

[00220] Disclosed herein, in certain embodiments, are methods of killing a *Pseudomonas* species comprising introducing into a *Pseudomonas* species any of the bacteriophages disclosed herein.

[00221] Further disclosed herein, in certain embodiments, are methods of modifying a mixed population of bacterial cells having a first bacterial species that comprises a target nucleotide sequence in the essential gene and a second bacterial species that does not comprise a target nucleotide sequence in the essential gene, the method comprising introducing into the mixed population of bacterial cells any of the bacteriophages disclosed herein.

[00222] Also disclosed herein, in certain embodiments, are methods of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual any of the bacteriophages disclosed herein.

[00223] In some embodiments, the *Pseudomonas* species is killed solely by lytic activity of the bacteriophage. In some embodiments, the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the processing of the CRISPR array by a CRISPR-Cas system to produce a processed crRNA capable of directing CRISPR-Cas based endonuclease activity and/or cleavage at the target nucleotide sequence in the target gene of the bacterium.

[00224] In some embodiments, the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the Type I CRISPR-Cas system. In some embodiments, the *Pseudomonas* species is killed by the activity of the Type I CRISPR-Cas system, independently of the lytic activity of the bacteriophage. In some embodiments, the activity of the Type I CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage. In some embodiments, the activity of the Type I CRISPR-Cas system and the lytic activity of the bacteriophage are additive.

[00225] In some embodiments, the lytic activity of the bacteriophage and the activity of the Type I CRISPR-Cas system is synergistic. In some embodiments, a synergistic activity is defined as an activity resulting in a greater level of phage kill than the additive combination of the lytic activity of the bacteriophage and the Type I CRISPR-Cas system. In some embodiments, the lytic activity of the bacteriophage is modulated by a concentration of the bacteriophage. In some embodiments, the activity of the Type I CRISPR-Cas system is modulated by a concentration of the bacteriophage.

[00226] In some embodiments, the synergistic killing of the bacterium is modulated to favor killing by the lytic activity of the bacteriophage over the activity of the first CRISPR-Cas system by increasing the concentration of bacteriophage administered to the bacterium. In some

embodiments, the synergistic killing of the bacterium is modulated to disfavor killing by the lytic activity of the bacteriophage over the activity of the CRISPR-Cas system by decreasing the concentration of bacteriophage administered to the bacterium. In some embodiments, at low concentrations, lytic replication allows for amplification and killing of the target bacteria. In some embodiments, at high concentrations, amplification of a phage is not required. In some embodiments, the synergistic killing of the bacterium is modulated to favor killing by the activity of the CRISPR-Cas system over the lytic activity of the bacteriophage by altering the number, the length, the composition, the identity, or any combination thereof, of the spacers so as to increase the lethality of the CRISPR array. In some embodiments, the synergistic killing of the bacterium is modulated to disfavor killing by the activity of the CRISPR-Cas system over the lytic activity of the bacteriophage by altering the number, the length, the composition, the identity, or any combination thereof, of the spacers so as to decrease the lethality of the CRISPR array.

[00227] In one aspect, provided herein is a method of treating a *Pseudomonas* infection in a subject, the method comprising administering to the subject a composition comprising a bacteriophage, wherein the bacteriophage comprises a nucleic acid sequence encoding a Type I CRISPR-Cas system that causes cell death by targeting and degrading the *Pseudomonas* bacterial genome. In some embodiments, the CRISPR-Cas system that targets a *Pseudomonas* bacteria comprises a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; a Cascade polypeptide; and a Cas3 polypeptide. In some embodiments, the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120. In some embodiments, the CRISPR array further comprises at least one repeat sequence. In some embodiments, the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end. In some embodiments, the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30. In some embodiments, the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87. In some embodiments, the target nucleotide sequence comprises a coding sequence. In some embodiments, the target nucleotide sequence comprises a non-coding or intergenic sequence. In some embodiments, the target nucleotide sequence comprises all or a part of a promoter sequence. In some embodiments, the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11. In some embodiments, the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene.

[00228] In one embodiment, the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA,*

rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, or *metK*. In some embodiments, the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system. In some embodiments, the Cascade complex comprises: (i) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system); (ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system); (iii) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system); (iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system); (v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); (vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system). In some embodiments, the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system). In some embodiments, the nucleic acid sequence further comprises a promoter sequence.

[00229] In one embodiment, provided herein is a method for treatment of a selected group of subjects suffering from a *Pseudomonas* infection. In one embodiment, the subjects are refractory to one or more commonly practiced therapies, e.g. therapy comprising one or more antibiotic compounds.

[00230] In one embodiment, the selected group of subjects are identified as subjects that are infected with a MDR strain of a *Pseudomonas* sp. In one embodiment, the selected group of subjects are identified as subjects that are immunocompromised. In some embodiments, the infection is a nosocomial infection. In some embodiments, the infection is a persistent or recurring infection. In some embodiments, the subject is symptomatic. In some embodiments, the subject suffers from a chronic *Pseudomonas* induced infection and disease. In one embodiment, the composition is administered to the subject once as a single dose.

[00231] In some embodiments, provided herein is a method of treating subjects suffering from a *Pseudomonas* infection by administering a composition, e.g. a pharmaceutical composition comprising one or more bacteriophages, e.g., a bacteriophage cocktail, wherein the bacteriophage in the composition e.g., the bacteriophage cocktail are from the lineage consisting of a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus,

Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus. In some embodiments, the composition comprises the bacteriophage cocktail 511. In some embodiments, the composition comprises the bacteriophage cocktail PACK512. In some embodiments, provided herein is a pharmaceutical composition wherein the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage are from a group consisting of p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. In some embodiments, the compositions disclosed herein, such as one or more bacteriophages, engineered bacteriophages or bacteriophage cocktail described herein is used to treat cancer. In some embodiments, the bacteriophage is selected from the Table 1A, Table 5A, and/or from the Table 5B.

[00232] In some embodiments, the treatment is administered as an intravenous or intramuscular drug. In some embodiments, the treatment is administered via oral route. In some embodiments, the treatment is administered via a nebulizer. In some embodiments, the treatment is administered via a patient-operable nebulizer. In some embodiments, the treatment is administered via a metered dose nebulizer.

[00233] In some embodiments, the treatment is administered in combination with one or more other drugs or therapeutics, e.g., an antibiotic, such as Tobramycin. In some embodiments an exemplary therapeutic co-administered with the composition comprising one or more bacteriophage could also be an antibiotic such as ampicillin, penicillin, penicillin derivatives, cephalosporins, monobactams, carbapenems, ofloxacin, ciproflaxacin, levofloxacin, gatifloxacin, norfloxacin, lomefloxacin, trovafloxacin, moxifloxacin, sparfloxacin, gemifloxacin, pazufloxacin or any antibiotic disclosed herein. . In some embodiments, the additional therapeutic comprises a drug for improving airway function. In some embodiments, the additional therapeutic comprises a drug for reducing airway responsiveness. In some embodiments, the additional therapeutic comprises a drug for reducing airway inflammation. In some embodiments, the additional therapeutic comprises a bronchodilator. In some embodiments, the additional therapeutic comprises a drug for improving oxygen availability. In some embodiments, the additional therapeutic comprises a drug for reducing airway mucogenesis. In some embodiments, the additional therapeutic comprises a DNAse. In some embodiments, the additional therapeutic is saline. In some embodiments, the additional therapeutic is a therapeutic method comprising coughing practices, e.g., as used for treating cystic fibrosis.

[00234] In one embodiment, the composition is administered to the subject more than once, e.g., multiple doses. In one embodiment, the composition is administered to the subject 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more doses. In one embodiment, the

composition is administered to the subject once a day, once in 2 days, once in 3 days, once in 4 days, once in 5 days, once in 6 days, or once a week. In one embodiment, the composition is administered to the subject once in 10 days. In one embodiment, the composition is administered to the subject once in 12 days. In one embodiment, the composition is administered to the subject once in 2 weeks. In one embodiment, the composition is administered to the subject once in 3 weeks. In one embodiment, the composition is administered to the subject once in 1 month.

[00235] In one embodiment, the first composition is administered multiple doses to the subject over a period of one month, 2 months, 3 months, 4 months 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months. 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months or more.

[00236] In one aspect, provided herein is a method of treating a *Pseudomonas* infection in a subject, the method comprising administering to the subject a first composition comprising a bacteriophage, wherein the bacteriophage comprises a nucleic acid sequence encoding a Type I CRISPR-Cas system that targets a *Pseudomonas* bacterium; and administering to the subject a second therapeutic. In some embodiments, the second therapeutic is an antibiotic or an antibacterial composition. In one embodiment, the first composition and the second therapeutic are administered on the same day. In one embodiment, the first composition and the second therapeutic are administered on the different days.

Administration Routes and Dosage

[00237] Dose and duration of the administration of a composition disclosed herein will depend on a variety of factors, including the subject's age, subject's weight, and tolerance of the phage. In some embodiments, a bacteriophage disclosed herein is administered to a subject intra-arterially, intravenously, intraurethrally, intramuscularly, orally, subcutaneously, by inhalation, or any combination thereof. In some embodiments, a bacteriophage disclosed herein is administered to a subject by oral administration. In some embodiments, a bacteriophage disclosed herein is administered to patients by topical, cutaneous, transdermal, transmucosal, implantation, sublingual, buccal, rectal, vaginal, ocular, otic, or nasal administration. In some embodiments, a bacteriophage disclosed herein is administered to a subject by any combination of the aforementioned routes of administration. In some embodiments, a bacteriophage disclosed herein is administered to a subject by inhalation. In some embodiments, a bacteriophage disclosed herein is administered to a subject by inhalation using a nebulizer.

[00238] In some embodiments, the composition and methods described herein are for treatment of a lung infection or a disease. In some embodiments, the lung infection or disease is cystic fibrosis. In some embodiments, administration of the composition comprising the

bacteriophage to a patient with cystic fibrosis or cystic fibrosis-associated bronchiectasis is via a nebulizer. In some embodiments, the treatment is administered via a patient-operable nebulizer. In some embodiments, the treatment is administered via a metered dose nebulizer. In some embodiments, the treatment is administered in combination with one or more other drugs or therapeutics, e.g., an antibiotic or bronchodilator. In some embodiments, the treatment is a bacteriophage, a bacteriophage composition, and/or a bacteriophage cocktail as described herein. For instance, a composition comprising p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695. The composition may be in a nebulizable formulation for pulmonary delivery.

[00239] In some embodiments, a dose of phage between 10^3 and 10^{20} PFU is administered to a subject. In some embodiments, a dose of phage between 10^3 and 10^{10} PFU is administered to a subject. In some embodiments, a dose of phage between 10^6 and 10^{20} PFU is administered to a subject. In some embodiments, a dose of phage between 10^6 and 10^{10} PFU is administered to a subject. For example, in some embodiments, a composition comprising a bacteriophage in an amount between 10^3 and 10^{11} PFU is administered to a subject. In some embodiments, a composition comprising a bacteriophage in an amount about 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, 10^{21}, 10^{22}, 10^{23}, 10^{24} PFU or more is administered to a subject. In some embodiments, a composition comprising a bacteriophage in an amount of less than 10^1 PFU is administered to a subject. In some embodiments, a composition comprising a bacteriophage in an amount between 10^1 and 10^8, 10^4 and 10^9, 10^5 and 10^{10}, or 10^7 and 10^{11} PFU is administered to a subject. In some embodiments, a composition comprising two or more bacteriophage is administered to a subject, wherein each bacteriophage is administered in an amount about 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15}, 10^{16}, 10^{17}, 10^{18}, 10^{19}, 10^{20}, 10^{21}, 10^{22}, 10^{23}, 10^{24} PFU or more. In some embodiments, a composition comprising two or more bacteriophage is administered to a subject, wherein each bacteriophage is administered in an amount of less than 10^1 PFU. In some embodiments, a composition comprising two or more bacteriophage is administered to a subject, wherein each bacteriophage is administered in an amount between 10^1 and 10^8, 10^4 and 10^9, 10^5 and 10^{10}, or 10^7 and 10^{11} PFU.

[00240] In some embodiments, a bacteriophage or a mixture is administered to a subject in need thereof 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 times a day. In some embodiments, a bacteriophage or a mixture is administered to a subject in need thereof at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 times a week. In some embodiments, a bacteriophage or a mixture is administered to a subject in need thereof at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80,

81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 times a month. In some embodiments, a bacteriophage or a mixture is administered to a subject in need thereof every 2, 4, 6, 8, 10, 12, 14, 18, 20, 22, or 24 hours.

[00241] In some embodiments, the compositions (bacteriophage) disclosed herein are administered before, during, or after the occurrence of a disease or condition. In some embodiment, the timing of administering the composition containing the bacteriophage varies. In some embodiments, the pharmaceutical compositions are used as a prophylactic and are administered continuously to subjects with a propensity to conditions or diseases in order to prevent the occurrence of the disease or condition. In some embodiments, pharmaceutical compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In some embodiments, the administration of the compositions is initiated within the first 48 hours of the onset of the symptoms, within the first 24 hours of the onset of the symptoms, within the first 6 hours of the onset of the symptoms, or within 3 hours of the onset of the symptoms. In some embodiments, the initial administration of the composition is via any route practical, such as by any route described herein using any formulation described herein. In some embodiments, the compositions is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. In some embodiments, the length of treatment will vary for each subject.

Bacterial Infections

[00242] Disclosed herein, in certain embodiments, are methods of treating bacterial infections. In some embodiments, the bacteriophages disclosed herein treat or prevent diseases or conditions mediated or caused by bacteria as disclosed herein in a human or animal subject. In some embodiments, the bacteriophages disclosed herein treat or prevent diseases or conditions caused or exacerbated by bacteria as disclosed herein in a human or animal subject. Such bacteria are typically in contact with tissue of the subject including: gut, oral cavity, lung, armpit, ocular, vaginal, anal, ear, nose or throat tissue. In some embodiments, a bacterial infection is treated by modulating the activity of the bacteria and/or by directly killing of the bacteria.

[00243] In some embodiments, the target bacteria is *Pseudomonas*. In some embodiments, the bacterium is *Pseudomonas aeruginosa*.

[00244] In some embodiments, one or more target bacteria present in a bacterial population are pathogenic. In some embodiments, the pathogenic bacteria are uropathogenic. In some embodiments, the pathogenic bacteria are pulmonary pathogens. In some embodiments, the pathogenic bacteria are bloodstream pathogens.

[00245] In some embodiments, the bacteriophages disclosed herein are used to treat an infection, a disease, or a condition, in the pulmonary system of a subject. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria within the pulmonary microbiome of a subject. In some embodiments, the bacteriophages are used to selectively modulate and/or kill one or more target bacteria from a plurality of bacteria within the pulmonary microbiome of a subject. In some embodiments, the bacteriophages are used to selectively modulate and/or kill one or more target pathogenic bacteria from a plurality of bacteria within the pulmonary microbiome of a subject.

[00246] In some embodiments, the bacteriophages disclosed herein are used to treat an infection, a disease, or a condition, in the urinary tract of a subject. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria within the urinary tract flora of a subject. In some embodiments, the bacteriophages are used to selectively modulate and/or kill one or more target uropathogenic bacteria from a plurality of bacteria within the urinary tract flora of a subject.

[00247] In some embodiments, the bacteriophages disclosed herein are used to treat an infection, a disease, or a condition, on the skin of a subject. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria on the skin of a subject.

[00248] In some embodiments, the bacteriophages disclosed herein are used to treat an infection, a disease, or a condition, on a mucosal membrane of a subject. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria on the mucosal membrane of a subject.

[00249] In some embodiments, the pathogenic bacteria are antibiotic resistant.

[00250] In some embodiments, the one or more target bacteria present in the bacterial population form a biofilm. In some embodiments, the biofilm comprises pathogenic bacteria. In some embodiments, the bacteriophage disclosed herein is used to treat a biofilm.

[00251] In some embodiments, the bacteriophage treats acne and other related skin infections.

[00252] In some embodiments, a *Pseudomonas* species is a multiple drug resistant (MDR) bacteria strain. An MDR strain is a bacteria strain that is resistant to at least one antibiotic. In some embodiments, a bacteria strain is resistant to an antibiotic class such as a cephalosporin, a fluoroquinolone, a carbapenem, a colistin, an aminoglycoside, vancomycin, streptomycin, and methicillin. In some embodiments, a bacteria strain is resistant to an antibiotic such as a Ceftobiprole, Ceftaroline, Clindamycin, Dalbavancin, Daptomycin, Linezolid, Mupirocin, Oritavancin, Tedizolid, Telavancin, Tigecycline, Vancomycin, an Aminoglycoside, a Carbapenem, Ceftazidime, Cefepime, Ceftobiprole, a Fluoroquinolone, Piperacillin, Ticarcillin,

Linezolid, a Streptogramin, Tigecycline, Daptomycin, or any combination thereof. In some embodiments, the MDR strain is *Pseudomonas aeruginosa.*

[00253] In some embodiments, the bacterium is a *Pseudomonas* species. In some embodiments, the bacterium is *Pseudomonas* aeruginosa. In some embodiments, the methods and compositions disclosed herein are for use in veterinary and medical applications as well as research applications.

[00254] In some embodiments, the bacterial infection is present in a subject with cystic fibrosis. In some embodiments the bacterial infection is present in a subject with non-cystic fibrosis bronchiectasis. In some embodiments, the bacterial infection is present in a subject with pneumonia. In some embodiments, the bacterial infection contributes to the pneumonia. As non-limiting examples, the pneumonia is hospital acquired pneumonia, ventilator acquired pneumonia, community acquired pneumonia, or health care acquired pneumonia. In some embodiments, the bacterial infection is a blood system infection (BSI).

[00255] In some embodiments, the methods described herein comprise administering an additional therapeutic. In some embodiments, the additional therapeutic is an antibiotic. In some embodiments, the antibiotic comprises tobramycin.

Microbiome

[00256] "Microbiome", "microbiota", and "microbial habitat" are used interchangeably hereinafter and refer to the ecological community of microorganisms that live on or in a subject's bodily surfaces, cavities, and fluids. Non-limiting examples of habitats of microbiome include: gut, colon, skin, skin surfaces, skin pores, vaginal cavity, umbilical regions, conjunctival regions, intestinal regions, stomach, nasal cavities and passages, gastrointestinal tract, urogenital tracts, saliva, mucus, and feces. In some embodiments, the microbiome comprises microbial material including, but not limited to, bacteria, archaea, protists, fungi, and viruses. In some embodiments, the microbial material comprises a gram-negative bacterium. In some embodiments, the microbial material comprises a gram-positive bacterium. In some embodiments, the microbial material comprises *Proteobacteria, Actinobacteria, Bacteroidetes,* or *Firmicutes.*

[00257] In some embodiments, the bacteriophages as disclosed herein are used to modulate or kill target bacteria within the microbiome of a subject. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria within the microbiome by the CRISPR-Cas system, lytic activity, or a combination thereof. In some embodiments, the bacteriophages are used to modulate and/or kill target bacteria within the microbiome of a subject. In some embodiments, the bacteriophages are used to selectively modulate and/or kill one or more target bacteria from a plurality of bacteria within the microbiome of a subject.

[00258] In some embodiments, the bacteriophages are used to modulate or kill target single or plurality of bacteria within the pulmonary microbiome of a subject. Modification (e.g., dysbiosis) of the pulmonary microbiome increases the risk for health conditions such as diabetes, mental disorders, ulcerative colitis, colorectal cancer, autoimmune disorders, obesity, diabetes, diseases of the central nervous system and inflammatory bowel disease.

[00259] In some embodiments, a bacteriophage disclosed herein is administered to a subject to promote a healthy microbiome. In some embodiments, a bacteriophage disclosed herein is administered to a subject to restore a subject's microbiome to a microbiome composition that promotes health. In some embodiments, a composition comprising a bacteriophage disclosed herein comprises a prebiotic or a third agent. In some embodiment, microbiome related disease or disorder is treated by a bacteriophage disclosed herein.

Environmental Therapy

[00260] In some embodiments, bacteriophages disclosed herein are further used for food and agriculture sanitation (including meats, fruits and vegetable sanitation), hospital sanitation, home sanitation, vehicle and equipment sanitation, industrial sanitation, etc. In some embodiments, bacteriophages disclosed herein are used for the removal of antibiotic-resistant or other undesirable pathogens from medical, veterinary, animal husbandry, or any additional environments bacteria are passed to humans or animals.

[00261] Environmental applications of phage in health care institutions are for equipment such as endoscopes and environments such as ICUs which are potential sources of nosocomial infection due to pathogens that are difficult or impossible to disinfect. In some embodiments, a phage disclosed herein is used to treat equipment or environments inhabited by bacterial genera which become resistant to commonly used disinfectants. In some embodiments, phage compositions disclosed herein are used to disinfect inanimate objects. In some embodiments, an environment disclosed herein is sprayed, painted, or poured onto with aqueous solutions with phage titers. In some embodiment a solution described herein comprises between 10^1-10^{20} plaque forming units (PFU)/ml. In some embodiments, a bacteriophage disclosed herein is applied by aerosolizing agents that include dry dispersants to facilitate distribution of the bacteriophage into the environment. In some embodiments, objects are immersed in a solution containing bacteriophage disclosed herein.

Sanitation

[00262] In some embodiments, bacteriophages disclosed herein are used as sanitation agents in a variety of fields. Although the terms "phage" or "bacteriophage" may be used, it should be noted that, where appropriate, this term should be broadly construed to include a single

bacteriophage, multiple bacteriophages, such as a bacteriophage mixtures and mixtures of a bacteriophage with an agent, such as a disinfectant, a detergent, a surfactant, water, etc.

[00263] In some embodiments, bacteriophages are used to sanitize hospital facilities, including operating rooms, patient rooms, waiting rooms, lab rooms, or other miscellaneous hospital equipment. In some embodiments, this equipment includes electrocardiographs, respirators, cardiovascular assist devices, intraaortic balloon pumps, infusion devices, other patient care devices, televisions, monitors, remote controls, telephones, beds, etc. In some situations, the bacteriophage is applied through an aerosol canister. In some embodiments, bacteriophage is applied by wiping the phage on the object with a transfer vehicle.

[00264] In some embodiments, a bacteriophage described herein is used in conjunction with patient care devices. In some embodiment, bacteriophage is used in conjunction with a conventional ventilator or respiratory therapy device to clean the internal and external surfaces between patients. Examples of ventilators include devices to support ventilation during surgery, devices to support ventilation of incapacitated patients, and similar equipment. In some embodiments, the conventional therapy includes automatic or motorized devices, or manual bag-type devices such as are commonly found in emergency rooms and ambulances. In some embodiments, respiratory therapy includes inhalers to introduce medications such as bronchodilators as commonly used with chronic obstructive pulmonary disease or asthma, or devices to maintain airway patency such as continuous positive airway pressure devices.

[00265] In some embodiment, a bacteriophage described herein is used to cleanse surfaces and treat colonized people in an area where highly-contagious bacterial diseases, such as meningitis or enteric infections are present.

[00266] In some embodiments, water supplies are treated with a composition disclosed herein. In some embodiments, bacteriophage disclosed herein is used to treat contaminated water, water found in cisterns, wells, reservoirs, holding tanks, aqueducts, conduits, and similar water distribution devices. In some embodiments, the bacteriophage is applied to industrial holding tanks where water, oil, cooling fluids, and other liquids accumulate in collection pools. In some embodiments, a bacteriophage disclosed herein is periodically introduced to the industrial holding tanks in order to reduce bacterial growth.

[00267] In some embodiments, bacteriophages disclosed herein are used to sanitize a living area, such as a house, apartment, condominium, dormitory, or any living area. In some embodiments, the bacteriophage is used to sanitize public areas, such as theaters, concert halls, museums, train stations, airports, pet areas, such as pet beds, or litter boxes. In this capacity, the bacteriophage is dispensed from conventional devices, including pump sprayers, aerosol containers, squirt bottles, pre-moistened towelettes, etc, applied directly to (e.g., sprayed onto) the

area to be sanitized, or be transferred to the area via a transfer vehicle, such as a towel, sponge, etc. In some embodiments, a phage disclosed herein is applied to various rooms of a house, including the kitchen, bedrooms, bathrooms, garage, basement, etc. In some embodiments, a phage disclosed herein is in the same manner as conventional cleaners. In some embodiments, the phage is applied in conjunction with (before, after, or simultaneously with) conventional cleaners provided that the conventional cleaner is formulated so as to preserve adequate bacteriophage biologic activity.

[00268] In some embodiments, a bacteriophage disclosed herein is added to a component of paper products, either during processing or after completion of processing of the paper products. Paper products to which a bacteriophage disclosed herein is added include, but are not limited to, paper towels, toilet paper, moist paper wipes.

Food Safety

[00269] In some embodiments, a bacteriophage described herein is used in any food product or nutritional supplement, for preventing contamination. Examples for food or pharmaceuticals products are milk, yoghurt, curd, cheese, fermented milks, milk based fermented products, ice-creams, fermented cereal based products, milk based powders, infant formulae or tablets, liquid suspensions, dried oral supplement, wet oral supplement, or dry-tube-feeding.

[00270] The broad concept of bacteriophage sanitation is applicable to other agricultural applications and organisms. Produce, including fruits and vegetables, dairy products, and other agricultural products. For example, freshly-cut produce frequently arrive at the processing plant contaminated with pathogenic bacteria. This has led to outbreaks of food-borne illness traceable to produce. In some embodiments, the application of bacteriophage preparations to agricultural produce substantially reduce or eliminate the possibility of food-borne illness through application of a single phage or phage mixture with specificity toward species of bacteria associated with food-borne illness. In some embodiments, bacteriophages are applied at various stages of production and processing to reduce bacterial contamination at that point or to protect against contamination at subsequent points.

[00271] In some embodiments, specific bacteriophages are applied to produce in restaurants, grocery stores, produce distribution centers. In some embodiments, bacteriophages disclosed herein are periodically or continuously applied to the fruit and vegetable contents of a salad bar. In some embodiments, the application of bacteriophages to a salad bar or to sanitize the exterior of a food item is a misting or spraying process or a washing process.

[00272] In some embodiments, a bacteriophage described herein is used in matrices or support media containing with packaging containing meat, produce, cut fruits and vegetables, and other foodstuffs. In some embodiments, polymers that are suitable for packaging are impregnated with a bacteriophage preparation.

[00273] In some embodiments, a bacteriophage described herein is used in farm houses and livestock feed. In some embodiments, on a farm raising livestock, the livestock is provided with bacteriophage in their drinking water, food, or both. In some embodiments, a bacteriophage described herein is sprayed onto the carcasses and used to disinfect the slaughter area.

[00274] The use of specific bacteriophages as biocontrol agents on produce provides many advantages. For example, bacteriophages are natural, non-toxic products that will not disturb the ecological balance of the natural microflora in the way the common chemical sanitizers do, but will specifically lyse the targeted food-borne pathogens. Because bacteriophages, unlike chemical sanitizers, are natural products that evolve along with their host bacteria, new phages that are active against recently emerged, resistant bacteria are rapidly identified when required, whereas identification of a new effective sanitizer is a much longer process, several years.

Pharmaceutical Compositions

[00275] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising (a) the nucleic acid sequences as disclosed herein; and (b) a pharmaceutically acceptable excipient. Also disclosed herein, in certain embodiments, are pharmaceutical compositions comprising (a) the bacteriophages as disclosed herein; and (b) a pharmaceutically acceptable excipient. Further disclosed herein, in certain embodiments, are pharmaceutical compositions comprising (a) the compositions as disclosed herein; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable excipient comprises a surfactant. In some embodiments, the pharmaceutically acceptable excipient is a buffer.

[00276] In some embodiments, the disclosure provides pharmaceutical compositions and methods of administering the same to treat bacterial, archaeal infections or to disinfect an area. In some embodiments, the pharmaceutical composition comprises any of the reagents discussed above in a pharmaceutically acceptable carrier. In some embodiments, a pharmaceutical composition or method disclosed herein treats a *Pseudomonas* bacterial infection. In some embodiments, the bacterial infection is a *P. aeruginosa* bloodstream infection. In some embodiments, the bacterial infection is a *P. aeruginosa* respiratory infection. In some embodiments, a pharmaceutical composition of method disclosed herein treats cystic fibrosis-associated bronchiectasis. In some embodiments, a pharmaceutical composition or method disclosed herein treats non-cystic fibrosis-associated bronchiectasis. In some embodiments, a pharmaceutical composition of method disclosed herein treats malignant external otitis, endophthalmitis, endocarditis, meningitis, pneumonia, or septicemia.

[00277] In some embodiments, compositions disclosed herein comprise medicinal agents, pharmaceutical agents, carriers, adjuvants, dispersing agents, diluents, and the like.

[00278] In some embodiments, the bacteriophages disclosed herein are formulated for administration in a pharmaceutical carrier in accordance with suitable methods. In some embodiments, the manufacture of a pharmaceutical composition according to the disclosure, the bacteriophage is admixed with, inter alia, an acceptable carrier. In some embodiments, the carrier is a solid (including a powder) or a liquid, or both, and is preferably formulated as a unit-dose composition. In some embodiments, one or more bacteriophages are incorporated in the compositions disclosed herein, which are prepared by any suitable method of a pharmacy.

[00279] In some embodiment, a method of treating subject's *in-vivo*, comprising administering to a subject a pharmaceutical composition comprising a bacteriophage disclosed herein in a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is administered in a therapeutically effective amount. In some embodiments, the administration of the bacteriophage to a human subject or an animal in need thereof are by any means known in the art.

[00280] In some embodiment, methods and compositions suitable for administering bacteriophages disclosed herein to a surface of an object or subject includes aqueous solutions. In some embodiments, such aqueous solutions are sprayed onto the surface of an object or subject. In some embodiment, the aqueous solutions are used to irrigate and clean a physical wound of a subject form foreign debris including bacteria.

[00281] In some embodiments, methods and compositions suitable for nasal administration or otherwise administered to the lungs of a subject include any suitable means, e.g., administered by an aerosol suspension of respirable particles comprising the bacteriophage compositions, which the subject inhales. In some embodiments, the respirable particles are liquid or solid. As used herein, "aerosol" includes any gas-borne suspended phase, which is capable of being inhaled into the bronchioles or nasal passages. In some embodiments, aerosols of liquid particles are produced by any suitable means, such as with a pressure-driven aerosol nebulizer, an ultrasonic nebulizer, or a mesh nebulizer. In some embodiments, aerosols of solid particles comprising the composition is produced with any solid particulate medicament aerosol generator, by techniques known in the pharmaceutical art.

[00282] Nebulizers are liquid aerosol generators that convert bulk liquids, usually aqueous-based compositions, into mists or clouds of small droplets, having diameters less than 5 microns mass median aerodynamic diameter (MMAD), which can be inhaled into the lower respiratory tract. The bulk liquid contains particles of the therapeutic agent(s) or a solution of the therapeutic agent(s) and any necessary excipients. The droplets carry the therapeutic agent(s) into the nose, upper airways or deep lungs when the aerosol cloud is inhaled.

[00283] Pneumatic (jet) nebulizers use a pressurized gas supply as a driving force for liquid atomization. Compressed gas is delivered through a nozzle or jet to create a low pressure field which entrains a surrounding bulk liquid and shears it into a thin film or filaments. The film or filaments are unstable and break up into small droplets which are carried by the compressed gas flow into the inspiratory breath. Baffles inserted into the droplet plume screen out the larger droplets and return them to the bulk liquid reservoir. Examples include the PARI LC® Plus®, or Sprint® nebulizers, the Devilbiss PulmoAide® nebulizer and the Boehringer Ingelheim Respimat® inhaler.

[00284] Electromechanical nebulizers use electrically generated mechanical force to atomize liquids. The electromechanical driving force is applied by vibrating the bulk liquid at ultrasonic frequencies or by forcing the bulk liquid through small holes in a thin film. The forces generate thin liquid films or filament streams which break up into small droplets to form a slow moving aerosol stream which can be entrained in a respiratory flow.

[00285] One form of electromechanical nebulizers is ultrasonic nebulizers, in which the bulk liquid is coupled to a vibrator oscillating at frequencies in the ultrasonic range. The coupling is achieved by placing the liquid in direct contact with the vibrator such as a plate or ring in a holding cup, or by placing large droplets on a solid vibrating projector. The vibrations generate circular standing films which break up into droplets at their edges to atomize the liquid. Examples include the DuroMist® nebulizer, Drive Medical's Beetle Neb® nebulizer, Octive Tech's Densylogic® nebulizer and the John Bunn Nano-Sonic® nebulizer. Another form of an electromechanical nebulizer is a mesh nebulizer, in which the bulk liquid is driven through a mesh or membrane with small holes ranging from 2 to 8 microns in diameter, to generate thin filaments which immediately break up into small droplets. In some designs, the liquid is forced through the mesh by applying pressure with a solenoid piston driver (AERx®) or by sandwiching the liquid between a piezoelectrically vibrated plate and the mesh, which results in an oscillatory pumping action (EFlow®, AerovectRx, TouchSpray™). In a second design type the mesh vibrates back and forth through a standing column of the liquid to pump it through the holes. Examples include the AeroNeb®, AeroNeb Go®, Pro®; PARI EFlow®; Omron 22UE®; and Aradigm AERx®.

[00286] In some embodiments, bacteriophages disclosed herein are for oral administration. In some embodiments, the bacteriophages are administered in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. In some embodiments, compositions and methods suitable for buccal (sub-lingual) administration include lozenges comprising the bacteriophages in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the bacteriophages in an inert base such as gelatin and glycerin or sucrose and acacia.

[00287] In some embodiments, methods and compositions of the present disclosure are suitable for parenteral administration comprising sterile aqueous and non-aqueous injection solutions of the bacteriophage. In some embodiments, these preparations are isotonic with the blood of the intended recipient. In some embodiments, these preparations comprise antioxidants, buffers, bacteriostals and solutes which render the composition isotonic with the blood of the intended recipient. In some embodiments, aqueous and non-aqueous sterile suspensions include suspending agents and thickening agents. In some embodiments, compositions disclosed herein are presented in unit\dose or multi-dose containers, for example sealed ampoules and vials, and are stored in a freeze-dried(lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water for injection on immediately prior to use.

[00288] In some embodiment, methods and compositions suitable for rectal administration are presented as unit dose suppositories. In some embodiments, these are prepared by admixing the bacteriophage with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture. In some embodiments, methods and compositions suitable for topical application to the skin are in the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. In some embodiments, carriers which are used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

[00289] In some embodiments, methods and compositions suitable for transdermal administration are presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time.

[00290] In some embodiments, the bacteriophages disclosed herein are administered to the subject in a therapeutically effective amount. In some embodiments, at least one bacteriophage composition disclosed herein is formulated as a pharmaceutical formulation. In some embodiments, a pharmaceutical formulation comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more bacteriophage disclosed herein. In some instances, a pharmaceutical formulation comprises a bacteriophage described herein and at least one of: an excipient, a diluent, or a carrier.

[00291] In some embodiments, a pharmaceutical formulation comprises an excipient. Excipients are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986) and includes but are not limited to solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, and lubricants.

[00292] Non-limiting examples of suitable excipients include but is not limited to a buffering agent, a preservative, a stabilizer, a binder, a compaction agent, a lubricant, a chelator, a dispersion enhancer, a disintegration agent, a flavoring agent, a sweetener, a coloring agent.

[00293] In some embodiments, an excipient is a buffering agent. Non-limiting examples of suitable buffering agents include but is not limited to sodium citrate, magnesium carbonate, magnesium bicarbonate, calcium carbonate, and calcium bicarbonate. In some embodiments, a pharmaceutical formulation comprises any one or more buffering agent listed: sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide and other calcium salts.

[00294] In some embodiments an excipient is a preservative. Non-limiting examples of suitable preservatives include but is not limited to antioxidants, such as alpha-tocopherol and ascorbate, and antimicrobials, such as parabens, chlorobutanol, and phenol. In some embodiments, antioxidants include but not limited to Ethylenediaminetetraacetic acid (EDTA), citric acid, ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), sodium sulfite, p-amino benzoic acid, glutathione, propyl gallate, cysteine, methionine, ethanol and N- acetyl cysteine. In some embodiments, preservatives include validamycin A, TL-3, sodium ortho vanadate, sodium fluoride, N-a-tosyl-Phe- chloromethylketone, N-a-tosyl-Lys-chloromethylketone, aprotinin, phenylmethylsulfonyl fluoride, diisopropylfluorophosphate, protease inhibitor, reducing agent, alkylating agent, antimicrobial agent, oxidase inhibitor, or other inhibitor.

[00295] In some embodiments, a pharmaceutical formulation comprises a binder as an excipient. Non-limiting examples of suitable binders include starches, pregelatinized starches, gelatin, polyvinylpyrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, polyvinylalcohols, C_{12}-C_{18} fatty acid alcohol, polyethylene glycol, polyols, saccharides, oligosaccharides, and combinations thereof.

[00296] In some embodiments, the binders that are used in a pharmaceutical formulation are selected from starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol and water or a combination thereof.

[00297] In some embodiments, a pharmaceutical formulation comprises a lubricant as an excipient. Non-limiting examples of suitable lubricants include magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil. In some embodiments, lubricants that are in a pharmaceutical formulation are selected from metallic stearates (such as magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols (PEG), metallic lauryl sulphates (such as sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc or a combination thereof.

[00298] In some embodiments, an excipient comprises a flavoring agent. In some embodiments, flavoring agents includes natural oils; extracts from plants, leaves, flowers, and fruits; and combinations thereof.

[00299] In some embodiments, an excipient comprises a sweetener. Non-limiting examples of suitable sweeteners include glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as a sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; and sugar alcohols such as sorbitol, mannitol, sylitol, and the like.

[00300] In some instances, a pharmaceutical formulation comprises a coloring agent. Non-limiting examples of suitable color agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C).

[00301] In some embodiments, the pharmaceutical formulation disclosed herein comprises a chelator. In some embodiments, a chelator includes ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); a disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salt of EDTA; a barium, calcium, cobalt, copper, dysprosium, europium, iron, indium, lanthanum, magnesium, manganese, nickel, samarium, strontium, or zinc chelate of EDTA.

[00302] In some instances, a pharmaceutical formulation comprises a diluent. Non-limiting examples of diluents include water, glycerol, methanol, ethanol, and other similar biocompatible diluents. In some embodiments, a diluent is an aqueous acid such as acetic acid, citric acid, maleic acid, hydrochloric acid, phosphoric acid, nitric acid, sulfuric acid, or similar.

[00303] In some embodiments, a pharmaceutical formulation comprises a surfactant. In some embodiments, surfactants are be selected from, but not limited to, polyoxyethylene sorbitan fatty acid esters (polysorbates), sodium lauryl sulphate, sodium stearyl fumarate, polyoxyethylene

alkyl ethers, sorbitan fatty acid esters, polyethylene glycols (PEG), polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, amino acids such as L- leucine, sugar esters of fatty acids, glycerides of fatty acids or a combination thereof.

[00304] In some instances, a pharmaceutical formulation comprises an additional pharmaceutical agent. In some embodiments, an additional pharmaceutical agent is an antibiotic agent. In some embodiments, an antibiotic agent is of the group consisting of aminoglycosides, ansamycins, carbacephem, carbapenems, cephalosporins (including first, second, third, fourth and fifth generation cephalosporins), lincosamides, macrolides, monobactams, nitrofurans, quinolones, penicillin, sulfonamides, polypeptides or tetracycline.

[00305] In some embodiments, an antibiotic agent described herein is an aminoglycoside such as Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin or Paromomycin. In some embodiments, an antibiotic agent described herein is an Ansamycin such as Geldanamycin or Herbimycin.

[00306] In some embodiments, an antibiotic agent described herein is a carbacephem such as Loracarbef. In some embodiments, an antibiotic agent described herein is a carbapenem such as Ertapenem, Doripenem, Imipenem/Cilastatin or Meropenem.

[00307] In some embodiments, an antibiotic agent described herein is a cephalosporins (first generation) such as Cefadroxil, Cefazolin, Cefalexin, Cefalotin or Cefalothin, or alternatively a Cephalosporins (second generation) such as Cefaclor, Cefamandole, Cefoxitin, Cefprozil or Cefuroxime. In some embodiments, an antibiotic agent is a Cephalosporins (third generation) such as Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftibuten, Ceftizoxime and Ceftriaxone or a Cephalosporins (fourth generation) such as Cefepime or Ceftobiprole.

[00308] In some embodiments, an antibiotic agent described herein is a lincosamide such as Clindamycin and Azithromycin, or a macrolide such as Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Troleandomycin, Telithromycin and Spectinomycin.

[00309] In some embodiments, an antibiotic agent described herein is a monobactams such as Aztreonam, or a nitrofuran such as Furazolidone or Nitrofurantoin.

[00310] In some embodiments, an antibiotic agent described herein is a penicillin such as Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Nafcillin, Oxacillin, Penicillin G or V, Piperacillin, Temocillin and Ticarcillin.

[00311] In some embodiments, an antibiotic agent described herein is a sulfonamide such as Mafenide, Sulfonamidochrysoidine, Sulfacetamide, Sulfadiazine, Silver sulfadiazine,

Sulfamethizole, Sulfamethoxazole, Sulfanilimide, Sulfasalazine, Sulfisoxazole, Trimethoprim, or Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX).

[00312] In some embodiments, an antibiotic agent described herein is a quinolone such as Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin and Temafloxacin.

[00313] In some embodiments, an antibiotic agent described herein is a polypeptide such as Bacitracin, Colistin or Polymyxin B.

[00314] In some embodiments, an antibiotic agent described herein is a tetracycline such as Demeclocycline, Doxycycline, Minocycline or Oxytetracycline.

Enumerated embodiments:

1. A bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array comprising one or more spacer sequences complementary to a target nucleotide sequence in a *Pseudomonas* species;

(b) a Cascade polypeptide; and

(c) a Cas3 polypeptide.

2. The bacteriophage of embodiment 1, wherein the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120.

3. The bacteriophage of any one of embodiments 1-2, wherein the CRISPR array further comprises at least one repeat sequence.

4. The bacteriophage of embodiment 3, wherein the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end.

5. The bacteriophage of any one of embodiments 3-4, wherein the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30.

6. The bacteriophage of any one of embodiments 1-5, wherein the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87.

7. The bacteriophage of any one of embodiments 1-6, wherein the target nucleotide sequence comprises a coding sequence.

8. The bacteriophage of any one of embodiments 1-6, wherein the target nucleotide sequence comprises a non-coding or intergenic sequence.

9. The bacteriophage of any one of embodiments 1-6, wherein the target nucleotide sequence comprises all or a part of a promoter sequence.

10. The bacteriophage of embodiment 9, wherein the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

11. The bacteriophage of embodiment 1, wherein the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene.

12. The bacteriophage of embodiment 11, wherein the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*.

13. The bacteriophage of any one of embodiments 1-12, wherein the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system.

14. The bacteriophage of embodiment 13, wherein the Cascade complex comprises:

(i) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system);

(ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system);

(iii) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system);

(iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system);

(v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); or

(vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system).

15. The bacteriophage of embodiment 13, wherein the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 (optionally SEQ ID NO: 82) polypeptide (Type I-C CRISPR-Cas system).

16. The bacteriophage of any one of embodiments 1-15, wherein the nucleic acid sequence further comprises a promoter sequence.

17. The bacteriophage of any one of embodiments 1-16, wherein the bacteriophage is an obligate lytic bacteriophage.

18. The bacteriophage of any one of embodiments 1-16, wherein the bacteriophage is a temperate bacteriophage that is rendered lytic.

19. The bacteriophage of embodiment 18, wherein the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene.

20. The bacteriophage of any one of embodiments 17-19, wherein the *Pseudomonas* species is killed solely by lytic activity of the bacteriophage.

21. The bacteriophage of any one of embodiments 1-19, wherein the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system.

22. The bacteriophage of any one of embodiments 17-19, wherein the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system.

23. The bacteriophage of embodiment 22, wherein the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage.

24. The bacteriophage of embodiment 22, wherein the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage.

25. The bacteriophage of embodiment 22, wherein the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic.

26. The bacteriophage of any one of embodiments 17-25, wherein the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage.

27. The bacteriophage of any one of embodiments 1-26, wherein the bacteriophage infects multiple bacterial strains of the *Pseudomonas* species.

28. The bacteriophage of any one of embodiments 1-27, wherein the bacteriophage comprises a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus.

29. The bacteriophage of embodiment 28, wherein the bacteriophage comprises at least 80% sequence identity to a phage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof.

30. The bacteriophage of embodiment 29, wherein the bacteriophage comprises p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt,

p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof.

31. The bacteriophage of any one of embodiments 1-30, wherein the nucleic acid sequence is inserted into a non-essential bacteriophage gene.

32. A pharmaceutical composition comprising:

(a) the bacteriophage of any one of embodiments 1-31; and

(b) a pharmaceutically acceptable excipient.

33. The pharmaceutical composition of embodiment 32, wherein the pharmaceutical composition comprises at least two bacteriophage.

34. The pharmaceutical composition of embodiment 33, wherein the bacteriophage are from the lineage consisting of a PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus and Pbunavirus.

35. The pharmaceutical composition of embodiment 33, wherein the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

36. The pharmaceutical composition of any one of embodiments 32-35, wherein the pharmaceutical composition is in the form of a tablet, a capsule, a liquid, a syrup, an oral formulation, an intravenous formulation, an intranasal formulation, an ocular formulation, an otic formulation, a subcutaneous formulation, a topical formulation, a transdermal formulation, a transmucosal formulation, an inhalable respiratory formulation, a suppository, a lyophilized formulation, a nebulizable formulation, and any combination thereof.

37. A method of killing a *Pseudomonas* species comprising introducing into the target bacterium a nucleic acid sequence encoding a Type I CRISPR-Cas system from a bacteriophage, the nucleic acid sequence comprising:

(a) a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in the *Pseudomonas* species;

(b) a Cascade polypeptide; and

(c) a Cas3 polypeptide.

38. The method of embodiment 37, wherein the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120.

39. The method of any one of embodiments 37-38, wherein the CRISPR array further comprises at least one repeat sequence.

40. The method of embodiment 39, wherein the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end.

41. The method of any one of embodiments 39-40, wherein the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30.

42. The method of any one of embodiments 37-41, wherein the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87.

43. The method of any one of embodiments 37-42, wherein the target nucleotide sequence comprises a coding sequence.

44. The method of any one of embodiments 37-42, wherein the target nucleotide sequence comprises a non-coding or intergenic sequence.

45. The method of any one of embodiments 37-42, wherein the target nucleotide sequence comprises all or a part of a promoter sequence.

46. The method of embodiment 45, wherein the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

47. The method of any one of embodiments 37-43, wherein the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene.

48. The method of embodiment 47, wherein the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*.

49. The method of any one of embodiments 37-48, wherein the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system.

50. The method of embodiment 49, wherein the Cascade complex comprises:

(i) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system);

(ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system);

(iii) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system);

(iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system);

(v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); or

(vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system).

51. The method of embodiment 49, wherein the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system).

52. The method of any one of embodiments 37-51, wherein the nucleic acid sequence further comprises a promoter sequence.

53. The method of any one of embodiments 37-52, wherein the bacteriophage is an obligate lytic bacteriophage.

54. The method of any one of embodiments 37-52, wherein the bacteriophage is a temperate bacteriophage that is rendered lytic.

55. The method of embodiment 54, wherein the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene.

56. The method of any one of embodiments 37-55, wherein the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system.

57. The method of any one of embodiments 53-55, wherein the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system.

58. The method of embodiment 57, wherein the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage.

59. The method of embodiment 57, wherein the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage.

60. The method of embodiment 57, wherein the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic.

61. The method of any one of embodiments 53-60, wherein the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage.

62. The method of any one of embodiments 37-61, wherein the bacteriophage infects multiple bacterial strains of the *Pseudomonas* species.

63. The method of any one of embodiments 37-62, wherein the bacteriophage comprises at least 80% identity to p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof.

64. The method of embodiment 63, wherein the bacteriophage comprises at least 80% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof.

65. The method of any one of embodiments 37-64, wherein the nucleic acid sequence is inserted in place of or adjacent to a non-essential bacteriophage gene.

66. The method of any one of embodiments 37-65, wherein a mixed population of bacterial cells comprises the *Pseudomonas* species.

67. The method of any one of embodiments 37-66, further comprising administering at least one additional bacteriophage.

68. The method of embodiment 67, comprising administering at least six bacteriophage, wherein the bacteriophage comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

69. A method of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array;

(b) a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and

(c) a Cas3 polypeptide.

70. The method of embodiment 69, wherein the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120.

71. The method of any one of embodiments 69-70, wherein the CRISPR array further comprises at least one repeat sequence.

72. The method of embodiment 71, wherein the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end.

73. The method of any one of embodiments 71-72, wherein the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30.

74. The method of any one of embodiments 69-73, wherein the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87.

75. The method of any one of embodiments 69-74, wherein the target nucleotide sequence comprises a coding sequence.

76. The method of any one of embodiments 69-74, wherein the target nucleotide sequence comprises a non-coding or intergenic sequence.

77. The method of any one of embodiments 69-74, wherein the target nucleic acid sequence comprises all or a part of a promoter sequence.

78. The method of embodiment 77, wherein the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

79. The method of any one of embodiments 69-74, wherein the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene.

80. The method of embodiment 79, wherein the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*.

81. The method of any one of embodiments 69-80, wherein the Cascade polypeptide forms a Cascade complex of a Type I-A CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-C CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system.

82. The method of embodiment 81, wherein the Cascade complex comprises:

(i) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system);

(ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system);

(iii) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system);

(iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system);

(v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); or

(vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system).

83. The method of embodiment 82, wherein the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system).

84. The method of any one of embodiments 69-83, wherein the nucleic acid sequence further comprises a promoter sequence.

85. The method of any one of embodiments 69-84, wherein the bacteriophage is an obligate lytic bacteriophage.

86. The method of any one of embodiments 69-84, wherein the bacteriophage is a temperate bacteriophage that is rendered lytic.

87. The method of embodiment 86, wherein the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene.

88. The method of any one of embodiments 69-87, wherein the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system.

89. The method of any one of embodiments 85-87, wherein the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system.

90. The method of embodiment 89, wherein the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage.

91. The method of embodiment 89, wherein the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage.

92. The method of embodiment 89, wherein the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic.

93. The method of any one of embodiments 85-92, wherein the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage

94. The method of any one of embodiments 69-93, wherein the bacteriophage infects multiple bacterial strains.

95. The method of any one of embodiments 69-87, wherein the bacteriophage comprises at least 80% identity to p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof.

96. The method of embodiment 95, wherein the bacteriophage comprises at least 80% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt,

p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof.

97. The method of any one of embodiments 69-96, wherein the nucleic acid sequence is inserted in place of or adjacent to a non-essential bacteriophage gene.

98. The method of any one of embodiments 69-97, further comprising administering at least one additional bacteriophage.

99. The method of embodiment 98, comprising administering at least six bacteriophage, wherein the bacteriophage comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

100. The method of any one of embodiments 69-99, wherein the disease or condition is a bacterial infection, cystic fibrosis, non-cystic fibrosis bronchiectasis, or pneumonia.

101. The method of embodiment 100, wherein the bacterial infection is associated with cystic fibrosis or non-cystic fibrosis bronchiectasis, or wherein the bacterial infection is a blood stream infection.

102. The method of any one of embodiments 69-101, wherein the *Pseudomonas* species causing the disease or condition is a drug resistant *Pseudomonas* species.

103. The method of embodiment 102, wherein the drug resistant *Pseudomonas* species is resistant to at least one antibiotic.

104. The method of any one of embodiments 69-103, wherein the *Pseudomonas* species causing the disease or condition is a multidrug resistant *Pseudomonas* species.

105. The method of embodiment 104, wherein the multi-drug resistant *Pseudomonas* species is resistant to at least one antibiotic.

106. The method of any one of embodiments 103 or 105, wherein the antibiotic comprises a cephalosporin, a fluoroquinolone, a carbapenem, a colistin, an aminoglycoside, vancomycin, streptomycin, or methicillin.

107. The method of any one of embodiments 69-106, wherein the *Pseudomonas* species is *Pseudomonas aeruginosa.*

108. The method of any one of embodiments 69-107, wherein the administering is intra-arterial, intravenous, intraurethral, intramuscular, oral, subcutaneous, inhalation, topical, cutaneous, transdermal, transmucosal, implantation, sublingual, buccal, rectal, vaginal, ocular, otic, or nasal administration or any combination thereof.

109. The method of any one of embodiments 69-108, further comprising administering an additional therapeutic.

110. The method of embodiment 109, wherein the additional therapeutic comprises tobramycin.

111. The method of any one of embodiments 69-110, wherein the individual is a mammal.

112. A bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species;

(b) a Cascade polypeptide comprising Cas5, Cas8c and Cas7; and

(c) a Cas3 polypeptide.

113. The bacteriophage of embodiment 112, wherein the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120.

114. The bacteriophage of any one of embodiments 112-113, wherein the CRISPR array further comprises at least one repeat sequence.

115. The bacteriophage of embodiment 114, wherein the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end.

116. The bacteriophage of any one of embodiments 112-115, wherein the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30.

117. The bacteriophage of any one of embodiments 112-116, wherein the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87.

118. The bacteriophage of any one of embodiments 112-117, wherein the target nucleotide sequence comprises a coding sequence.

119. The bacteriophage of any one of embodiments 112-117, wherein the target nucleotide sequence comprises a non-coding or intergenic sequence.

120. The bacteriophage of any one of embodiments 112-117, wherein the target nucleotide sequence comprises all or a part of a promoter sequence.

121. The bacteriophage of embodiment 120, wherein the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

122. The bacteriophage of any one of embodiments 112-121, wherein the target nucleotide sequence comprises all or a part of a nucleotide sequence located on a coding strand of a transcribed region of an essential gene.

123. The bacteriophage of embodiment 122, wherein the essential gene is *Tsf, acpP, gapA, infA, secY, csrA, trmD, ftsA, fusA, glyQ, eno, nusG, dnaA, dnaS, pheS, rplB, gltX, hisS, rplC, aspS, gyrB, glnS, dnaE, rpoA, rpoB, pheT, infB, rpsC, rplF, alaS, leuS, serS, rplD, gyrA, glmS, fus, adk, rpsK, rplR, ctrA, parC, tRNA-Ser, tRNA-Asn,* or *metK*.

124. The bacteriophage of any one of embodiments 112-123, wherein the nucleic acid sequence further comprises a promoter sequence.

125. The bacteriophage of any one of embodiments 112-124, wherein the bacteriophage is an obligate lytic bacteriophage.

126. The bacteriophage of any one of embodiments 112-124, wherein the bacteriophage is a temperate bacteriophage that is rendered lytic.

127. The bacteriophage of embodiment 126, wherein the temperate bacteriophage is rendered lytic by the removal, replacement, or inactivation of a lysogeny gene.

128. The bacteriophage of any one of embodiments 125-127, wherein the *Pseudomonas* species is killed solely by lytic activity of the bacteriophage.

129. The bacteriophage of any one of embodiments 125-127, wherein the *Pseudomonas* species is killed solely by activity of the CRISPR-Cas system.

130. The bacteriophage of any one of embodiments 125-127, wherein the *Pseudomonas* species is killed by lytic activity of the bacteriophage in combination with activity of the CRISPR-Cas system.

131. The bacteriophage of embodiment 130, wherein the *Pseudomonas* species is killed by the activity of the CRISPR-Cas system, independently of the lytic activity of the bacteriophage.

132. The bacteriophage of embodiment 130, wherein the activity of the CRISPR-Cas system supplements or enhances the lytic activity of the bacteriophage.

133. The bacteriophage of embodiment 130, wherein the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic.

134. The bacteriophage of any one of embodiments 125-133, wherein the lytic activity of the bacteriophage, the activity of the CRISPR-Cas system, or both, is modulated by a concentration of the bacteriophage

135. The bacteriophage of any one of embodiments 112-134, wherein the bacteriophage infects multiple bacterial strains.

136. The bacteriophage of any one of embodiments 112-135, wherein the bacteriophage comprises at least 80% identity to p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof.

137. The bacteriophage of embodiment 136, wherein the bacteriophage comprises at least 80% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof.

138. The bacteriophage of any one of embodiments 112-137, wherein the nucleic acid sequence is inserted into a non-essential bacteriophage gene.

139. A pharmaceutical composition comprising:

(a) the bacteriophage of any one of embodiments 112-138; and

(b) a pharmaceutically acceptable excipient.

140. The pharmaceutical composition of embodiment 139, wherein the pharmaceutical composition comprises at least two bacteriophage.

141. The pharmaceutical composition of embodiment 140, wherein the pharmaceutical composition comprises at least six bacteriophage, wherein the bacteriophage comprise p1106e003, p1835e002, p1772e005, p2131e002, p4430, and p1695.

142. The pharmaceutical composition of any one of embodiments 139-141, wherein the pharmaceutical composition is in the form of a tablet, a capsule, a liquid, a syrup, an oral formulation, an intravenous formulation, an intranasal formulation, an ocular formulation, an otic formulation, a subcutaneous formulation, a topical formulation, a transdermal formulation, a transmucosal formulation, an inhalable respiratory formulation, a suppository, a lyophilized formulation, a nebulizable formulation, and any combination thereof.

143. A method of sanitizing a surface in need thereof, the method comprising administering to the surface a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array;

(b) a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and

(c) a Cas3 polypeptide.

144. The method of embodiment 143, wherein the surface is a hospital surface, a vehicle surface, an equipment surface, or an industrial surface.

145. A method of preventing contamination in a food product or a nutritional supplement, the method comprising administering to the food product or the nutritional supplement a bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array;

(b) a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and

(c) a Cas3 polypeptide.

146. The method of embodiment 145, wherein the food product or nutritional supplement comprises milk, yoghurt, curd, cheese, fermented milks, milk based fermented products, ice-creams, fermented cereal based products, milk based powders, infant formulae or tablets, liquid suspensions, dried oral supplement, wet oral supplement, or dry-tube-feeding.

147. A bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array comprising spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species, wherein the spacer sequences comprise SEQ ID NOs: 12, 16, and 20;

(b) a Cascade polypeptide; and

(c) a Cas3 polypeptide.

148. A bacteriophage comprising at least 80% sequence identity to a phage selected from p1106, p1194, p1587, p1695, p1772, p1835, p2037, p2131, p2132, p2167, p2363, p2421, p2973, p3278, p4430, or PB1, or two or more phage thereof.

149. The bacteriophage of embodiment 148, wherein the bacteriophage comprises at least 80% identity to p1106e003, p1106wt, p1194wt, p1587e002, p1587wt, p1695wt, p1772e005, p1772wt, p1835e002, p1835wt, p2037e002, p2037wt, p2131e002, p2131wt, p2132e002, p2132wt, p2167wt, p2363e003, p2363wt, p2421e002, p2421wt, p2973e002, p2973wt, p3278wt, p4430wt, PB1e002, or PB1wt, or two or more phage thereof.

150. The bacteriophage of embodiment 148, further comprising

(a) a CRISPR array;

(b) a Cascade polypeptide comprising one or more spacer sequences complementary to target nucleotide sequence in a *Pseudomonas* species; and

(c) a Cas3 polypeptide.

151. The bacteriophage of embodiment 150, wherein the one or more spacer sequence comprises at least one of SEQ ID NOs: 12-23, 31-74, or 88-120 or at least 90% sequence identity to any one of SEQ ID NOs: 12-23, 31-74, or 88-120.

152. The bacteriophage of any one of embodiments 150-151, wherein the CRISPR array further comprises at least one repeat sequence.

153. The bacteriophage of embodiment 151, wherein the at least one repeat sequence is operably linked to the one or more spacer sequences at either its 5' end or its 3' end.

154. The bacteriophage of any one of embodiments 151-153, wherein the repeat sequence comprises at least about 90% sequence identity to any one of SEQ ID NOS: 26-30.

155. The bacteriophage of any one of embodiments 151-154, wherein the CRISPR array comprises at least about 90% sequence identity to a sequence as set forth in Figs. 1A-1E or SEQ ID NOS: 83-87.

156. The bacteriophage of any one of embodiments 151-155, wherein the target nucleotide sequence comprises a coding sequence.

157. The bacteriophage of any one of embodiments 151-156, wherein the target nucleotide sequence comprises a non-coding or intergenic sequence.

158. The bacteriophage of any one of embodiments 151-157, wherein the target nucleotide sequence comprises all or a part of a promoter sequence.

159. The bacteriophage of embodiment 158, wherein the promoter sequence comprises at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

160. A composition comprising at least four bacteriophage, comprising:

(a) a first bacteriophage comprising at least 80% sequence identity with p1106e003;

(b) a second bacteriophage comprising at least 80% sequence identity with p1835e002;

(c) a third bacteriophage comprising at least 80% sequence identity with p1772e005; and

(d) a fourth bacteriophage comprising at least 80% sequence identity with p2131e002.

161. The composition of embodiment 160, further comprising a fifth bacteriophage comprising at least 80% sequence identity with p1194.

162. The composition of embodiment 160, further comprising a fifth bacteriophage comprising at least 80% sequence identity with p1695.

163. The composition of embodiment 160, further comprising a fifth bacteriophage comprising at least 80% sequence identity with p4430.

164. The composition of embodiment 161 or 163, further comprising a sixth bacteriophage comprising at least 80% sequence identity with p1695.

EXAMPLES

Example 1: Engineered phage used in this application

[00315] Bacteriophage were engineered to contain a crArray and Cas construct. **Table 1A** depicts the components of the phage used in the following application. **Table 1B** depicts the sequences of the promoters used to drive expression of both the crArray and the Cas promoter. **Table 1C** depicts the sequence of the spacer sequence in the crArray used to target specific sites. Further, **Figs. 1A-1E** depict the sequence and alignment of crArray1-crArray5 used in the following examples. The full sequence of the combined crArray1 and *Pseudomonas* Type I C CRISPR insert is shown in **FIGS. 1F-1K** and **Table 1D.** The full sequence of the combined crArray3 and *Pseudomonas* Type I C CRISPR insert is shown in **FIGS. 1L-1Q** and **Table 1D**.

Table 1A: Components of phage

Phage name	Accession Number	crArray Promoter	crArray ID	Cas Promoter	CasID
p1106e003	PTA-127023	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p1106wt	PTA-127024	N/A	N/A	N/A	N/A
p1194wt	PTA-127025	N/A	N/A	N/A	N/A

p1587e002	PTA-127026	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p1587wt	PTA-127027	N/A	N/A	N/A	N/A
p1695wt	PTA-127028	N/A	N/A	N/A	N/A
p1772e005	PTA-127029	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p1772wt	PTA-127030	N/A	N/A	N/A	N/A
p1772e004	N/A	N/A	N/A	BBa_J23109	PaIC
p1772e006	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	N/A	N/A
p1772e008	N/A	ACR	crArray 2 (FIG. 1B, SEQ ID NO: 84)	BBa_J23109	PaIC
p1772e016	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p1772e017	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23106	PaIC
p1772e018	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	P16	PaIC
p1772e019	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	Gp105	PaIC
p1772e020	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	Gp245	PaIC
p1772e021	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	PAMP	PaIC
p1772e022	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	Plpp	PaIC
p1772e023	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	pTat	PaIC
p1835e002	PTA-127031	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p1835wt	PTA-127032	N/A	N/A	N/A	N/A
p2037e002	PTA-127033	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2037wt	PTA-127034	N/A	N/A	N/A	N/A

p2131e002	PTA-127035	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2131wt	PTA-127036	N/A	N/A	N/A	N/A
p2132e002	PTA-127037	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2132wt	PTA-127038	N/A	N/A	N/A	N/A
p2167wt	PTA-127039	N/A	N/A	N/A	N/A
p2363e003	PTA-127040	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2363wt	PTA-127041	N/A	N/A	N/A	N/A
p2421e002	PTA-127042	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2421wt	PTA-127043	N/A	N/A	N/A	N/A
p2973e002	PTA-127044	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p2973wt	PTA-127045	N/A	N/A	N/A	N/A
p3278wt	PTA-127046	N/A	N/A	N/A	N/A
p4430wt	PTA-127047	N/A	N/A	N/A	N/A
PB1e002	PTA-127048	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
PB1wt	PTA-127049	N/A	N/A	N/A	N/A
p4209	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
p4209e001	N/A	N/A	N/A	N/A	PaIC
p4209e002	N/A	ACR	crArray 1 (FIG. 1A, SEQ ID NO: 83)	BBa_J23109	PaIC
pArray3	N/A	ACR	crArray 3 (FIG. 1C, SEQ ID NO: 85)	BBa_J23109	PaIC
PArray4	N/A	ACR	crArray 4 (FIG. 1D, SEQ ID NO: 86)	BBa_J23109	PaIC

Table 1B: Promoter sequences

SEQ ID NO	Promoter	Source	Sequence
1	ACR	phage genome	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCA CAATGTGCCTAATCTAACGTCATGCCAGCCACAAC GGCGAGGCGCCAAGAAGGATAGAAGCC
2	BBa_J23109	BioBrick	TTTACAGCTAGCTCAGTCCTAGGGACTGTGCTAGC
3	endogenous (promoter + RBS)	P. aeruginosa genome	GATTTTTTTCGGGTGAGGTTGCGGGCTGTTCGGTA GGTTTATAAACACTGCTATCCAAAGCTATGGACAC GCTCGGCTACGAGAACAGTTGGCGTGATGGCCTCT AGCAATTAGATTGTTATGCGACATCCGCAGACTTG GCAGGGAGCGCACCT
4	BBa_J23106	BioBrick	TTTACGGCTAGCTCAGTCCTAGGTATAGTGCTAGC
5	P16 (promoter + RBS)	P. aeruginosa genome	ATCCGAGGGATACGGGCCTTGTCAGCACGGTGTTG CTAATGAGAGCCTTTGCCCGGGCAATAGTACGGGC AGTGTGTAGCGGATTGAAAGACGCTGAATCACTG ACAGGCATGAAGACTATCGATAGAGTCTGATAGTG TCGCCGCCGCACAGCGGATAGAGTCCACAGTCATT GAAGTGTTAATCCGCGATCAAGCTC
6	gp105 (promoter + RBS)	phage genome	GACCTAGCTTTTATAGCGGGTTTCGTGGTTTATAGC CCATTGAAAAAAATCTCACATCTATATCACAGGTGT GCACTCGTTCCCGAAAGGTTCTGAGTCTACTTGAT CAAGTATTGAAATACCATCGTAAAGGAAAAAGACA TGTCTATTCGTGATAGCGAAAACAACAACGGCCAA CAGCAGCAGACCGCGCAAACTGCCGCCCCCGCCC CGCAA
7	gp245 (promoter + RBS)	phage genome	TTCAATTTAAGTAGTAACGAGGTCAGCCCGGAATC TTTGGGTATTCTTAAGGTATTTCTGACTCAGTGTGG TTGGGACAGCTTCACTGTACATTGCACTGGATTTG TTAATTTCTTATACCGGGGCACCATGGGCAGCAAAT CGTGTTACGAATTCCGTCTAACCAATAAGCGAGCT AAATA
8	Pamp	plasmid	CGCGGAACCCCTATTTGTTTATTTTTCTAAATACATT CAAATATGTATCCGCTCATGAGACAATAACCCTGAT AAATGCTTCAATAATATTGAAAAAGGAAGAGT
9	Plpp (promoter + RBS)	P. aeruginosa genome	CTTCAAGAATTCGTATTGACCCCATAGACAGCTTC GTCGACGCCCGTCCCGGCCCCCTTGGGCTTGCCGG ACGGCTTATGTCATGATGGCGCCACCCTCGCAGGT TCAAGGCCGGCTTTCTTCCTCTATGAACAAATCCC TTGCGCTGACTACGTAATCAC
10	Ptat (promoter + RBS)	P. aeruginosa genome	CTTCAAGAATTCGGGGTATTCCTGATCCTGCGCCG CTAGCGCCGCGCACGGCCACTAGGCCCGCGCCGA TAGCCAGTCGCGCTCCCGGCTGGCACACTACTCCC ATTTCCGCCGGAAACGCGCGCAACGTACCGGCAA CGAACGTGGAAAGACCATGAAAGACTGGCTGGAT GAGATTCACTGGAACGCCGTGACCTACGTATGCAC
11	rrnB P1	E. coli	GAAAATTATTTTAAATTTCCTCTAGTCAGGCCGGAA TAACTCCCTATAATGCGACACCA

Table 1C: Spacer sequences for targeting *Pseudomonas spp.*

Array ID	Spacer Target	SEQ ID NO	Sequence
Spacer 1			
crArray 1	hypothetical protein / intergenic region	12	AGAAGGGTCAGGGCCATGCGGTTTTTCCTCTGTG
crArray 2	Non-targeting control	13	GCTCGACTGGTCGGTAACCACTTGTGTGTGGTGA
crArray 3	ftsA	14	GGTGCTGACCGAGGACGAGAAGGAACTGGGCGTG
crArray 4	glnS	15	GATGACACCAACCCGGCCAAGGAAGACCAGGAGT
Spacer 2			
crArray 1	phnW (pyruvate aminotransferase)	16	GAGACCGAAGAGAACGTGCCGACCACCGCCGCTG
crArray 2	Non-targeting control	17	CAGTGCATGGCAGCGAACGCCGAGAGCCGACCACC
crArray 3	dnaA	18	TCCGCGATGAGCTGCCGTCCCAACAATTCAACAC
crArray 4	dnaN	19	AACGCGAAGCCCTGTTGAAACCGCTGCAACTGGT
Spacer 3			
crArray 1	rpmF / intergenic region / hypothetical protein	20	TGCTGAACAGCCATGATTGATTAACTCCTAAACG
crArray 2	Non-targeting control	21	CGTAAACCTAATGGGCCTGATCTACAGTAATCTA
crArray 3	gyrB	22	ACCACCGAGACGCCCACACCGTGCAAGCCGCCGG
crArray 4	rpoB	23	CTATCGCGAATTCCTGCAGGCTGGCGCAACCAAG
Additional Spacer Sequences			
	GyraseB	31	CGCCAGATGCCCGAGCTGATCGAGCGTGGCTACA
	Non-coding sequence	32	GAACCAACGCATGGCAGGATCAAAACCTGCTGCC
	phosphoribosyltransferase	33	GCCGCCGGAGGTCTCGTTGCGGTAACGGGTCGCA
	tsf	34	CGGGTTGCCGCCTTTCAGGTTGACCACGACACCG
	acpP	35	CAGAGCCATCACCAGCTCGACGGTGTCAAGGGAG

	gapA	36	ACCAGCCGCGACAAAGCCGCTGCCCACCTG CAGG
	infA	37	CGTGTGGAGTTGGAAAATGGGCACGTCGTC ACCG
	secY	38	AGCGGCTGCCCCGGAGCGATCGCTTGCGCG ACGT
	csrA	39	CCTTTGACACCCAGTACCGTCACGGTGACGT CGT
	trmD	40	TTCATCGACGTGCTCTTCGATGAAGCGCTCG TCG
crArray 3	ftsA	41	GGTGCTGACCGAGGACGAGAAGGAACTGGG CGTG
	fusA	42	AACATCATCGACACCCCCGGCCACGTCGACT TCA
	glyQ	43	TGGTGGAACACGTCGCCATAGGTGACCTTGC CGA
	eno	44	CAGCCGGCCCAGTCGGACTCGTCCATGCCGT CCT
	nusG	45	GGCTTGGGCTTGTCGCCGCTATCGGCCACGC GAC
crArray 3	dnaA	46	TCCGCGATGAGCTGCCGTCCCAACAATTCAA CAC
	pheS	47	CACCTGGTGGAACATCGGCGAGTGGGTCAG GTCG
	rplB	48	AGCTCGATACCATGAACAGTGCTACCCACCG GGA
	gltX	49	TCGCGCTCGTCCGGCATCGACCAGCCCATCC GCC
	hisS	50	CACGCCCATGGCGAAACCGACACCCGGGGT CGGC
	rplC	51	CAGCGCTTGATGGTGCCCGCGAAGCCCTTAC CCT
	aspS	52	GCCGCTACCTGGACGACAACGGCTTCCTCGA CGT
	gyrB	53	CGCCAGATGCCCGAGCTGATCGAGCGTGGCT ACA
crArray 3	gyrB	54	ACCACCGAGACGCCCACACCGTGCAAGCCG CCGG
crArray 4	glnS	55	GATGACACCAACCCGGCCAAGGAAGACCAG GAGT
	dnaE	56	CTGGTACAGGATGATGCCGTAGGTGGGCTTG AGC

	rpoA	57	GGGATCCAGAGTGCCGTTGGTTTCCAGGTCC AGG
	pheT	58	CCCGTCGGCTACCACCGTTAGTTCCAGGGCT TGC
	infB	59	CTTGATCGGCTTGCCGTTCTCGTCGAGCATG GCG
	rpsC	60	GTAGGTGGCATAGTCGATATCGGCGCGCAG GGTG
	rplF	61	GTAATCAACCGGATGGGAGAAGCCGAGGGA CAGG
	alaS	62	TGGGCGATGGGCGATACCGGACCCTGCGGT CCCT
	leuS	63	GACGCCATCGGCGCCGACCTCGAGGCCAAG GGCC
	serS	64	CAGCGCTTCGTAGGAGGTGGCCGGATCGAC GATC
	rplD	65	AGACCCAGGGTGTCCAGCTTGGCAACCAGG CCCT
	gyrA	66	CTGGTATTCGGAGAGCAGCTTCTCGTGCTCC AGG
	glmS	67	CGGGCCGGCCTGGGTCAGCAGGGTCAGGTC GGAT
	adk	68	GGCGGGTTGTGCTCGGTGTGGTACACGCGGC CGG
	rpsK	69	AGAGCGCGAACGGCGGACTCGCGGCCCGGG CCCG
	rplR	70	TTGGCTGCATCGATGTTGCCGGTGGCACCTT CGC
	parC	71	GAAGCTGGCCCCCGGCGGCGGCGTCAGCCG GCCG
	tRNA-Ser	72	GAACCCCCGACACCCTTTTGAGGTGTACTCC CTT
	tRNA-Asn	73	CGCGATAGCTCAGTCGGTAGAGCAAATGAC TGTT
	metK	74	CGGGTTGTGCTGGGTGGACAGCACCACCGC ATCG
	Pseudomonas	88	AGAAGGGTCAXGGXCATGCGGTTTTTCCTCT XTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	89	AGAAGGXTCAGGGXCATGCGGTTTTTCCTCT XTG, where each X is independently selected from A, T, C, or G

	Pseudomonas	90	AGAAGGXTCAXGGCCATGCGGTTTTTCCTCT XTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	91	AGAAGGXTCAXGGXCATGCGGTTTTTCCTCT GTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	92	AGAAGGXTCAXGGXCATGCGGTTTTTCCTCT XTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	93	AGAAGGGTCAGGGXCATGCGGTTTTTCCTCT GTG, where X is A, T, C, or G
	Pseudomonas	94	AGAAGGGTCAGGGTCATGCGGTTTTTCCTCT GTG
	Pseudomonas	95	AGAAGGGTCAGGGCCATGCGGTTTTTCCTCT XTG, where X is A, T, C, or G
	Pseudomonas	96	AGAAGGGTCAGGGCCATGCGGTTTTTCCTCT ATG
	Pseudomonas	97	AGAAGGXTCAGGGCCATGCGGTTTTTCCTCT GTG, where X is A, T, C, or G
	Pseudomonas	98	AGAAGGATCAGGGCCATGCGGTTTTTCCTCT GTG
	Pseudomonas	99	AGAAGGXTCAXGGCCATGCGGTTTTTCCTCT GTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	100	AGAAGGATCAAGGCCATGCGGTTTTTCCTCT GTG
	Pseudomonas	101	AGAAGGGTCAGGGCCATGCGGTTTTTCCTCT XTG, where X is A, T, C, or G
	Pseudomonas	102	AGAAGGGTCAGGGCCATGCGGTTTTTCCTCT ATG
	Pseudomonas	103	GAGACCGAAGAGXAXGTGCCGACCACXGCC GCTG, where each X is independently selected from A, T, C, or G
	Pseudomonas	104	GAGACCGAAGAGAAXGTGCCGACCACCGCC GCTG, where X is A, T, C, or G
	Pseudomonas	105	GAGACCGAAGAGAATGTGCCGACCACCGCC GCTG
	Pseudomonas	106	GAGACCGAAGAGAACGTGCCGACCACXGCC GCTG, where X is A, T, C, or G
	Pseudomonas	107	GAGACCGAAGAGAACGTGCCGACCACTGCC GCTG
	Pseudomonas	108	GAGACCGAAGAGXACGTGCCGACCACCGCC GC, where X is A, T, C, or G

	Pseudomonas	109	GAGACCGAAGAGGACGTGCCGACCACCGCC GC
	Pseudomonas	110	TGCTGAACAGCCATXAXXXATTAACTCCTAA ACG, where each X is independently selected from A, T, C, or G
	Pseudomonas	111	TGCTGAACAGCCATXATTGATTAACTCCTAA ACG, where X is A, T, C, or G
	Pseudomonas	112	TGCTGAACAGCCATAATTGATTAACTCCTAA ACG
	Pseudomonas	113	TGCTGAACAGCCATXATTXATTAACTCCTAA ACG, where each X is independently selected from A, T, C, or G
	Pseudomonas	114	TGCTGAACAGCCATAATTAATTAACTCCTAA ACG
	Pseudomonas	115	TGCTGAACAGCCATXAXTGATTAACTCCTAA ACG, where each X is independently selected from A, T, C, or G
	Pseudomonas	116	TGCTGAACAGCCATAACTGATTAACTCCTAA ACG
	Pseudomonas	117	TGCTGAACAGCCATXATXXATTAACTCCTAA ACG, where each X is independently selected from A, T, C, or G
	Pseudomonas	118	TGCTGAACAGCCATAATCAATTAACTCCTAA ACG
	Pseudomonas	119	TGCTGAACAGCCATXAXTXATTAACTCCTAA ACG, where each X is independently selected from A, T, C, or G
	Pseudomonas	120	TGCTGAACAGCCATAACTCATTAACTCCTAA ACG

Table 1D: PaIC Insert Sequence

Array	**SEQ ID NO**	**Sequence**
crArray 1 (FIG. 1A)	83	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACAGAAGGGTCAGGGCCATGCGGTTTTTCCTCTGTGGTCG CGCCCCGCACGGGCGCGTGGATTGAAACGAGACCGAAGAGAACGTGCCGACCACC GCCGCTGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACTGCTGAACAGCCATGAT TGATTAACTCCTAAACGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGCAA GCTTGGCGTAGCTTCGTCCCTATCAAAGCTTGGAG

crArray 2 (FIG. 1B)	84	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACGCTCGACTGGTCGGTAACCACTTGTGTGTGGTGAGTCG CGCCCCGCACGGGCGCGTGGATTGAAACCAGTGCATGGCAGCGAACGCCGAGAGC CGACACCGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCGTAAACCTAATGGGC CTGATCTACAGTAATCTAGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGCA AGCTTGGCGTAGGCCGCTTCGTCCCTATCAAAGCTTGGAG
crArray 3 (FIG. 1C)	85	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACGGTGCTGACCGAGGACGAGAAGGAACTGGGCGTGGTC GCGCCCCGCACGGGCGCGTGGATTGAAACTCCGCGATGAGCTGCCGTCCCAACAAT TCAACACGTCGCGCCCCGCACGGGCGCGTGGATTGAAACACCACCGAGACGCCCA CACCGTGCAAGCCGCCGGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGC AAGCTTGGCGTAGCTTCGTCCCTATCAAAGCTTGGAG
crArray 4 (FIG. 1D)	86	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACGATGACACCAACCCGGCCAAGGAAGACCAGGAGTGTC GCGCCCCGCACGGGCGCGTGGATTGAAACAACGCGAAGCCCTGTTGAAACCGCTG CAACTGGTGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCTATCGCGAATTCCTG CAGGCTGGCGCAACCAAGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGC AAGCTTGGCGTAGCTTCGTCCCTATCAAAGCTTGGAG
crArray 5 (FIG. 1E)	87	GAAAATTATTTTAAATTTCCTCTAGTCAGGCCGGAATAACTCCCTATAATGCGACA CCAGTCGCGCCCCGCACGGGCGCGTGGATTGAAACATTTATCACAAAAGGATTGTT CGATGTCCAACAAGTCGCGCCCCGCACGGGCGCGTGGATTGAAACGCACTCCCGTT CTGGATAAT

crArray 3-PAIC	24	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACGGTGCTGACCGAGGACGAGAAGGAACTGGGCGTGGTC GCGCCCCGCACGGGCGCGTGGATTGAAACTCCGCGATGAGCTGCCGTCCCAACAAT TCAACACGTCGCGCCCCGCACGGGCGCGTGGATTGAAACACCACCGAGACGCCCA CACCGTGCAAGCCGCCGGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGC AAGCTTGGCGTAGGCCGCTTCGTCCCTATCAAAGCTTGGAGTTTACAGCTAGCTCA GTCCTAGGGACTGTGCTAGCATTAAAGAGGAGAAAATGGACGCGGAGGCTAGCGA TACTCACTTTTTTGCTCACTCCACCTTAAAGGCAGATCGCAGCGATTGGCAGCCTCT GGTCGAGCATCTACAGGCTGTTGCCCGTTTGGCAGGAGAGAAGGCTGCCTTCTTCG GCGGCGGTGAATTAGCTGCTCTTGCTGGTCTGTTGCATGACTTGGGTAAATACACT GACGAGTTTCAGCGGCGTATTGCGGGTGATGCCATCCGTGTCGATCACTCTACTCG CGGGGCCATACTGGCGGTAGAACGCTATGGCGCGCTAGGTCAATTGCTAGCCTACG GCATCGCTGGCCACCATGCCGGGTTGGCCAATGGCCGCGAGGCTGGTGAGCGAACT GCCTTGGTCGACCGCCTGAAAGGGGTTGGGCTGCCACGGTTATTGGAGGGGTGGTG CGTGGAAATCGTGCTACCCGAGCGCCTTCAACCACCGCCACTAAAAGCGCGCCTGG AAAGAGGTTTCTTTCAGTTGGCCTTTCTTGGCCGGATGCTCTTTTCCTGCTTGGTTG ATGCGGATTATCTAGATACCGAAGCCTTCTACCACCGCGTCGAAGGACGGCGCTCC CTTCGCGAGCAAGCGCGGCCGACCTTGGCCGAGTTACGCGCAGCCCTTGATCGGCA TCTGACTGAGTTCAAGGGAGATACGCCGGTCAACCGCGTTCGCGGGGAGATATTGG CCGGCGTGCGCGGCAAGGCGAGCGAACTTCCCGGGCTGTTTTCTCTCACAGTGCCC ACAGGAGGCGGCAAGACCCTGGCCTCTCTGGCTTTCGCCCTGGATCACGCTCTAGC TCATGGGCTGCGCCGGGTGATCTACGTGATTCCCTTCACTAGCATCGTCGAGCAGA ACGCTGCGGTATTCCGTCGTGCACTCGGGGCCTTAGGCGAAGAGGCGGTGCTGGAG CATCACAGCGCCTTCGTTGATGACCGCCGGCAGAGCCTGGAGGCCAAGAAGAAAC TGAACCTAGCGATGGAGAACTGGGACGCGCCTATCGTGGTGACCACTGCAGTGCA GTTCTTCGAAAGCCTGTTTGCCGACCGTCCAGCCCAGTGCCGCAAGCTACACAACA TCGCCGGCAGCGTGGTGATTCTTGACGAGGCACAGACCCTACCGCTCAAGCTGTTG CGGCCCTGCGTTGCCGCCCTTGATGAACTGGCGCTCAACTACCGTTGTAGCCCAGTT CTCTGTACTGCCACGCAGCCAGCGCTTCAATCGCCGGATTTCATCGGTGGGCTGCA GGACGTACGTGAGCTGGCGCCCGAGCCGCAGCGGCTGTTCCGGGAGTTGGTGCGG GTACGAATACGGACATTGGGCCCGCTCGAAGATGCGGCCTTGACTGAGCAGATCGC CAGGCGTGAACAAGTGCTGTGCATCGTCAACAATCGACGCCAGGCCCGTGCGCTCT ATGAGTCGCTTGCCGAGTTGCCCGGTGCCCGCCATCTCACCACCCTGATGTGCGCC AAGCACCGTAGCAGCGTGCTGGCCGAGGTGCGCCAGATGCTCAAAAAGGGGGAGC CCTGTCGCCTGGTGGCCACCTCGCTGATCGAGGCCGGTGTGGATGTGGATTTTCCC GTGGTACTGCGTGCCGAGGCTGGATTGGATTCCATCGCCCAGGCCGCGGGACGCTG CAATCGCGAAGGCAAGCGGCCGCTGGCCGAAAGCGAGGTGCTGGTGTTCGCCGCG GCCAATTCTGACTGGGCGCCACCCGAGGAACTCAAGCAGTTCGCCCAGGCCGCCCG CGAAGTGATGCGCCTGCACCCGGATGATTGCCTGTCCATGGCGGCCATCGAGCGGT ATTTTCGCATACTGTACTGGCAGAAGGGCGCGGAGGAGTTGGATGCGGGTAACCTG CTCGGCCTGATTGAGAGAGGCCGGCTCGATGGCCTGCCCTACGAGACTTTGGCCAC CAAGTTCCGCATGATCGACAGCCTTCAACTGCCGGTGATCATCCCATTTGATGACG AGGCCAGAGCAGCCCTGCGCGAGCTGGAGTTCGCCGACGGCTGCGCCGCCATCGC CCGTCGCCTGCAGCCATATCTGGTGCAGATGCCACGCAAGGGTTATCAGGCATTGC GGGAAGCCGGTGCGATCCAGGCGGCGGCAGGTACGCGTTATGGTGAGCAGTTTAT GGCGTTGGTCAACCCTGATCTGTATCACCACCAATTCGGGTTGCACTGGGATAATC CGGCCTTTGTCAGCAGCGAGCGGCTATGTTGGTAGTCGGGACGCGCAACAGCGGCC TGGCCTGGATGATGTGAAAGGGAGGGCCGATGGCCTACGGAATTCGCTTAATGGTC TGGGGCGAGCGTGCCTGCTTCACCCGCCCGGAAATGAAGGTGGAACGCGTCTCTTA CGATGCGATCACGCCGTCCGCCGCGCGCGGCATTCTCGAGGCTATCCACTGGAAGC CGGCGATTCGCTGGGTGGTGGATCGCATTCAAGTGCTTAAGCCGATCCGCTTCGAA TCCATCCGGCGCAACGAGGTCGGCGGCAAGCTGTCCGCTGTCAGCGTCGGTAAGGC AATGAAGGCCGGGCGTACTAATGGTCTGGTGAATCTGGTCGAGGAGGATCGCCAG CAGCGCGCGACTACTCTGCTGCGCGATGTCTCCTATGTCATCGAGGCGCATTTCGA GATGACTGACAGGGCTGGCGCCGACGATACGGTGGGCAAGCATCTGGATATCTTCA ACCGTCGCGCACGGAAGGGGCAGTGCTTCCATACACCCTGCCTAGGCGTGCGCGAG TTTCCGGCCAGTTTTCGGTTGCTGGAAGAGGGCAGTGCCGAGCCTGAAGTCGATGC CTTTCTGCGCGGCGAGCGTGATCTGGGCTGGATGCTGCATGACATTGACTTCGCCG ATGGCATGACCCCGCACTTCTTCCGTGCCCTGATGCGCGATGGGCTGATCGAGGTG CCGGCCTTCAGGGCGGCAGAGGACAAGGCATGATCCTTTCGGCCCTCAATGACTAT TATCAGCGACTGCTGGAGCGGGGTGAAGCGAATATCTCACCCTTCGGCTACAGCCA

		AGAAAAGATCAGTTACGCCCTGCTGCTGTCCGCACAAGGAGAGTTGCTGGACGTGC AGGACATTCGCTTGCTCTCTGGCAAGAAGCCTCAACCCAGGCTTATGAGTGTGCCG CAGCCGGAGAAGCGCACCTCGGGCATCAAGTCCAACGTACTGTGGGACAAGACCA GCTATGTGCTGGGTGTTAGTGCCAAGGGCGGAGAGCGTACTCAGCAGGAGCACGA GTCCTTCAAGACGCTGCACCGGCAGATCTTGGTTGGGGAAGGCGACCCCGGTCTGC AGGCCTTGCTCCAGTTCCTCGACTGTTGGCAGCCGGAGCAGTTCAAGCCCCCGCTG TTCAGCGAAGCAATGCTCGACAGCAACTTAGTGTTCCGCCTAGACGGCCAACAACG CTATCTGCACGAGACTCCGGCGGCCCTGGCGTTGCGTACCCGGCTGTTGGCCGACG GCGACAGCCGCGAGGGGCTGTGCCTAGTCTGCGGCCAACGTCAGCCGTTGGCGCGC CTGCATCCAGCGGTCAAGGGCGTCAATGGTGCCCAGAGTTCGGGGGCTTCCATCGT CTCCTTCAACCTCGACGCTTTTTCCTCCTACGGCAAGAGCCAGGGGGAAAATGCTC CGGTCTCCGAACAGGCCGCCTTTGCCTACACCACGGTGCTCAACCATTTGTTGCGTC GCGACGAGCACAACCGCCAGCGCCTGCAGATTGGCGACGCGAGTGTGGTGTTCTG GGCGCAGGCGGATACTCCTGCTCAGGTGGCCGCCGCCGAGTCGACCTTCTGGAACC TGCTGGAGCCACCCGCAGATGATGGTCAGGAAGCGGAAAAGCTGCGCGGCGTGCT GGATGCTGTGGCCACGGGGCGGCCCTTGCATGAGCTCGACTCGCTAATGGAGGAA GGTACCCGCATTTTTGTGTTAGGGCTGGCGCCCAATACCTCGCGACTGTCCATTCGG TTCTGGGCAGTCGATAGCCTTGCGGTATTCACCCAGCATCTGGCCGAGCATTTCCG GGATATGCACCTTGAGCCTCTGCCCTGGAAGACGGAGCCGGCCATCTGGCGCTTGC TCTATGCTACCGCGCCCAGTCGTGACGGCAGAGCCAAGACCGAAGACGTACTCCCA CAACTGGCCGGTGAAATGACCCGCGCCATCCTGACCGGCAGCCGCTATCCGCGCAG TTTGCTAGCCAACCTGATCATGCGCATGCGTGCCGACGGCGACGTCTCTGGCATAC GCGTCGCGCTGTGCAAGGCCGTGCTCGCTCGCGAGGCACGCCTGAGCGGCAAAATT CACCAAGAGGAGCTACCTATGAGTCTCGACAAGGACGCCAGCAACCCCGGCTATC GCTTGGGGAGGCTGTTCGCCGTGTTGGAAGGCGCCCAGCGCGCAGCCCTGGGCGAC AGGGTCAATGCCACTATCCGTGACCGCTACTACGGTGCCGCGTCCAGCACGCCAGC CACGGTTTTCCCGATACTGCTGCGCAACACACAAAACCACTTGGCCAAGCTGCGCA AGGAGAAGCCCGGACTAGCAGTGAACCTAGAGCGCGATATAGGCGAAATCATTGA CGGTATGCAGAGCCAATTCCCGCGTTGCCTGCGCCTGGAGGACCAGGGACGCTTTG CTATTGGTTACTACCAACAGGCCCAGGCCCGTTTCAACCGTGGCCCCGATTCCGTC GAGTAAGGAGCAGAAGAATGACCGCCATCTCCAACCGCTACGAGTTCGTTTACCTC TTTGATGTCAGCAATGGCAATCCCAATGGCGACCCGGATGCTGGCAACATGCCGCG TCTCGATCCGGAAACCAACCAGGGGTTGGTCACTGACGTTTGCCTCAAGCGCAAGA TCCGCAACTACGTCAGCCTGGAGCAGGAAAGTGCCCCCGGCTATGCCATCTATATG CAGGAAAAATCCGTGCTGAATAACCAGCACAAACAGGCCTACGAGGCGCTCGGTA TCGAGTCAGAGGCAAAGAAACTGCCCAAGGACGAAGCCAAGGCGCGCGAACTGAC CTCTTGGATGTGCAAGAACTTCTTCGATGTGCGTGCTTTCGGGGCGGTGATGACCA CCGAGATTAATGCCGGCCAGGTGCGTGGACCGATCCAACTGGCATTCGCCACGTCT ATCGACCCGGTATTGCCTATGGAGGTATCCATCACCCGCATGGCGGTGACTAACGA AAAGGATTTGGAGAAGGAACGCACCATGGGACGCAAGCACATCGTGCCTTACGGC TTGTACCGCGCCCATGGTTTCATCTCTGCCAAGTTGGCCGAGCGAACCGGCTTTTCC GACGACGACTTGGAACTGCTATGGCGCGCTTTGGCCAATATGTTCGAACACGACCG CTCGGCGGCACGTGGCGAGATGGCAGCGCGCAAGTTGATCGTCTTCAAGCATGAGC ATGCCATGGGCAATGCACCCGCCCATGTGCTGTTCGGCAGCGTTAAGGTCGAGCGA GTCGAGGGGGACGCAGTTACACCAGCACGCGGTTTCCAGGATTACCGTGTCAGCAT CGATGCGGAAGCTCTGCCTCAGGGCGTGAGCGTGCGCGAGTACCTCTAG

crArray 1	25	ACAAGCGGCACATTGTGCCTATTGCGAATTAGGCACAATGTGCCTAATCTAACGTC ATGCCAGCCACAACGGCGAGGCGCCAAGAAGGATAGAAGCCGTCGCGCCCCGCAC GGGCGCGTGGATTGAAACAGAAGGGTCAGGGCCATGCGGTTTTTCCTCTGTGGTCG CGCCCCGCACGGGCGCGTGGATTGAAACGAGACCGAAGAGAACGTGCCGACCACC GCCGCTGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACTGCTGAACAGCCATGAT TGATTAACTCCTAAACGGTCGCGCCCCGCACGGGCGCGTGGATTGAAACCATGCAA GCTTGGCGTAGGCCGCTTCGTCCCTATCAAAGCTTGGAGTTTACAGCTAGCTCAGTC CTAGGGACTGTGCTAGCATTAAAGAGGAGAAAATGGACGCGGAGGCTAGCGATAC TCACTTTTTTGCTCACTCCACCTTAAAGGCAGATCGCAGCGATTGGCAGCCTCTGGT CGAGCATCTACAGGCTGTTGCCCGTTTGGCAGGAGAGAAGGCTGCCTTCTTCGGCG GCGGTGAATTAGCTGCTCTTGCTGGTCTGTTGCATGACTTGGGTAAATACACTGAC GAGTTTCAGCGGCGTATTGCGGGTGATGCCATCCGTGTCGATCACTCTACTCGCGG GGCCATACTGGCGGTAGAACGCTATGGCGCGCTAGGTCAATTGCTAGCCTACGGCA TCGCTGGCCACCATGCCGGGTTGGCCAATGGCCGCGAGGCTGGTGAGCGAACTGCC TTGGTCGACCGCCTGAAAGGGGTTGGGCTGCCACGGTTATTGGAGGGGTGGTGCGT GGAAATCGTGCTACCCGAGCGCCTTCAACCACCGCCACTAAAAGCGCGCCTGGAA AGAGGTTTCTTTCAGTTGGCCTTTCTTGGCCGGATGCTCTTTTCCTGCTTGGTTGATG CGGATTATCTAGATACCGAAGCCTTCTACCACCGCGTCGAAGGACGGCGCTCCCTT CGCGAGCAAGCGCGGCCGACCTTGGCCGAGTTACGCGCAGCCCTTGATCGGCATCT GACTGAGTTCAAGGGAGATACGCCGGTCAACCGCGTTCGCGGGGAGATATTGGCC GGCGTGCGCGGCAAGGCGAGCGAACTTCCCGGGCTGTTTTCTCTCACAGTGCCCAC AGGAGGCGGCAAGACCCTGGCCTCTCTGGCTTTCGCCCTGGATCACGCTCTAGCTC ATGGGCTGCGCCGGGTGATCTACGTGATTCCCTTCACTAGCATCGTCGAGCAGAAC GCTGCGGTATTCCGTCGTGCACTCGGGGCCTTAGGCGAAGAGGCGGTGCTGGAGCA TCACAGCGCCTTCGTTGATGACCGCCGGCAGAGCCTGGAGGCCAAGAAGAAACTG AACCTAGCGATGGAGAACTGGGACGCGCCTATCGTGGTGACCACTGCAGTGCAGTT CTTCGAAAGCCTGTTTGCCGACCGTCCAGCCCAGTGCCGCAAGCTACACAACATCG CCGGCAGCGTGGTGATTCTTGACGAGGCACAGACCCTACCGCTCAAGCTGTTGCGG CCCTGCGTTGCCGCCCTTGATGAACTGGCGCTCAACTACCGTTGTAGCCCAGTTCTC TGTACTGCCACGCAGCCAGCGCTTCAATCGCCGGATTTCATCGGTGGGCTGCAGGA CGTACGTGAGCTGGCGCCCGAGCCGCAGCGGCTGTTCCGGGAGTTGGTGCGGGTAC GAATACGGACATTGGGCCCGCTCGAAGATGCGGCCTTGACTGAGCAGATCGCCAG GCGTGAACAAGTGCTGTGCATCGTCAACAATCGACGCCAGGCCCGTGCGCTCTATG AGTCGCTTGCCGAGTTGCCCGGTGCCCGCCATCTCACCACCCTGATGTGCGCCAAG CACCGTAGCAGCGTGCTGGCCGAGGTGCGCCAGATGCTCAAAAAGGGGGAGCCCT GTCGCCTGGTGGCCACCTCGCTGATCGAGGCCGGTGTGGATGTGGATTTTCCCGTG GTACTGCGTGCCGAGGCTGGATTGGATTCCATCGCCCAGGCCGCGGGACGCTGCAA TCGCGAAGGCAAGCGGCCGCTGGCCGAAAGCGAGGTGCTGGTGTTCGCCGCGGCC AATTCTGACTGGGCGCCACCCGAGGAACTCAAGCAGTTCGCCCAGGCCGCCCGCGA AGTGATGCGCCTGCACCCGGATGATTGCCTGTCCATGGCGGCCATCGAGCGGTATT TTCGCATACTGTACTGGCAGAAGGGCGCGGAGGAGTTGGATGCGGGTAACCTGCTC GGCCTGATTGAGAGAGGCCGGCTCGATGGCCTGCCCTACGAGACTTTGGCCACCAA GTTCCGCATGATCGACAGCCTTCAACTGCCGGTGATCATCCCATTTGATGACGAGG CCAGAGCAGCCCTGCGCGAGCTGGAGTTCGCCGACGGCTGCGCCGCCATCGCCCGT CGCCTGCAGCCATATCTGGTGCAGATGCCACGCAAGGGTTATCAGGCATTGCGGGA AGCCGGTGCGATCCAGGCGGCGGCAGGTACGCGTTATGGTGAGCAGTTTATGGCGT TGGTCAACCCTGATCTGTATCACCACCAATTCGGGTTGCACTGGGATAATCCGGCC TTTGTCAGCAGCGAGCGGCTATGTTGGTAGTCGGGACGCGCAACAGCGGCCTGGCC TGGATGATGTGAAAGGGAGGGCCGATGGCCTACGGAATTCGCTTAATGGTCTGGG GCGAGCGTGCCTGCTTCACCCGCCCGGAAATGAAGGTGGAACGCGTCTCTTACGAT GCGATCACGCCGTCCGCCGCGCGCGGCATTCTCGAGGCTATCCACTGGAAGCCGGC GATTCGCTGGGTGGTGGATCGCATTCAAGTGCTTAAGCCGATCCGCTTCGAATCCA TCCGGCGCAACGAGGTCGGCGGCAAGCTGTCCGCTGTCAGCGTCGGTAAGGCAAT GAAGGCCGGGCGTACTAATGGTCTGGTGAATCTGGTCGAGGAGGATCGCCAGCAG CGCGCGACTACTCTGCTGCGCGATGTCTCCTATGTCATCGAGGCGCATTTCGAGAT GACTGACAGGGCTGGCGCCGACGATACGGTGGGCAAGCATCTGGATATCTTCAACC GTCGCGCACGGAAGGGGCAGTGCTTCCATACACCCTGCCTAGGCGTGCGCGAGTTT CCGGCCAGTTTTCGGTTGCTGGAAGAGGGCAGTGCCGAGCCTGAAGTCGATGCCTT TCTGCGCGGCGAGCGTGATCTGGGCTGGATGCTGCATGACATTGACTTCGCCGATG GCATGACCCCGCACTTCTTCCGTGCCCTGATGCGCGATGGGCTGATCGAGGTGCCG GCCTTCAGGGCGGCAGAGGACAAGGCATGATCCTTTCGGCCCTCAATGACTATTAT CAGCGACTGCTGGAGCGGGGTGAAGCGAATATCTCACCCTTCGGCTACAGCCAAG

		AAAAGATCAGTTACGCCCTGCTGCTGTCCGCACAAGGAGAGTTGCTGGACGTGCAG GACATTCGCTTGCTCTCTGGCAAGAAGCCTCAACCCAGGCTTATGAGTGTGCCGCA GCCGGAGAAGCGCACCTCGGGCATCAAGTCCAACGTACTGTGGGACAAGACCAGC TATGTGCTGGGTGTTAGTGCCAAGGGCGGAGAGCGTACTCAGCAGGAGCACGAGT CCTTCAAGACGCTGCACCGGCAGATCTTGGTTGGGGAAGGCGACCCCGGTCTGCAG GCCTTGCTCCAGTTCCTCGACTGTTGGCAGCCGGAGCAGTTCAAGCCCCCGCTGTTC AGCGAAGCAATGCTCGACAGCAACTTAGTGTTCCGCCTAGACGGCCAACAACGCTA TCTGCACGAGACTCCGGCGGCCCTGGCGTTGCGTACCCGGCTGTTGGCCGACGGCG ACAGCCGCGAGGGGCTGTGCCTAGTCTGCGGCCAACGTCAGCCGTTGGCGCGCCTG CATCCAGCGGTCAAGGGCGTCAATGGTGCCCAGAGTTCGGGGGCTTCCATCGTCTC CTTCAACCTCGACGCTTTTTCCTCCTACGGCAAGAGCCAGGGGGAAAATGCTCCGG TCTCCGAACAGGCCGCCTTTGCCTACACCACGGTGCTCAACCATTTGTTGCGTCGCG ACGAGCACAACCGCCAGCGCCTGCAGATTGGCGACGCGAGTGTGGTGTTCTGGGC GCAGGCGGATACTCCTGCTCAGGTGGCCGCCGCCGAGTCGACCTTCTGGAACCTGC TGGAGCCACCCGCAGATGATGGTCAGGAAGCGGAAAAGCTGCGCGGCGTGCTGGA TGCTGTGGCCACGGGGCGGCCCTTGCATGAGCTCGACTCGCTAATGGAGGAAGGTA CCCGCATTTTTGTGTTAGGGCTGGCGCCCAATACCTCGCGACTGTCCATTCGGTTCT GGGCAGTCGATAGCCTTGCGGTATTCACCCAGCATCTGGCCGAGCATTTCCGGGAT ATGCACCTTGAGCCTCTGCCCTGGAAGACGGAGCCGGCCATCTGGCGCTTGCTCTA TGCTACCGCGCCCAGTCGTGACGGCAGAGCCAAGACCGAAGACGTACTCCCACAA CTGGCCGGTGAAATGACCCGCGCCATCCTGACCGGCAGCCGCTATCCGCGCAGTTT GCTAGCCAACCTGATCATGCGCATGCGTGCCGACGGCGACGTCTCTGGCATACGCG TCGCGCTGTGCAAGGCCGTGCTCGCTCGCGAGGCACGCCTGAGCGGCAAAATTCAC CAAGAGGAGCTACCTATGAGTCTCGACAAGGACGCCAGCAACCCCGGCTATCGCTT GGGGAGGCTGTTCGCCGTGTTGGAAGGCGCCCAGCGCGCAGCCCTGGGCGACAGG GTCAATGCCACTATCCGTGACCGCTACTACGGTGCCGCGTCCAGCACGCCAGCCAC GGTTTTCCCGATACTGCTGCGCAACACACAAAACCACTTGGCCAAGCTGCGCAAGG AGAAGCCCGGACTAGCAGTGAACCTAGAGCGCGATATAGGCGAAATCATTGACGG TATGCAGAGCCAATTCCCGCGTTGCCTGCGCCTGGAGGACCAGGGACGCTTTGCTA TTGGTTACTACCAACAGGCCCAGGCCCGTTTCAACCGTGGCCCCGATTCCGTCGAG TAAGGAGCAGAAGAATGACCGCCATCTCCAACCGCTACGAGTTCGTTTACCTCTTT GATGTCAGCAATGGCAATCCCAATGGCGACCCGGATGCTGGCAACATGCCGCGTCT CGATCCGGAAACCAACCAGGGGTTGGTCACTGACGTTTGCCTCAAGCGCAAGATCC GCAACTACGTCAGCCTGGAGCAGGAAAGTGCCCCCGGCTATGCCATCTATATGCAG GAAAAATCCGTGCTGAATAACCAGCACAAACAGGCCTACGAGGCGCTCGGTATCG AGTCAGAGGCAAAGAAACTGCCCAAGGACGAAGCCAAGGCGCGCGAACTGACCTC TTGGATGTGCAAGAACTTCTTCGATGTGCGTGCTTTCGGGGCGGTGATGACCACCG AGATTAATGCCGGCCAGGTGCGTGGACCGATCCAACTGGCATTCGCCACGTCTATC GACCCGGTATTGCCTATGGAGGTATCCATCACCCGCATGGCGGTGACTAACGAAAA GGATTTGGAGAAGGAACGCACCATGGGACGCAAGCACATCGTGCCTTACGGCTTGT ACCGCGCCCATGGTTTCATCTCTGCCAAGTTGGCCGAGCGAACCGGCTTTTCCGAC GACGACTTGGAACTGCTATGGCGCGCTTTGGCCAATATGTTCGAACACGACCGCTC GGCGGCACGTGGCGAGATGGCAGCGCGCAAGTTGATCGTCTTCAAGCATGAGCAT GCCATGGGCAATGCACCCGCCCATGTGCTGTTCGGCAGCGTTAAGGTCGAGCGAGT CGAGGGGGACGCAGTTACACCAGCACGCGGTTTCCAGGATTACCGTGTCAGCATCG ATGCGGAAGCTCTGCCTCAGGGCGTGAGCGTGCGCGAGTACCTCTAG

Example 2: Exogenous Cas operon and crRNA spacers killed bacteria.

[00316] *P. aeruginosa* strains with a functional Type I-C Cas operon were transformed with Cas-only or crRNA-containing plasmids. In the presence of an endogenous Type I-C Cas system, the expression of a crRNA causes the bacteria to self-target and degrade its own DNA. The number of transformants was determined by counting the number of colonies that grow on an agar plate with antibiotic selection specific to the plasmid. The only bacteria that can form colonies are those that both acquire the plasmid and survive self-targeting. These data show that exogenous Cas

expression improved self-targeting over the endogenous system and functions when the endogenous system is not present, as seen in **Fig. 2A.** The top two panels showed the results of transforming a Cas-only plasmid, plasmids containing single targeting spacers, or a plasmid containing a 3-spacer targeting array into strains containing an endogenous Type I-C Cas system. In this experimental set-up, the individual spacers or the array acted with the endogenous Cas system and were sufficient to kill most transformants. The bottom panel shows that the addition of an exogenous Type I-C Cas operon to the crRNA plasmid further enhanced kill upon transformation, with the level of bacteria present being below the level of detection.

[00317] The plasmids were transformed into a *P. aeruginosa* strain that did not contain a functional Type I-C Cas operon. The transformed plasmids expressed either a spacer array alone or the spacer array and the Type I-C Cas operon. **Fig. 2B** shows the number of bacterial transformants obtained per mL of transformation into a Cas operon null mutant of *P. aeruginosa* strain b1121. Array 1 targets the bacteria while array 2 is a non-targeting control. The different plasmids were normalized by molarity to the empty vector control plasmid. When cells were transformed with both Cas and targeting array 1, there was a decrease in the number of transformants detected. Cells transfected with only targeting array 1, or with Cas and the non-targeting array 2 did not show a decrease in number of transformants when compared to the number of transformants received with an empty vector.

[00318] Plasmids containing individual spacers or unique arrays were transformed into *P. aeruginosa* strain b1121, which has an endogenous Type I-C Cas system, or a Cas operon null mutant of the same strain. Cell death was observed in b1121 transfected cells, but not in the Cas operon null mutant. These data, as depicted in **Fig. 2C** indicated that individual spacers targeting rpoB and ftsA, as well as Array 3 and Array 4, were able to work with the endogenous Type I-C Cas system to kill the cells.

Example 3: Stability of phage engineered with CRISPR-Cas full construct

[00319] **Fig. 3A** depicts a schematic representation of the genome of wild type phage p1772 and its engineered variants. The bar below the genome axis indicates the region of the genome that was removed and replaced. The schematics below the phage genome illustrate the DNA that was used to replace WT phage genes in the deleted region. CRISPR arrays crArray 1, crArray 3, and crArray 4 target the bacteria and are expected to kill bacteria in the presence of an active Type I-C Cas system. crArray 2 is made from non-targeting spacers, but is structurally the same as the three targeting arrays, and serves as a control to demonstrate Type I Cas specific self-targeting activity.

[00320] Phage carrying the CRISPR-Cas3 construct were serially passaged to assess the stability of the repeats contained in the phage genome. p1772e005 was serially amplified on *P.*

aeruginosa strain b1126 (a Type I-F strain). Amplifications one through eight were performed as one step amplifications where 50 uL of a bacterial overnight culture was added to 5 mL of LB in a 15 mL falcon tube followed by the immediate addition of 1 µL of the previous lysate. The mixtures were grown for 10-16 hours at 37 °C in a shaking incubator. Following incubation, phage-bacterial mixtures were centrifuged for 10 min at 5,000 rcf and the supernatants were filtered through 0.45 µm syringe filters and stored at 4 °C. For amplification nine, serial ten-fold dilutions of amplification eight were spotted onto soft agar overlays of strain b1121 or b1126. A single plaque from each plate was picked with a pipette into 200 µL of PBS to obtain amplification nine. Ten microliters of amplification nine, were added to 50 µL of b1121 or b1126 overnight and 5 mL of LB, then grown for ~16 hours followed by centrifugation and filtration. For sanger sequencing, phage DNA was amplified by PCR from lysates using primers flanking the engineering site. Sanger and NGS sequencing confirmed stability and integrity of the CRISPR-Cas3 construct when loaded onto the phage genome (shown in **Fig. 3B**).

Example 4. Bacteriophage morphology with CRISPR constructs

[00321] 1.5 mL of crude lysate was centrifuged for 1 hr at 4°C and 24,000 × g. A fraction of the supernatant (approximately 1.4 mL) was gently discarded, and 1 mL of ammonium acetate (0.1 M, pH 7.5) was added to the remaining lysate, which was then centrifuged. This step was performed twice. Washed phage samples were visualized by negative-stain transmission electron microscopy. A glow-discharged formvar/carbon-coated 400 mesh copper grid (Ted Pella, Inc., Redding, CA) was floated on a 25-µL droplet of the sample suspension for five min, transferred quickly to two drops of deionized water followed by a droplet of 2% aqueous uranyl acetate stain for 30 sec. The grid was blotted with filter paper and air-dried. Samples were observed using a JEOL JEM-1230 transmission electron microscope operating at 80 kV and images were taken using a Gatan Orius SC1000 CCD camera with Gatan Microscopy Suite 3.0 software. Results are exemplified in **Fig. 4.** There were no apparent observable changes in phage morphology after modification.

Example 5. Amplification of phage engineered with CRISPR-Cas full construct

[00322] p1772wt (wild type) and engineered variants p1772e004 (Cas system only) and p1772e005 (targeting crArray1 + Cas system) were mixed with an exponentially growing culture of b1126 at a multiplicity of infection (MOI) of 1. At 0 min, 15 min, 30 min, 1 h, 2 h, 4 h, 7 h 10 min, and 24h after infection, samples were collected for plaque forming units (PFU) enumeration (**Fig. 5A-5B**) and RNA isolation and quantification. For PFU enumeration, the samples collected at each time point were filtered through 0.45 µm filters to separate the phage from the host bacteria. A soft agar overlay was prepared as described for slide 3. 10-fold serial dilutions of the phage

samples were spotted onto the overlay and incubated at 37°C. The following day, plaques were counted and used to calculate the PFU/mL in the initial sample. Based on these data, no significant differences in phage growth patterns were observed and each phage reached a similar maximum titer.

[00323] p1772wt, p1772e004, and p1772e005 were diluted to a particle count of 1e6, and each individual phage was used to infect a panel of 34 different bacteria at an MOI of 0.01. Optical Density (OD) readings at a wavelength of 600 nm were captured every hour over a 20 hour time course. The resulting OD readings were used to generate bacterial growth curves in the presence of one of the three phages. Integration was used to calculate the Area Under the Curve (AUC) for each growth curve, where a smaller AUC upon phage addition indicates reduced bacterial load. Host range was determined by monitoring the OD600 (turbidity) of the culture over time to obtain a bacterial growth curve with the starting amount of introduced phage indicated on the bottom of the graph (input phage titer in plaque forming units per milliliter). The AUC for a given strain was compared in the presence and absence of phage. **Fig. 5C** exemplifies the AUC Ratio, in which the AUC calculation of strain growth in the presence of phages is divided by the AUC of strain growth in the absence of phage. Each row represents a unique bacterial strain. Darker values in the heatmap indicate stronger reductions in bacterial loads. The phage was considered to infect a given strain if (AUC in the presence of phage)/(AUC in the absence of phage) was less than 0.65. The heat map of AUC ratio demonstrates that the engineered phage variants had comparable host range to the wild type parent in this assay. The host range of p1772wt, p1772e004, and p1772e005 were similar to one another and were within error of the assay. Host range confirmation of AUC hits by plaquing shows no difference between WT and CRISPR-Cas3.

[00324] **Table 2** shows data from a representative growth experiment of two unique full construct-containing engineered phages pArray3 (targeting crArray3 + Cas system) and pArray4 (targeting crArray4 + Cas system). In this assay, an amplification was performed by inoculating LB growth medium with a single colony of bacteria and adding phage as indicated in the "Input PFU/mL" column. Amplifications were incubated overnight. Following incubation, the bacteria were removed by filtration and phage titer in the lysate was quantified by the soft agar overlay method. The titer of the lysate is indicated in the "Output PFU/mL" column. These data indicate that the engineered phages replicated effectively. These data also demonstrate the relative precision of the titration assay.

Table 2: Growth of pArray3 and pArray4

Phage name	Replicate	Input PFU/ml	Output PFU/ml	Fold increase
pArray3	1	3.00e+6	2.25e+9	750
pArray3	2	1.90e+6	4.00e+9	2105
pArray4	1	1.00e+5	8.00e+9	80000
pArray4	2	5.00e+5	2.50e+9	5000

Example 6. CRISPR-Cas system expression in the engineered phage

[00325] This example shows that the Cas system and a crArray was successfully expressed from the phage genome. **Fig. 6A** depicts the arrangement of the spacer array (crArray) and Cas operon that are engineered into p1772 and other phages described herein. Arrows represent the binding locations of primers pairs used for quantitative reverse transcription PCR (qRT-PCR) analysis of gene expression.

[00326] p1772wt (wild type), which does not contain the Cas operon, was used as a control. For RNA isolation, the samples collected at each time point were added directly to RNAprotect. Samples were incubated for 5 minutes at room temperature, centrifuged for 10 minutes and 5000 x g, and the supernatant discarded. Pellets were stored at -80°C. RNA was then isolated using the Qiagen RNeasy Mini Kit. cDNA was synthesized using the BioRad iScript cDNA synthesis kit. qRT-PCR was performed using BioRad SsoAdvanced Universal SYBR Green Supermix. All data was the average of two biological replicates. Fold change was $2^{-\Delta\Delta Ct}$, using *Pseudomonas aeruginosa* gene *rpsH* as the housekeeping gene and comparing each data point to the cells only control at the same time point.

[00327] **Figs. 6B-6D** show relative expression levels of the indicated RNA following infection of a *P. aeruginosa* strain by different variants of phage p1772. The data in these graphs are presented as the fold change in expression compared to a vehicle control with no phage present. Each time point was normalized to the uninfected control for that time point. Changes in bacterial concentration were accounted for by normalizing the samples using the bacterial housekeeping gene *rpsH*. These data indicate that the phage produces crArray, *Cas3*, and *Cas8c* transcripts while infecting *P. aeruginosa*. The bacterial host used in panels B-D contained an endogenous Cas operon, so the difference between p1772e005 (targeting crArray1 + Cas system) and p1772wt represents the phage-mediated increase in expression over endogenous expression.

[00328] **Fig. 6E** shows the relative expression of *cas3* mRNA from different engineered phage genomes. These data indicated that there is more *cas3* expression from p1772e005 than from

two other engineered phages, p2131e002 (targeting crArray1 + Cas system) and p2132e002 (targeting crArray1 + Cas system), at 1h post-infection. However, at 24h post-infection, the phages expressed close to the same amount of *cas3*. These data were calculated by comparing *cas3* RNA expression to the amount of phage gDNA and normalizing to p1772e005 at 1h post infection. The bacterial strain used in these assays was Cas null, so there is no contribution from endogenous *cas3* expression.

Example 7. Phage lytic activity when engineered with CRISPR-Cas full construct

[00329] Top agar overlays were prepared by mixing 100 µL of a saturated overnight culture of the p1772 indicator strain b1121 with 6 mL of 0.375% agar in LB containing 10 mM $MgCl_2$ and 10 mM $CaCl_2$. After the top agar solidified, 2 µL drops of serial 10-fold dilution series of p1772wt (wild type) and p1772e004 (Cas system only) and p1772e005 (targeting crArray1 + Cas system) were spotted onto the surface of the top agar. Plates were incubated at 37°C for ~18h, then imaged using a Keyence BZ-X800 microscope at 4X and 10X magnification. **Fig. 7** illustrates the improved plaque morphology of p1772 phage. The morphology of the wild-type phage was observed to produce hazy plaques, while the engineered variant p1772e005 produced plaques of a similar size that have a hazy halo but are clear in the center. This data suggests that p1772e005 killed the bacteria more completely than p1772wt.

Example 8: Phage containing the crArray and the Cas operon were more effective in killing bacteria than phage containing only the crArray

[00330] p1772 wildtype and engineered phage were mixed with bacteria in logarithmic growth and plated immediately in 2 ul spots on LB agar. The ratio of phage to bacteria was altered through the dilution series so that the amount of bacteria stays constant at each dilution but the amount of phage was a 1 to 4 dilution. At the highest dilution, the multiplicity of infection (MOI) was 100, meaning there were approximately 100 phages per bacteria. In **Fig. 8A**, both p1772e005 (targeting crArray1 + Cas system), and p1772e006 (targeting crArray1 only) consistently killed the majority of the bacteria present in Type I-C strains after overnight incubation, as indicated by little to no bacterial colonies that grew in those spots whereas the wildtype phage did not control bacterial colony formation. Thus, wildtype and p1772e004 (Cas system only) were unable to control bacterial replication, even at an MOI of 100. **Fig. 8B** shows that p1772e006 killed bacteria more effectively than wildtype in this bacteria strain due to the endogenous Cas system in the bacteria, however it did not appear to be as effective as phage that also contains an exogenous Cas system (p1772e005). This was because with extended incubation time, the more bacteria form colonies in spots exposed to p1772e006 than p1772e005.

[00331] **Fig. 8C** is a quantification of a single MOI from the same type of assay performed in Figs. 8A-8B. In contrast to Figs. 8AB-8B, the bacterial strain in panel C did not have an endogenous Cas system but had a genomically integrated copy of the mCherry gene. The plate was imaged and the fluorescence of each spot was quantified. The results for an MOI of 1.5 are shown, but MOIs above 0.4 all have results consistent with the MOI of 1.5. Due to the lack of an endogenous Cas system, the crArray-only phage (p1772e006) behaved similarly to the wild type phage. The fully engineered phage containing a non-targeting crArray (p1772e008) was also not improved relative wild type. However, the fully engineered phage containing a targeting crArray (p1772e005) inhibited cell growth to a significantly greater extent than any other phage variant. This data shows that the fully engineered variant did not require an endogenous Cas system to be effective.

[00332] A *P. aeruginosa* strain (b1121) with an active endogenous Type I-C Cas system was grown to mid-logarithmic phase and infected with phage in liquid culture at the indicated multiplicity of infection (MOI). In all cases, the phage successfully killed the bacteria, as depicted in **Figs. 9A-9C**, indicated by a reduction in colony forming units (CFU)/mL recovered compared to an uninfected control. Both p1772e005 (targeting crArray1 + Cas system) and p1772e006 (targeting crArray1 only) killed the bacteria more efficiently than the wild type phage. p1772e004 (Cas system only) did not have improved activity relative to p1772wt (wild type) or the self-targeting variants, demonstrating that both the self-targeting crRNA and Type I CRISPR-Cas components were required to improve phage efficacy. Notably, p1772e006 and p1772e005 killed to equal levels, demonstrating that the engineered phage variants were able to kill by expression of bacterial-targeting Cas systems from the phage in the presence of a compatible and active Cas system. The dotted lines in these figures represents the limit of detection (LOD) for the assay. Samples for which no colonies were obtained are shown at the LOD.

Example 9: Multiple different *P aeruginosa* targeting spacers improved phage efficacy

[00333] p1772 wildtype and engineered phage variants were mixed with mCherry expressing bacteria in logarithmic growth and plated immediately onto LB agar. The ratio of phage to bacteria was altered by performing a dilution series of the phage, so that the amount of bacteria remained constant in each spot but the amount of phage changed. The highest multiplicity of infection (MOI) was 100, meaning there are approximately 100 phages per bacterium. After overnight incubation, bacterial growth was recorded by imaging the plate by brightfield and mCherry fluorescence. Quantification was performed on the samples based on these images.

[00334] Five different phage variants were used to determine the effect of lytic phage delivering non-targeting crRNAs with an exogenous Type I-C Cas system (p1772e008), a self-

targeting crRNA alone without an exogenous CRISPR-Cas system (p1772e006), two different self-targeting crArrays delivered with an exogenous Type I-C Cas system (pArray3 and pArray4) and the parent wild-type phage (p1772wt). In these assays, a *P. aeruginosa* strain lacking any endogenous Cas system and the indicated phage were combined at the indicated ratio and immediately plated on LB plates. The host bacterial strain used in these assays was Cas-null and had a chromosomally integrated mCherry gene to facilitate observation and quantification of bacteria through measurement of relative fluorescence. The results are depicted in **Figs. 10A-10B.** Darker spots represent higher bacterial growth. The numbers to the right of each image represent the multiplicity of infection (MOI). At the highest MOI, there were approximately 100 phage for every 1 bacterium. These plate images show that at higher MOIs, phages pArray3 and pArray4 (both p1772 phage encoding an active Type I-C Cas system and each with a unique crArray composed of three distinct self-targeting spacers each) killed *P. aeruginosa* more effectively than p1772wt, the phage with the Cas operon and non-targeting spacers (p1772e008), or p1772 containing the crArray but no exogenous Cas system (p1772e006). As expected, the crRNA only phage (p1772e006) did not improve phage efficacy as the bacteria do not have an endogenous Cas system.

[00335] **Fig. 10C** is a higher resolution view of the box in **Fig. 10A**, and highlights the differences between the fully engineered phage (pArray3) and a phage with a crArray only and no Cas operon (p1772e006). In the bottom row (MOI 0.00610), pArray3 formed clearer plaques than did p1772e006 (i.e., the light spots in the pArray3 samples were lighter). In the top row (MOI 0.0244), pArray3 inhibited bacterial growth (dark spots) better than p1772e006.

[00336] **Figs. 10D-10E** show the quantification of the fourth row down (MOI ~1.5) of the corresponding fluorescent images of the same plates shown in Fig 10A and Fig 10B that quantify the relative amount of fluorescent bacteria present. Consistent with the brightfield images, at an MOI of about 1.5, samples treated with pArray3 and pArray4 had significantly less fluorescent signal (indicating loss of viable bacterial cells) than samples treated with wildtype phage or the non-targeting (p1772e008) and crArray-only (p1772e006) engineered phages.

Example 10: Efficacy of the crArray/Cas insert with different promoters driving expression of the cas operon.

[00337] p1772 wildtype and engineered phage variants were mixed with mCherry expressing bacteria in logarithmic growth and plated immediately onto LB agar. The ratio of phage to bacteria was altered by performing a dilution series of the phage, so that the amount of bacteria remained constant in each spot but the amount of phage changed. The highest multiplicity of infection (MOI) was 100, meaning there were approximately 100 phages per bacterium. After

overnight incubation, bacterial growth was recorded by imaging the plate by brightfield and mCherry fluorescence. Quantification was performed on the samples based on these images. **Fig. 11A** shows bacterial kill by p1772 wild type and multiple engineered variants of the phage containing the Cas system and crArray expressed by different promoters. All of the engineered phage variants had the same structure as p1772e005 (see **Fig. 3A**) and differ only in the identity of the promoter driving expression of the Cas operon. p1772e016 used the promoter that drives the endogenous Type I-C Cas system in *P. aeruginosa*. p1772e005, p1772e017, p1772e021 all used *E. coli* promoters or derivatives of *E. coli* bacterial promoters. p1772e018, p1772e022, and p1772e023 all used *P. aeruginosa* bacterial promoters. p1772e019 and p1772e020 used *P. aeruginosa* phage promoters. Both plates were from the same assay and controls (p1772wt and p1772e005) are from the same phage-bacteria mixture prior to plating the spots. The bacterial host strain used was a Cas-null *P. aeruginosa* strain that expressed mCherry from the chromosome. Individual images were acquired using a 4x objective and brightfield illumination, then stitched together to obtain the images shown here. **Fig. 11B** shows the quantification of the fourth row down (MOI ~1.5) of the corresponding fluorescent images of the same plates shown in **Fig. 11A**. Differences in overall efficacy were observed across different promoters used, indicated by significantly less fluorescent signal (indicating loss of viable bacterial cells) compared to p1772wt.

Example 11: Multiple different phages have improved efficacy for log reduction

[00338] Wildtype and engineered phage variants were mixed with mCherry expressing bacteria in logarithmic growth and plated immediately onto LB agar. The results shown are from a multiplicity of infection (MOI) of 1.5, meaning there were approximately 1.5 phages per single bacterium. After overnight incubation, bacterial growth was recorded by imaging the plate for mCherry fluorescence. Quantification as depicted in **Figs. 12A-12B** was performed on the samples based on these images. Two unique wildtype phages (p2131 and p2973) and their engineered counterparts containing the Cas system and crArray 1 (p2132e002 and p2973e002) were tested. At an MOI of about 1.5, the engineered phage had far less viable bacteria than wildtype phage. These results show that the phage-delivered Cas system works in multiple unique phages.

Example 12: The efficacy of the spacer array/Cas Insert in alternative phages and *Pseudomonas* strains

[00339] An assay was performed with p4209wt (wild type) and p4209e002 (targeting crArray1 + Cas system) against a panel of *Pseudomonas* strains. Briefly, early log phase bacterial culture was mixed with phage to obtain the final titers listed in the figure. Samples were plated immediately (t = 0h) and after 3 and 24h of incubation at 37°C. Plates were imaged and differences

between the wild type and full construct variants tabulated. p4209 wildtype and engineered phage variants were mixed with bacteria in logarithmic growth and plated immediately onto LB agar, or incubated in liquid for the indicated amount of time before plating. The ratio of phage to bacteria was altered by performing a dilution series of the phage, so that the amount of bacteria stays constant in each spot but the amount of phage changes. The relative ratio of the phage and bacteria shifted over the course of the experiment as the bacteria replicated and succumbed to the phage. After overnight incubation, bacterial growth was recorded by imaging the plate. The label at the top of each set of images denotes the Cas type of the bacterial strain shown in that image. **Fig 13A** shows the results of this assay. In strain b2550 at all timepoints, p4209e002 fully inhibited bacterial growth at a titer of 1×10^9 PFU/mL compared to p4209wt at the same titer. In strain b2631 at t=0h, no growth was observed for p4209e002 at a titer of 1×10^5 PFU/mL while growth was visibly greater for p4209wt at the same titer. In the same strain at t=3h, no growth was observed for p4209e002 at any titer while there was visible growth for p4209wt at all titers. In strain b2816 at t=0h, slightly less growth was observed for p4209e002 at a titer of 1×10^9 PFU/mL than for p4209wt at the same titer. In the same strain at t=3h, very little growth was observed for p4209e002 at a titer of 1×10^9 PFU/mL while there was significant growth for p4209wt at the same titer. In strain b2825 at t=0h, no growth was observed for p4209e002 at a titer of 1×10^7 PFU/mL while significant growth as observed for p4209wt at the same titer. In the same strain at t=3h, some growth was observed for p4209e002 at titers of 1×10^9 PFU/mL and 1×10^7 PFU/mL, while there was visibly more growth for p4209wt at the same titers. Taken together, these data show that a unique phage, p4209e002, had improved Cas and crRNA spacer activity against several unrelated *P. aeruginosa* strains.

[00340] p4209wt, p4209e001 (Cas system only), and p4209e002 (targeting crArray1 + Cas system) were plaqued on multiple bacterial strains to examine the efficiency of plaquing. *P. aeruginosa* strain b1121 supported all variants equivalently and is provided as a titer reference. On *P. aeruginosa* strain b2631, the wild type variant plaqued at a significantly decreased level, the Cas-only variant did not plaque at all, and the fully engineered variant plaqued with no loss of efficiency compared to b1121. On *P. aeruginosa* strain b2816, neither the wild type nor Cas-only variants showed any evidence of activity, while the fully engineered variant produced zones of clearing. On *P. aeruginosa* strain b2825, the wild type and Cas only variants had significantly reduced plaquing efficiency, while the fully engineered variant maintained comparable efficiency to b1121. Both b2631 and b2825 show examples of an engineering event (insertion of the Cas system) having detrimental effects – that is, either a decrease in efficiency of plaquing (b2631) or in plaque clarity (b2825). In both cases, addition of the targeting crArray (which enables activity of the Cas system) not only rescued the decreased activity but improved activity beyond that seen

in the wild type parent. The label at the bottom of plate image denotes the bacterial strain shown in that image and the type of endogenous Cas system it contains. These results further support that the Cas system and targeting crArray improved the phages ability to replicate and kill various bacterial strains.

Example 13. In vivo efficacy study

[00341] **Fig. 15A** outlines the materials and methods utilized for *in vivo* efficacy modeling with p1772wt (wild type) and p1772e005 (targeting crArray1 + Cas system). Female, ICR mice from Envigo were rendered neutropenic via two intraperitoneal injections of cyclophosphamide (150 mg/kg and 100 mg/kg, respectively) on Days -4 and -1. Following induction of neutropenia, mice were infected with *P. aeruginosa* b1121 by a single intramuscular injection. Previous model development determined that ~5e6 CFU was the ideal inoculum of this particular strain. At 3 h post-infection (p.i), mice were treated with either vehicle (1 x TBS + 10 mM salts), p1772wt, or p1772e005 by a single intramuscular injection in the infected thigh. The table on the bottom left details the total PFU delivered to each infected thigh in each experiment. Mice were euthanized and the thigh muscle harvested at the indicated time point post-inoculation. The thighs were homogenized using a bead beater system. Homogenate was serially diluted and plated for CFU quantification. Homogenate was also filtered through a 0.45 um filter. Filtrate was serially diluted and plated for PFU quantification on a b1121 overlay plate. All CFU and PFU measurements were normalized to g tissue.

[00342] Both the bacterial colony forming units (CFU) and phage plaque forming units (PFU) are shown for each experiment. **Fig 15B-15C** show phage efficacy in mice where the phage were administered intramuscularly. Thigh muscle tissue was harvested at the indicated time points. Both replicates show that the fully engineered phage decreases colonization to a greater extent than does the wild type phage. **Fig 15D** shows phage efficacy in mice where the phage were administered intravenously. Thigh muscle tissue was harvested at the indicated time points. The fully engineered phage destroys the bacteria to a greater extent than does the wild type phage. Taken together, these data from Figs. 15B-15D indicate that phage delivered by different routes enters the thigh and kills the bacteria. At every time point, the CFU/g of thigh tissue in mice treated with fully engineered phage is lower than that in mice treated with the wildtype phage. **Fig. 15E** is a schematic showing the experimental design for a model establishing the dose-response of phage treatment in a mouse infection model. This experiment was performed similarly those shown in **Fig. 15A**, but additionally includes an antibiotic treatment group to represent the current standard of care. The phage dose is also titrated between the different groups.

[00343] **Fig. 15F** shows the results of treatment with phage at different doses or antibiotic in mice. Overall, these data indicate that the engineered p1772e005 was more effective in a mouse infection model than p1772wt. Moreover, the engineered phage performed better than the antibiotic treatment given. In panels B-D and F, data is shown as mean ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Statistical significance is determined using a One- way ANOVA with multiple comparisons or Two-way ANOVA with Tukey's test.

Example 14. In vivo efficacy study

[00344] A culture of b1121 was grown overnight, back diluted into LB + 10 mM $MgCl_2$ + 10 mM $CaCl_2$ and grown to an OD600 of 0.45. The culture was split and treated with either LB/salts (cells only control), p1772e005 (MOI = 0.1), PB1e002 (MOI = 0.1), or a cocktail of p1772e005 + PB1e002 (MOI = 0.1 per phage). All samples were incubated in a microtiter plate at 37°C with shaking for 24 h and the OD at 630 nm was measured every 10 minutes. Data is presented as a mean of 12 replicates. Error bars represent the standard deviation. The data show that the cocktail of the two full construct phages suppresses culture rebound to a greater extent than either phage by itself. **Fig. 16** shows cooperativity between p1772e005 and PB1e002.

Example 15: The activity of different repeat sequences

[00345] A culture of *P. aeruginosa* cultures were transformed with vectors comprising the different repeat sequences. The vectors were either an empty vector pUCP19 (empty vector) or contained an pUCP19 vector comprises a *Pseudomonas* Type I C Cas system and a spacer targeting the gyrB gene flanked by the repeat sequence listed in **Table 3.** An aliquot was taken of each test condition, diluted and spotted to enumerated bacterial CFUs.

Table 3: Repeat sequences

SEQ ID NO	Repeat	Sequence
26	Repeat 1	GTCGCGCCCCGCACGGGCGCGTGGATTGAAAC
27	Repeat 2	GTCGCGCCCCGCACGGGCGCGTGGAGTGAAAG
28	Repeat 3	GTCGCGCCCCGCACGGGTGCGTGGATTGAAAC
29	Repeat 4	GTCGCGCCCCGCATGGGCGCGTGGATTGAACA
30	Repeat 5	GTCGCGCCCTACGCGGGCGCGTGGAGTGAAAG

[00346] The results of this assay are depicted in **Fig. 17**. Specific sequences resulted in different number of transformants. Both repeat 1 and repeat 3 both resulted in a lower number of

transformants than the empty vector or bacteria transformed with repeat 2, 4, or 5. This indicates that the sequence of the repeat sequence effects the efficacy of phage targeting in the *Pseudomonas* cultures.

Example 16: Designing and validating spacer sequences to target a target bacterium

Spacer design

[00347] A spacer sequence is designed using the following protocol. First, suitable search set of representative genomes for the organism/species/target of interest are acquired. Examples of suitable databases include NCBI genbank and the PATRIC (Pathosystems Resource Integration Center) database. The genomes are downloaded in bulk via FTP (File Transfer Protocol) servers, enabling rapid and programmatic dataset acquisition.

[00348] The genomes are searched with relevant parameters to locate suitable spacer sequences. The genomes can be read from start to end, in both the forward and reverse complement orientations, to locate contiguous stretches of DNA that contain a PAM (Protospacer Adjacent Motif) site. The spacer sequence will be the N-length DNA sequence 3' adjacent to the PAM site, where N is specific to the Cas system of interest and is generally known ahead of time. Characterizing the PAM sequence and spacer sequences are generally performed during the discovery and initial research of a Cas system. Every observed PAM-adjacent spacer can be saved to a file and/or database for downstream use.

[00349] Next, the quality of a spacer for use in a CRISPR engineered phage is determined using the following process. First, each observed spacer can be evaluated to determine how many of the evaluated genomes they are present in. The observed spacers can additionally be evaluated to see how many times they may occur in each given genome. Spacers that occur in more than one location per genome can be advantageous because the Cas system may not be able to recognize the target site if a mutation occurs, and each additional "backup" site increases the likelihood that a suitable, non-mutated target location will be present. The observed spacers can be evaluated to determine whether they occur in functionally annotated regions of the genome. If such information is available, the functional annotations can be further evaluated to determine whether those regions of the genome are "essential" for the survival and function of the organism. Focusing on spacers that occur in all, or nearly all, evaluated genomes of interest (>= 99) ensures broad applicability to justify the spacer selection. Provided a large selection pool of conserved spacers exists, preference may be given to spacers that occur in regions of the genome that have known function, with higher preference given if those genomic regions are "essential" for survival and occur more than 1 time per genome.

Spacer validation

[00350] The identified spacer sequences can then be validated by completing the following procedure. First, a plasmid that replicates in the organism(s) of interest and has a selectable marker (e.g. an antibiotic-resistance gene) is identified. The genes encoding the Cas system are inserted into the plasmid such that they will be expressed in the organism of interest. Upstream of the Cas system, a promoter is included that is recognized by the organism of interest to drive expression of the Cas system. Between the promoter and the Cas system, a ribosomal binding site (RBS) is included that is recognized by the organism of interest.

[00351] Next, genome-targeting spacers that have been identified bioinformatically are inserted into the plasmid that expresses the Cas system. Upstream of the repeat-spacer-repeat, promoter is included that is recognized by the organism of interest to drive expression of the crRNA. Examples of such promoters are listed in **Table 1B.** This cloning must be performed in an organism or strain that is not targeted by the spacer being cloned.

[00352] Next, a non-targeting spacer is inserted into the plasmid that expresses the Cas system. The sequence of this spacer can be randomly generated and then confirmed bioinformatically to not have targeting sites in the genome of the organism of interest. Upstream of the repeat-spacer-repeat, a promoter that is recognized by the organism of interest to drive expression of the crRNA is included.

[00353] Next, the killing efficacy of each tested spacer is determined. The plasmids listed in **Table 4** are normalized to the same molar concentration. Each plasmid is transferred to the organism of interest by transformation, conjugation, or any other method for introducing a plasmid into a cell. The transformed cells are plated onto the appropriate selective media (e.g. antibiotic-containing agar). Following cell growth into colonies, the colonies that resulted from each different plasmid transfer are enumerated. Plasmids containing targeting spacers with a significantly lower transfer rate than the control plasmid containing the non-targeting spacer are considered to be successful at targeting the bacterial genome.

Table 4: Plasmids and controls used

Plasmid	**Function**
Empty backbone vector	control for plasmid transfer efficiency
Vector containing the Cas system	control for Cas system toxicity
Vector containing the Cas system and the non-targeting spacer	control for off-target effects
Vector containing the Cas system and the targeting spacer	test sample

Example 17: Purified *P. aeruginosa* phage host range assay

[00354] Data for purified *P. aeruginosa* phage was acquired, reported was the best result from combined liquid and plaquing host range assays. The final result was the median of the binary hits across both liquid and plaquing host range for a given phage plus strain combination. Liquid host range involved the addition of 5uL of frozen, OD-controlled, culture material, 5uL of known titer phage material and 40uL of growth media into a well of a 364-well plate along with appropriate culture, phage, and media only controls. The plate was incubated for 20 hours at 37C while shaking and OD600 readings were taken by the liquid handler every hour. The results were calculated by determining the ratio between areas under the cover (AUC) for samples with phage added and their respective controls. Samples with AUC ratios below 0.65 were considered positive (+) hits while AUC ratios greater than or equal to 0.65 were negative (-) hits. For plaquing host range assays, bacterial strains of interest were cultured and screened for prophage. Bacteriophage of interest were serially diluted 50-fold across a microtiter plate from undiluted to 50-3 in 1X PBS. Agar overlays of strains used as titre host were poured and allowed to sit overnight. The following day, lysates for the bacterial strains of interest were spotted. After 15-20 min, the plates were imaged using the Hamilton-STAR-C062 and either counted by hand or run through an internally developed image analysis pipeline for transformation, background subtraction, and counting. Samples with a positive (+) number of plaque forming units were considered hits. The results of this assay involving *P. aeruginosa*, wildtype Pbunavirus phage subtypes, and engineered Pbunavirus phage subtypes were listed in **Table 5A.** The results of this assay involving *P. aeruginosa*, wildtype Samunavirus phage subtypes, engineered Samunavirus phage subtypes, wildtype PhiKZvirus, wildtype PhiKMVvirus, and wildtype Bruynoghevirus were listed in **Table 5B.** As listed in **Table 5A**, the wildtype Pbunavirus phage subtypes were p1106, p1587, p1835, p2037, p2363, p2421, and pb1, while the engineered Pbunavirus phage subtypes were p1106e003, p1587e002, p1835e002, p2037e002, p2363e003, and p2421e002. As listed in **Table 5B**, the wildtype Samunavirus phage subtypes were p1772, p2131, p2132, and p2973, the engineered Samunavirus phage subtypes were pb1e002, p1772e005, p2131e002, p2132e002, and p2973e002, the wildtype PhiKZvirus phage subtypes were p1194, and p4430, the wildtype PhiKMVvirus phage subtype was p2167, and the wildtype Bruynoghevirus phage subtypes were p1695, and p3278.

Table 5A: *P. aeruginosa* Phage Host Range

Target	Wildtype Pbunavirus							Engineered Pbunavirus						
	p1106	p1587	p1835	p2037	p2363	p2421	pb1	p1106e003	p1587e002	p1835e002	p2037e002	p2363e003	p2421e002	pb1e002
b002548	+	+	-	+	+	-	-	+	-	+	-	-	-	-
b002550	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002553	-	+	-	-	-	-	-	-	-	-	-	-	-	-
b002554	-	-	-	-	-	-	+	-	-	-	-	-	-	-
b002557	+	+	+	+	+	+	+	-	-	-	+	-	-	+
b002563	-	+	-	+	+	-	-	+	-	+	-	-	-	-
b002567	+	+	+	+	+	+	-	-	-	+	-	-	-	-
b002571	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002575	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002580	+	+	-	+	+	-	+	-	+	+	+	-	-	+
b002583	-	-	+	+	+	-	-	+	-	+	-	-	-	-
b002586	-	-	+	+	-	-	-	-	-	+	-	-	-	-
b002588	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002590	-	+	-	-	-	-	-	+	+	+	-	+	-	-
b002593	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b002599	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002600	-	-	-	-	-	-	-	+	-	+	-	-	+	-
b002601	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002609	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002614	+	-	+	+	-	-	-	-	-	+	-	-	-	-
b002617	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b002624	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002630	+	+	+	-	-	+	-	+	-	+	+	-	-	-
b002631	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002637	-	-	-	+	-	-	-	-	-	+	-	-	-	-
b002638	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b002658	+	+	+	+	+	+	-	+	+	+	+	-	+	-
b002660	+	-	-	-	+	-	-	+	-	+	-	-	-	-
b002775	+	+	-	-	-	+	-	-	-	+	-	-	-	-
b002776	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b002780	+	+	+	+	+	+	+	-	-	+	-	-	-	-
b002781	-	-	-	-	-	-	-	+	-	-	-	-	-	-
b002782	+	+	+	+	+	+	-	+	-	+	+	+	-	+
b002785	+	+	+	+	+	+	+	+	-	+	-	+	+	+
b002790	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b002797	-	-	-	-	-	-	-	-	-	-	-	-	-	-

b002807	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002809	-	-	+	+	-	-	-	-	-	+	-	-	-	-
b002811	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002816	+	+	+	+	+	+	+	+	+	+	-	+	+	+
b002819	+	+	+	-	-	+	-	-	-	+	-	-	-	-
b002820	-	+	+	-	-	+	-	+	-	+	-	-	+	-
b002825	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002827	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b002831	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b002832	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b002835	+	+	+	+	-	+	-	+	+	+	+	-	+	-
b002836	-	-	-	-	-	+	-	-	-	+	-	-	-	-
b002839	+	+	+	+	+	+	+	+	+	+	-	+	+	+
b002840	+	+	+	+	+	+	+	-	+	+	-	+	+	+
b002844	-	+	+	-	-	+	-	-	-	+	-	-	-	-
b002847	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b002856	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b002857	+	+	+	+	+	+	-	+	-	+	+	-	+	-
b002861	+	+	+	+	-	+	+	+	-	+	+	-	-	+
b002866	+	+	+	-	+	+	+	+	+	+	-	-	+	+
b002873	+	-	-	-	-	-	-	+	-	-	-	-	-	-
b002875	-	-	-	-	-	-	-	+	-	-	-	-	-	-
b002876	+	-	-	-	-	-	-	+	-	-	-	-	-	-
b002877	-	+	+	+	+	+	+	-	-	+	+	-	-	-
b002885	+	-	-	-	-	-	-	+	-	+	-	-	-	-
b002887	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b002890	+	-	-	-	-	-	-	+	-	+	-	-	-	-
b002893	-	+	+	-	+	-	+	+	-	+	-	-	-	+
b002898	+	+	+	+	-	+	-	+	+	+	+	-	+	-
b002906	+	+	+	+	-	+	-	+	+	+	-	-	-	-
b003049	-	-	+	+	-	-	-	-	-	-	+	-	-	-
b003052	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b003053	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b003056	+	+	+	+	+	+	+	+	-	+	-	+	-	-
b003064	+	+	+	+	+	+	+	+	-	+	+	-	+	+
b003065	-	+	-	-	-	-	-	+	-	+	-	-	-	-
b003068	+	+	+	-	+	+	-	+	-	+	-	-	-	-
b003075	-	+	-	-	-	-	-	-	-	+	-	-	-	-
b003076	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b003080	-	-	+	-	-	-	-	+	-	+	-	-	-	-
b003082	+	+	+	+	-	+	+	+	+	+	+	+	+	-
b003137	-	-	-	-	-	-	-	-	-	-	-	-	-	-
b003144	+	+	+	+	+	+	+	+	+	+	+	+	+	+
b003149	-	+	+	-	-	+	-	+	-	+	-	-	+	-
b003152	-	+	+	-	+	+	+	+	+	+	-	-	+	+
b003153	+	+	+	+	+	+	+	+	+	+	+	+	+	+

b003159	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b003168	-	-	-	-	-	-	-	+	-	+	-	-	-	-
b003172	-	-	-	-	-	-	-	-	-	+	-	-	-	-
b003177	+	+	-	+	+	+	-	+	+	-	-	-	+	-
b003190	-	-	+	-	-	-	-	+	-	-	-	-	-	-
b003194	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 5B: *P. aeruginosa* Phage Host Range

Target	Wildtype Samunavirus				Engineered Samunavirus				Wildtype PhiKZ-virus		Wildtype PhiKMV-virus	Wildtype Bruyno-ghevirus	
	p1772	p2131	p2132	p2973	p1772e005	p2131e002	p2132e002	p2973e002	p1194p.b008	p4430	p2167	p1695	p3278
b002548	-	-	-	-	-	-	-	-	-	-	-	-	-
b002550	-	-	-	-	-	-	-	-	+	+	-	+	-
b002553	-	+	-	+	-	-	-	-	-	-	-	-	-
b002554	-	-	-	-	-	-	-	-	-	-	-	-	-
b002557	-	-	-	-	-	-	-	-	-	-	-	-	+
b002563	-	-	-	-	-	-	-	-	-	-	-	-	-
b002567	+	+	+	+	+	+	+	+	+	+	+	+	+
b002571	-	+	-	+	-	+	+	-	-	-	-	-	-
b002575	-	-	-	-	+	-	-	-	-	+	-	+	-
b002580	-	-	-	-	-	-	-	-	-	-	-	-	-
b002583	-	-	-	-	+	-	-	-	-	-	-	-	-
b002586	-	-	-	-	-	-	-	-	-	+	-	-	-
b002588	+	+	+	+	-	+	+	-	+	+	-	+	-
b002590	-	-	-	-	-	-	-	-	-	-	-	+	+
b002593	-	-	-	-	-	-	-	-	-	-	-	+	+

b002599	-	-	-	-	-	-	-	-	-	-	-	-	-
b002600	-	-	-	-	-	-	-	-	-	-	-	-	-
b002601	-	+	+	-	+	+	+	-	+	+	-	-	-
b002609	-	+	+	+	+	-	+	+	+	+	-	+	+
b002614	+	+	-	-	-	-	-	-	-	+	-	-	-
b002617	-	+	+	-	+	+	-	-	-	-	-	+	-
b002624	-	-	-	-	-	-	-	-	-	-	-	+	-
b002630	-	-	-	-	-	-	-	-	+	+	-	-	+
b002631	+	+	+	+	+	+	+	+	+	+	+	+	+
b002637	-	-	-	-	-	-	-	-	-	-	-	-	-
b002638	-	-	-	-	-	+	-	-	+	+	-	+	+
b002658	-	-	-	-	-	-	-	-	-	+	-	-	-
b002660	-	-	-	-	-	-	-	-	-	-	-	-	+
b002775	-	+	+	-	+	-	-	+	+	+	-	+	-
b002776	-	-	-	-	+	-	-	-	+	+	-	+	-
b002780	-	-	-	-	-	-	-	-	-	-	-	+	-
b002781	-	-	-	-	+	-	-	-	-	+	-	-	-
b002782	-	-	-	-	-	-	-	-	+	+	-	+	+
b002785	-	-	-	-	-	-	-	-	-	-	-	+	-
b002790	-	-	+	-	+	-	-	-	+	+	+	-	-
b002797	-	-	-	-	-	-	-	-	-	+	-	-	-
b002807	-	-	-	-	-	-	-	-	-	-	-	-	-
b002809	-	-	-	-	-	-	-	-	-	+	+	-	-
b002811	-	-	-	-	-	-	-	-	+	+	-	+	+
b002816	-	-	-	-	-	-	-	-	+	+	-	+	-

b00281 9	-	+	+	+	+	+	+	-	+	+	-	+	+
b00282 0	-	-	-	-	-	-	-	-	+	+	-	+	-
b00282 5	+	+	+	+	+	+	+	+	-	+	-	-	-
b00282 7	-	-	-	-	+	-	-	-	-	-	+	-	-
b00283 1	-	-	-	-	-	-	-	-	+	+	-	-	-
b00283 2	-	-	-	-	-	-	-	-	+	+	-	+	+
b00283 5	-	-	-	-	-	-	-	-	+	+	-	+	+
b00283 6	-	-	-	-	-	-	-	-	-	-	-	+	+
b00283 9	-	+	+	+	+	+	+	+	+	+	+	+	+
b00284 0	-	+	+	+	-	-	+	-	+	+	+	-	+
b00284 4	-	+	+	+	+	-	+	-	+	+	-	+	-
b00284 7	+	+	+	+	+	+	+	+	+	+	-	+	+
b00285 6	-	-	-	+	+	-	+	+	+	+	-	-	+
b00285 7	-	+	+	+	+	-	-	-	+	+	-	+	-
b00286 1	-	-	-	-	-	-	-	-	+	+	-	+	+
b00286 6	-	+	+	-	-	-	-	-	+	+	+	+	+
b00287 3	-	-	-	-	-	-	-	-	+	+	-	-	-
b00287 5	-	-	+	+	+	-	+	-	+	+	-	+	-
b00287 6	-	-	-	-	-	-	-	-	+	+	-	+	-
b00287 7	-	-	+	-	-	-	-	-	-	+	-	+	-
b00288 5	-	-	-	-	-	-	-	-	-	-	-	-	-
b00288 7	-	-	-	-	-	-	-	-	-	-	-	-	-
b00289 0	-	+	-	+	+	-	-	-	+	+	-	-	+
b00289 3	-	-	-	-	-	-	-	-	+	+	-	+	+
b00289 8	-	+	+	-	+	+	-	-	+	+	-	+	+

b00290 6	-	+	+	+	+	-	+	-	+	+	+	-	-
b00304 9	-	-	-	-	-	-	-	-	+	+	-	+	-
b00305 2	-	-	-	-	-	-	-	-	-	+	-	-	-
b00305 3	-	-	-	-	-	-	-	-	+	+	-	-	-
b00305 6	-	-	-	-	-	-	-	-	-	-	-	-	+
b00306 4	+	+	+	+	+	+	+	+	+	+	+	+	-
b00306 5	-	-	-	-	+	+	-	-	-	-	-	-	-
b00306 8	+	+	+	+	+	+	+	+	+	+	+	+	+
b00307 5	-	-	-	-	-	-	-	-	-	-	-	+	+
b00307 6	-	-	-	-	-	-	-	-	-	-	-	-	-
b00308 0	-	-	-	-	-	-	-	-	-	-	-	+	-
b00308 2	-	-	-	-	-	-	-	-	+	+	+	-	-
b00313 7	-	-	-	-	-	-	-	-	+	+	+	+	+
b00314 4	+	+	+	+	+	+	+	+	+	+	+	+	+
b00314 9	-	+	+	+	+	+	+	+	-	-	-	-	-
b00315 2	-	+	+	-	-	-	+	+	-	+	-	+	+
b00315 3	-	+	-	+	-	-	-	-	+	+	+	+	+
b00315 9	-	-	-	-	-	-	-	-	-	+	-	-	-
b00316 8	-	-	-	-	-	-	-	-	+	+	-	+	+
b00317 2	-	-	-	-	+	-	-	-	-	-	-	-	-
b00317 7	-	-	-	-	-	-	-	-	+	+	+	+	-
b00319 0	-	-	-	-	-	-	-	-	-	-	-	+	+
b00319 4	-	-	-	-	-	-	-	-	+	+	-	+	-

Example 18: *P. aeruginosa* cocktail phage host range assay

[00355] Data for *P. aeruginosa* cocktail phage was acquired, reported is the best result from combined liquid and plaquing host range assays. The final result was the median of the binary hits across both liquid and plaquing host range for a given phage plus strain combination. Liquid host range involved the addition of 5uL of frozen, OD-controlled, culture material, 5uL of known titer phage material and 40uL of growth media into a well of a 364-well plate along with appropriate culture, phage, and media only controls. The plate was incubated for 20 hours at 37C while shaking and OD600 readings were taken by the liquid handler every hour. The results were calculated by determining the ratio between areas under the cover (AUC) for samples with phage added and their respective controls. Samples with AUC ratios below 0.65 were considered positive (+) hits while AUC ratios greater than or equal to 0.65 were negative (-) hits. For plaquing host range assays, bacterial strains of interest were cultured and screened for prophage. Bacteriophage of interest were serially diluted 50-fold across a microtiter plate from undiluted to 50-3 in 1X PBS. Agar overlays of strains used as titre host were poured and allowed to sit overnight. The following day, lysates for the bacterial strains of interest were spotted. After 15-20 min, the plates were imaged using the Hamilton-STAR-C062 and either counted by hand or run through an internally developed image analysis pipeline for transformation, background subtraction, and counting. Samples with a positive (+) number of plaque forming units were considered hits. The detailed composition of phage cocktails ck000125, ck000239, ck000240, ck000241, ck000511, and ck000512 (also referred to as PACK512, Cocktail 512, ck00512, CK512) was listed in **Table 6A.** As listed in **Table 6B,** phage cocktail ck000125 comprises p1106e003, p1835e002, p1772e005, and p2131e002. As listed in **Table 6B,** phage cocktail ck000239 comprises p1106e003, p1835e002, p1772e005, p2131e002, and p1194. As listed in **Table 6B,** phage cocktail ck000240 comprises p1106e003, p1835e002, p1772e005, p2131e002, and p4430. As listed in **Table 6B,** phage cocktail ck000241 comprises p1106e003, p1835e002, p1772e005, p2131e002, and p1695. As listed in **Table 6B,** phage cocktail ck000511 comprises p1106e003, p1835e002, p1772e005, p2131e002, p1194 and p1695. As listed in **Table 6B,** phage cocktail ck000512 comprises p1106e003, p1835e002, p1772e005, p2131e002, p4430 and p1695.

Table 6A: Host Range Phage Cocktail Composition

			Cocktails					
	Individual Phage		4-phage	5-phage Cocktails			6-phage Cocktails	
			CK000125	CK000239	CK000240	CK000241	CK000511	CK000512 (PACK512)
Engineered Phage	PB1	p1106e003	x	x	x	x	x	x
		p1835e002	x	x	x	x	x	x
	SM1	p1772e005	x	x	x	x	x	x
		p2131e002	x	x	x	x	x	x
Wild Type Phage	phiKZ	p1194		x			x	
		p4430			x			x
	Bruynoghe	p1695				x	x	x

[00356] The results of this assay involving *P. aeruginosa*, and phage cocktails ck000125, ck000239, ck000240, ck000241, ck000511, and ck000512 are listed in **Table 6A.** Overall, host range was increased in phage cocktail assays as shown by an increase in positive (+) hits listed on **Table 6B**, as compared to individual phage assays listed in **Table 5A** and **Table 5B**. As listed in **Table 6B**, cocktail ck000512 *P. aeruginosa* host range data increased consistently.

[00357] As shown in Table 6C, the host range of cocktails CK000125 and CK00512 was tested in 284 different *Pseudomonas* bacterial isolates. 111 isolates were from cystic fibrosis (CF) and 85 isolates were from non-cystic fibrosis bronchiectasis (NCFB). Of the 284 *Pseudomonas* isolates, 95 were multi-drug resistant, with 49 of those isolates from CF and 9 from NCFB. The host range for both cocktails was greater than 85%, with cocktail CK00512 have a host range of 100% for all MDF isolates.

Table 6B: *P. aeruginosa* Cocktail Phage Host Range

Target	Cocktails					
	ck000125	ck000239	ck000240	ck000241	ck000511	ck000512 (PACK512)
b002548	+	+	+	+	+	+
b002550	+	+	+	+	+	+
b002553	-	-	-	-	-	-
b002554	-	-	-	-	-	-
b002557	-	-	-	-	-	-
b002563	+	+	+	+	+	+
b002567	+	+	+	+	+	+
b002571	+	+	+	+	+	+
b002575	+	+	+	+	+	+
b002580	+	+	+	+	+	+
b002583	+	+	+	+	+	+
b002586	+	+	+	+	+	+
b002588	+	+	+	+	+	+
b002590	-	+	+	+	+	+
b002593	+	+	+	+	+	+
b002599	+	+	+	+	+	+
b002600	+	+	+	+	+	+
b002601	+	+	+	+	+	+
b002609	+	+	+	+	+	+
b002614	+	+	+	+	+	+
b002617	+	+	+	+	+	+
b002624	+	+	+	+	+	+
b002630	+	+	+	+	+	+
b002631	+	+	+	+	+	+
b002637	+	+	+	+	+	+
b002638	+	+	+	+	+	+
b002658	+	+	+	+	+	+
b002660	+	+	+	+	+	+
b002775	+	+	+	+	+	+
b002776	+	+	+	+	+	+
b002780	+	+	+	+	+	+
b002781	+	+	+	+	+	+
b002782	+	+	+	+	+	+
b002785	+	+	+	+	+	+
b002790	+	+	+	+	+	+
b002797	+	+	+	+	+	+
b002807	+	+	+	+	+	+
b002809	+	+	+	+	+	+
b002811	+	+	+	+	+	+
b002816	+	+	+	+	+	+
b002819	+	+	+	+	+	+
b002820	+	+	+	+	+	+

b002825	+	+	+	+	+	+
b002827	+	+	+	+	+	+
b002831	-	+	+	-	+	+
b002832	+	+	+	+	+	+
b002835	+	+	+	+	+	+
b002836	+	+	+	+	+	+
b002839	+	+	+	+	+	+
b002840	+	+	+	+	+	+
b002844	+	+	+	+	+	+
b002847	+	+	+	+	+	+
b002856	+	+	+	+	+	+
b002857	+	+	+	+	+	+
b002861	+	+	+	+	+	+
b002866	+	+	+	+	+	+
b002873	+	+	+	+	+	+
b002875	+	+	+	+	+	+
b002876	+	+	+	+	+	+
b002877	+	+	+	+	+	+
b002885	+	+	+	+	+	+
b002887	+	+	+	+	+	+
b002890	+	+	+	+	+	+
b002893	+	+	-	+	+	+
b002898	+	+	+	+	+	+
b002906	+	+	+	+	+	+
b003049	-	-	+	-	-	+
b003052	+	+	+	+	+	+
b003053	-	+	+	+	+	+
b003056	+	+	+	+	+	+
b003064	+	+	+	+	+	+
b003065	+	+	+	+	+	+
b003068	+	+	+	+	+	+
b003075	+	+	+	+	+	+
b003076	-	+	+	+	+	+
b003080	+	+	+	+	+	+
b003082	+	+	+	+	+	+
b003137	-	+	+	+	+	+
b003144	+	+	+	+	+	+
b003149	+	+	+	+	+	+
b003152	+	+	+	+	+	+
b003153	+	+	+	+	+	+
b003159	+	+	-	+	+	+
b003168	+	+	+	+	+	+
b003172	+	+	+	+	+	+
b003177	+	+	+	+	+	+
b003190	+	+	+	+	+	+
b003194	-	+	+	+	+	+

Table 6C: Cocktail Host Range

		CK000125	CK000512
Host Range % MDR (n=95; subset of n=284)	CF n=49	95.9	100
	NCFB n=9	100	100
	PIHP n=37	91.9	100
	Total HR n=95	94.7	100
Host Range % Total (n=284)	CF n=111	87.4	92.8
	NCFB n=85	92.9	94.1
	PIHP n=88	95.5	100
	Total HR n=284	91.5	95.4

Example 19: Off-target plaquing *P. aeruginosa* cocktail phage assay

[00358] As shown on **Table** 7, *P. aeruginosa* cocktail phage did not exhibit off-target plaquing. *P. aeruginosa* cocktail phage was plaqued on b2631 or b1121 in addition to b1233/PAO1 because not all phage infected this bacterial strain. *P. aeruginosa* cocktails CK000511 and CK000512 (PACK512); constitutive phage p1835e002, p1106e003, p1772e005, p2131e002, p1194, p1695, and p4430; and positive control phage were plaqued on off-target ESKAPE species. No off target plaquing was observed from any of the phage tested, as noted by (-). As detailed on **Table** 7, data acquired showed that phages only hit (+) *P. aeruginosa*.

Table 7: Off-target plaquing phage assay

		Bacterial Strains						
		S. aureus	*K. pneumoniae*	*P. aeruginosa*	*E. faecium*	*E. cloacae*	*A. baumanii*	*S. epidermidis*
		b3321 ATCC 12600	b3432 ATCC 13883	b2631/b1121 b1233 (PAO1)	b3434 ATCC 19434	b3433 ATCC 13047	b1212 ATCC 19606	b3431 ATCC 19606
Phage	Cocktail 511	-	-	+(b2631) +(b1233)	-	-	-	-
	Cocktail 512 (PACK512)	-	-	+(b2631) +(b1233)	-	-	-	-
	p1835e002	-	-	+(b2631) +(b1233)	-	-	-	-
	p1106e003	-	-	+(b2631) +(b1233)	-	-	-	-
	p1772e005	-	-	+(b2631)	-	-	-	-
	p2131e002	-	-	+(b2631)	-	-	-	-
	p1194	-	-	+(b2631) +(b1233)	-	-	-	-
	p1695	-	-	+(b1121) +(b1233)	-	-	-	-
	p4430	-	-	+(b2631) +(b1233)	-	-	-	-
	Positive control phage	+ p5570	+ p5179	+(b1233) p5724	+ p5722	+ p5723	N/A	+ PhageK

Example 20: *P. aeruginosa* cocktail is effective against *P. aeruginosa* respiratory/Cystic fibrosis isolates

[00359] ***Comparison of CRISPR-Phage and wild-type phage***

Preparation of challenge inoculum

[00360] Bacterial isolates, tobramycin MICs and challenge inoculum are described in Table 8. *Pseudomonas aeruginosa* isolate b1121 was used for this study. A loopful of the bacterial stock was scraped from the surface of a frozen vial of culture and streaked for isolation on several TSA plates. After 16h of growth at 37°C, the inoculum was removed from the plate, and suspended into PBS, pH 7.2 (Gibco 20012027) and adjusted to an $OD650_{nm}$ of 1.0 ± 0.3. Two cohorts of animals were challenged in the same study with independently prepared inocula.

Table 8: Bacterial strains

Isolate	Source	TOB MIC (µg/mL)	Challenge inoculum (log_{10} CFU per 0.05 mL)
b1121	Respiratory	0.5	8.14/8.20
b2631	CF isolate	0.5	7.21/7.27
b3144	CF isolate	2.0	8.04/7.96

CF, cystic fibrosis; CFU, colony-forming units; MIC, minimum inhibitory concentration; TOB, tobramycin.

Treatment of mice in an acute lower respiratory infection model (LRTI)

[00361] Tobramycin (75 mg/kg/day, HED 6 mg/kg/day) was tested as a comparator. Tobramycin sulfate (Xgen, Lot no. AZ1240B) was prepared in dH_2O, and administered subcutaneously in 0.2 mL. Treatment was initiated 1h post infection and continued twice daily (BID) at 12-hour intervals for a total of 4 doses. Tobramycin was prepared fresh daily and stored at 4°C between dosing. Individual bacteriophages were diluted to 4.25E+09 PFU/mL in PBS, pH 7.4 such that the final concentration of each individual phage was 10.7 Log10 PFU/dose. Phages were delivered under anesthesia intranasally 2h post-challenge. Additional doses were administered at 8, 24 and 32h post-challenge. Animals were randomized at the time of treatment and separated into two treatment groups. In both cohorts, animals were treated with p1772WT or p1772FC. Tobramycin and PBS were included as controls in both groups.

Murine pneumonia model

[00362] Specific pathogen-free 7-8-week-old female C57BL/6J mice (Jackson Laboratory, Bar Harbor Maine) were anesthetized with 3% isoflurane and maintained with oxygen at 3 liters/min before inoculation into both nares with 0.050 mL of *P. aeruginosa* suspension b1121. Mice were placed into the cage in a supine position and allowed to recover from anesthesia. At 24 and 48h post-challenge, animals were euthanized with CO_2 asphyxiation, lungs were removed aseptically and placed into homogenizing tubes. Moribund animals were humanely euthanized and counted as a mortality. High dose group determined by MFD (max feasible dose; targeting $10^{10\text{-}11}$ PFU/mL for highest strain). Necropsy for gross observations and standard tissue panel for histopathology; second lung lobe can be used for PD (PCR).

CFU determination in tissue

[00363] Lungs were harvested into soft tissue homogenizing tubes containing 1.4 mm ceramic beads (VWR 10158-610), and 1 mL PBS, pH7.4 (Gibco 10010023). Tissues were homogenized for 20s, followed by a 10s rest, and an additional 20s homogenization. Homogenates

were serially diluted 1:100 into 0.9% sterile saline (BBL, 221819) and plated on trypticase soy agar (TSA) plates for CFU enumeration using spiral plate methodology. CFU were determined following 20-22h incubation at 37°C. Bacterial counts were expressed as Log_{10} CFU per gram of tissue and data from both studies were combined for analyses.

[00364] **Fig. 18E** shows the efficacy of CRISPR phage p1772FC (p1772e005)as compared to wild-type phage.

Comparison of phage cocktails and individual phage

[00365] *P. aeruginosa* isolates b1121, b2631 or b3144 were used for these studies. *P. aeruginosa* suspension isolates were prepared for challenge. *P. aeruginosa* b3144 was diluted 1:3 in PBS, pH 7.2, and *P. aeruginosa* b2631 was diluted 1:10 in PBS. Isolate b1121 was not diluted after standardizing to OD650nm=1.0.

[00366] Tobramycin treatment was prepared and dosed as described in **Fig. 18A**. The animals were dosed BID at 12-hour intervals for a total of 3 doses. Treatment controls included tobramycin, tobramycin plus PACK512, and PBS. Cocktail 512, also referred to as PACK512, (described in Table 6A) was diluted to the maximum concentration available based on phage titer and EU/mL, and delivered under anesthesia intranasally 2h post-challenge. Additional doses were administered at 8, 24h post-challenge. Animals were randomized at the time of treatment and separated into two treatment groups. In cohort one, animals were treated with the cocktail and individual phages. In cohort two, animals were treated with PACK512. Tobramycin, tobramycin plus PACK512 and PBS were included in both cohorts, and data from both studies were combined for analyses.

[00367] Specific pathogen-free 7-8-week-old female C57BL/6J mice (Jackson Laboratory, Bar Harbor Maine) were anesthetized with 3% isoflurane and maintained with oxygen at 3 liters/min before inoculation into both nares with 0.050 mL of the P. aeruginosa suspension. Mice were placed into the cage in a supine position and allowed to recover from anesthesia. During recovery, cages were placed on a heating pad at 105°F until animals were fully awake and ambulatory.

[00368] At 24 and 48h post-challenge with P. aeruginosa suspension, lungs were harvested as described above, except that following serial dilution, homogenates were plated on *Pseudomonas* inhibition agar (PIA) plates for CFU enumeration using spiral plate methodology. CFU were determined for each animal following 16-22h incubation at 37°C. Bacterial counts were expressed as Log10 CFU per gram of tissue, and data were analyzed using t-tests, Mann-Whitney tests, analysis of variance (ANOVA), or log-rank test. All statistical analyses were performed using GraphPad Prism version 8.0. P values of <0.05 were considered statistically significant.

[00369] Treatment with the cocktail and the cocktail in combination with tobramycin resulted in levels of *Pseudomonas aeruginosa* below the level of detection for all 3 strains tested, as depicted in **Figs. 18B-18D**. Further, treatment with the cocktail resulted in a significant decrease in the detected CFU compared to treatment with tobramycin alone.

[00370] In similar assays described above, phage cocktail ck00125 was also tested. **Fig. 19A** illustrates the assay design for testing in vivo efficacy of ck00125 (CK125) in the acute LRTI model. **Figs. 19B-19D** demonstrate statistically significant reduction in bacterial load with CK125 alone, as early as at 24 hours post challenge and in all three strains of *Pseudomonas aeruginosa* tested. In combination of Tobramycin, the bacteria levels were below detection level. Therefore, an almost complete removal of bacteria was seen with the cocktail, similar to that observed with the ck00512 (PACK512) cocktail.

Example 21: Comparison of efficacy of cocktail over individual phages

[00371] *Materials and Methods:*

Preparation of challenge inoculum

[00372] *Pseudomonas aeruginosa* isolates b1121, b2631 or b3144 were used for these studies. Isolates were prepared for challenge as described above, with the following modifications. *P. aeruginosa* b3144 was diluted 1:3 in PBS, pH 7.2, and *P. aeruginosa* b2631 was diluted 1:10 in PBS. Isolate b1121 was not diluted after standardizing to OD650nm=1.0.

Treatment

[00373] Tobramycin was prepared and dosed as described above, except that animals were dosed BID at 12-hour intervals for a total of 3 doses. Individual bacteriophages and cocktail 512 (PACK512) were diluted to the maximum concentration available based on phage titer and EU/mL (table 2). The concentration of phage in both individual and cocktails was the same. Phages were delivered under anesthesia intranasally 2h post-challenge. Additional doses were administered at 8, 24h post-challenge. Animals were randomized at the time of treatment and separated into two treatment groups. In cohort one, animals were treated with the cocktail and individual phages. In cohort two, animals were treated with PACK512. Tobramycin, tobramycin plus PACK512 and PBS were included in both cohorts, and data from both studies were combined for analyses.

Murine pneumonia model

[00374] Specific pathogen-free 7-8-week-old female C57BL/6J mice (Jackson Laboratory, Bar Harbor Maine) were anesthetized with 3% isoflurane and maintained with oxygen at 3 liters/min before inoculation into both nares with 0.050 mL of the *P. aeruginosa* suspension. Mice were placed into the cage in a supine position and allowed to recover from anesthesia. During

recovery, cages were placed on a heating pad at 105°F until animals were fully awake and ambulatory

[00375] In an effort to understand the relative benefits of the cocktail PACK512 (also referred to as ck00512) over individual engineered phages, a comparison was performed between the phages p1106FC, p1772FC, P1835FC, p2131FC, p1685WT, p4430WT and cocktail 512 (PACK512), with or without Tobramycin. Experimental set up is shown in **FIG. 18F**. Results shown in **Figs. 18G, 18H** and **18I** for P. *aeruginosa* b2631, b3144 and p1121, respectively, indicate that PACK 512 exhibits superior efficacy relative to individual phage in the Acute LRTI Model, both with and without Tobramycin treatment.

CFU determination in tissue

[00376] Lungs were harvested as described above, except that following serial dilution, homogenates were plated on *Pseudomonas* inhibition agar (PIA) plates for CFU enumeration using spiral plate methodology. CFU were determined for each animal following 16-22h incubation at 37°C. Bacterial counts were expressed as Log_{10} CFU per gram of tissue.

Statistical analyses

[00377] Data were analyzed using *t*-tests, Mann-Whitney tests, analysis of variance (ANOVA) or log-rank test were appropriate. All statistical analyses were performed using GraphPad Prism version 8.0. P values of <0.05 were considered statistically significant.

Example 21: Effect of cocktail on *Pseudomonas aeruginosa* biofilms

In this example effect of a phage cocktail on *Pseudomonas* biofilms was tested. The assay setup is represented in **Fig. 20A**. As shown in **Fig. 20B**, cocktail CK125 exhibits anti-biofilm activity against pre-formed biofilms as indicated by high levels of bacterial inhibition at low MOI, at 24 and 48 hours of biofilm treatment with the cocktail, and was effective in multiple strains of *Pseudomonas*. PACK512 cocktail also exhibits inhibitory activity against pre-formed (**Fig. 22**) and newly forming biofilms (MBIC) and planktonic bacteria (MIC) from all three key strains (b1121, b2631, b3144).

Example 22: Bactericidal activity of cocktails in presence of mucin

[00378] Mucin is a glycoprotein abundant in mucus from healthy as well as diseased human subjects. Cystic fibrosis is characterized by hyperproduction of mucus by airway and lung epithelia which primarily form a barrier for access by therapeutic agents to the cells. In this experiment, airway epithelial tissue derived from healthy human was cultured for 1 month, and mucin was measured prior to subjecting the culture to bacterial infection for 30 minutes and then chasing with phage cocktail. After incubation for 19.5 hours the sample were collected and bacterial and phage loads were determined. As shown in **Figs. 22** and **23**, phage cocktail ck125 and PACK512

(respectively) successfully reduced bacterial burden in the cell culture infected with a *Pseudomonas aeruginosa* b1121 from respiratory isolate (left) and a b2631 from a CF patient isolate (right). Mucin levels at time of bacterial addition, as detected by Alcian Blue assay, were 1.3 ± 0.09 mg/mL (GEOMEAN of n=3 'T=0 harvest' transwells and n=2 sample dilutions per transwell).

Example 23. Persistence of phage in vivo

[00379] In an attempt to understand the time course of phage persistence in vivo, phage levels were determined in the LRTI mouse model over time. It was observed that the level of each phage was high despite bacterial clearance. An exemplary result is shown in **Fig. 24**, demonstrating presence of the phage quantitatively both by plaque assay and qPCR determination of individual phage copy numbers at 32h post treatment. This indicates that the phages are not readily cleared out of the system.

[00380] Phage genome copy (GC) levels per dose were determined by qPCR, multiplied by number of doses given and divided by GEOMEAN of lung weight within each treatment group.

[00381] PFU per dose was estimated based on the PFU/mL titers of NME phage stocks and the expected PFU/dose in formulated cocktail, then divided by GEOMEAN of lung weight within each treatment group.

[00382] Sequence Table

Gene	SEQ ID	Sequence (5'-3')
Cas3	75	ATGGACGCGGAGGCTAGCGATACTCACTTTTTTGCTCACTCCACCTTAAAGGCAGATCGCAGCGATTGG CAGCCTCTGGTCGAGCATCTACAGGCTGTTGCCCGTTTGGCAGGAGAGAAGGCTGCCTTCTTCGGCGGC GGTGAATTAGCTGCTCTTGCTGGTCTGTTGCATGACTTGGGTAAATACACTGACGAGTTTCAGCGGCGT ATTGCGGGTGATGCCATCCGTGTCGATCACTCTACTCGCGGGGCCATACTGGCGGTAGAACGCTATGGC GCGCTAGGTCAATTGCTAGCCTACGGCATCGCTGGCCACCATGCCGGGTTGGCCAATGGCCGCGAGGCT GGTGAGCGAACTGCCTTGGTCGACCGCCTGAAAGGGGTTGGGCTGCCACGGTTATTGGAGGGGTGGT GCGTGGAAATCGTGCTACCCGAGCGCCTTCAACCACCGCCACTAAAAGCGCGCCTGGAAAGAGGTTTCT TTCAGTTGGCCTTTCTTGGCCGGATGCTCTTTTCCTGCTTGGTTGATGCGGATTATCTAGATACCGAAGCC TTCTACCACCGCGTCGAAGGACGGCGCTCCCTTCGCGAGCAAGCGCGGCCGACCTTGGCCGAGTTACGC GCAGCCCTTGATCGGCATCTGACTGAGTTCAAGGGAGATACGCCGGTCAACCGCGTTCGCGGGGAGAT ATTGGCCGGCGTGCGCGGCAAGGCGAGCGAACTTCCCGGGCTGTTTTCTCTCACAGTGCCCACAGGAG GCGGCAAGACCCTGGCCTCTCTGGCTTTCGCCCTGGATCACGCTCTAGCTCATGGGCTGCGCCGGGTGA TCTACGTGATTCCCTTCACTAGCATCGTCGAGCAGAACGCTGCGGTATTCCGTCGTGCACTCGGGGCCTT AGGCGAAGAGGCGGTGCTGGAGCATCACAGCGCCTTCGTTGATGACCGCCGGCAGAGCCTGGAGGCC AAGAAGAAACTGAACCTAGCGATGGAGAACTGGGACGCGCCTATCGTGGTGACCACTGCAGTGCAGTT CTTCGAAAGCCTGTTTGCCGACCGTCCAGCCCAGTGCCGCAAGCTACACAACATCGCCGGCAGCGTGGT GATTCTTGACGAGGCACAGACCCTACCGCTCAAGCTGTTGCGGCCCTGCGTTGCCGCCCTTGATGAACT GGCGCTCAACTACCGTTGTAGCCCAGTTCTCTGTACTGCCACGCAGCCAGCGCTTCAATCGCCGGATTTC ATCGGTGGGCTGCAGGACGTACGTGAGCTGGCGCCCGAGCCGCAGCGGCTGTTCCGGGAGTTGGTGC GGGTACGAATACGGACATTGGGCCCGCTCGAAGATGCGGCCTTGACTGAGCAGATCGCCAGGCGTGAA CAAGTGCTGTGCATCGTCAACAATCGACGCCAGGCCCGTGCGCTCTATGAGTCGCTTGCCGAGTTGCCC GGTGCCCGCCATCTCACCACCCTGATGTGCGCCAAGCACCGTAGCAGCGTGCTGGCCGAGGTGCGCCA GATGCTCAAAAAGGGGGAGCCCTGTCGCCTGGTGGCCACCTCGCTGATCGAGGCCGGTGTGGATGTGG ATTTTCCCGTGGTACTGCGTGCCGAGGCTGGATTGGATTCCATCGCCCAGGCCGCGGGACGCTGCAATC GCGAAGGCAAGCGGCCGCTGGCCGAAAGCGAGGTGCTGGTGTTCGCCGCGGCCAATTCTGACTGGGC GCCACCCGAGGAACTCAAGCAGTTCGCCCAGGCCGCCCGCGAAGTGATGCGCCTGCACCCGGATGATT GCCTGTCCATGGCGGCCATCGAGCGGTATTTTCGCATACTGTACTGGCAGAAGGGCGCGGAGGAGTTG GATGCGGGTAACCTGCTCGGCCTGATTGAGAGAGGCCGGCTCGATGGCCTGCCCTACGAGACTTTGGC CACCAAGTTCCGCATGATCGACAGCCTTCAACTGCCGGTGATCATCCCATTTGATGACGAGGCCAGAGC AGCCCTGCGCGAGCTGGAGTTCGCCGACGGCTGCGCCGCCATCGCCCGTCGCCTGCAGCCATATCTGGT GCAGATGCCACGCAAGGGTTATCAGGCATTGCGGGAAGCCGGTGCGATCCAGGCGGCGGCAGGTACG CGTTATGGTGAGCAGTTTATGGCGTTGGTCAACCCTGATCTGTATCACCACCAATTCGGGTTGCACTGGG ATAATCCGGCCTTTGTCAGCAGCGAGCGGCTATGTTGGTAG
Cas5c	76	ATGGCCTACGGAATTCGCTTAATGGTCTGGGGCGAGCGTGCCTGCTTCACCCGCCCGGAAATGAAGGTG GAACGCGTCTCTTACGATGCGATCACGCCGTCCGCCGCGCGCGGCATTCTCGAGGCTATCCACTGGAAG CCGGCGATTCGCTGGGTGGTGGATCGCATTCAAGTGCTTAAGCCGATCCGCTTCGAATCCATCCGGCGC AACGAGGTCGGCGGCAAGCTGTCCGCTGTCAGCGTCGGTAAGGCAATGAAGGCCGGGCGTACTAATG GTCTGGTGAATCTGGTCGAGGAGGATCGCCAGCAGCGCGCGACTACTCTGCTGCGCGATGTCTCCTATG TCATCGAGGCGCATTTCGAGATGACTGACAGGGCTGGCGCCGACGATACGGTGGGCAAGCATCTGGAT ATCTTCAACCGTCGCGCACGGAAGGGGCAGTGCTTCCATACACCCTGCCTAGGCGTGCGCGAGTTTCCG GCCAGTTTTCGGTTGCTGGAAGAGGGCAGTGCCGAGCCTGAAGTCGATGCCTTTCTGCGCGGCGAGCG TGATCTGGGCTGGATGCTGCATGACATTGACTTCGCCGATGGCATGACCCCGCACTTCTTCCGTGCCCTG ATGCGCGATGGGCTGATCGAGGTGCCGGCCTTCAGGGCGGCAGAGGACAAGGCATGA
Cas8c	77	ATGATCCTTTCGGCCCTCAATGACTATTATCAGCGACTGCTGGAGCGGGGTGAAGCGAATATCTCACCCT TCGGCTACAGCCAAGAAAAGATCAGTTACGCCCTGCTGCTGTCCGCACAAGGAGAGTTGCTGGACGTGC AGGACATTCGCTTGCTCTCTGGCAAGAAGCCTCAACCCAGGCTTATGAGTGTGCCGCAGCCGGAGAAGC GCACCTCGGGCATCAAGTCCAACGTACTGTGGGACAAGACCAGCTATGTGCTGGGTGTTAGTGCCAAG GGCGGAGAGCGTACTCAGCAGGAGCACGAGTCCTTCAAGACGCTGCACCGGCAGATCTTGGTTGGGGA AGGCGACCCCGGTCTGCAGGCCTTGCTCCAGTTCCTCGACTGTTGGCAGCCGGAGCAGTTCAAGCCCCC GCTGTTCAGCGAAGCAATGCTCGACAGCAACTTAGTGTTCCGCCTAGACGGCCAACAACGCTATCTGCA

		CGAGACTCCGGCGGCCCTGGCGTTGCGTACCCGGCTGTTGGCCGACGGCGACAGCCGCGAGGGGCTGT GCCTAGTCTGCGGCCAACGTCAGCCGTTGGCGCGCCTGCATCCAGCGGTCAAGGGCGTCAATGGTGCCC AGAGTTCGGGGGCTTCCATCGTCTCCTTCAACCTCGACGCTTTTTCCTCCTACGGCAAGAGCCAGGGGGA AAATGCTCCGGTCTCCGAACAGGCCGCCTTTGCCTACACCACGGTGCTCAACCATTTGTTGCGTCGCGAC GAGCACAACCGCCAGCGCCTGCAGATTGGCGACGCGAGTGTGGTGTTCTGGGCGCAGGCGGATACTCC TGCTCAGGTGGCCGCCGCCGAGTCGACCTTCTGGAACCTGCTGGAGCCACCCGCAGATGATGGTCAGG AAGCGGAAAAGCTGCGCGGCGTGCTGGATGCTGTGGCCACGGGGCGGCCCTTGCATGAGCTCGACTCG CTAATGGAGGAAGGTACCCGCATTTTTGTGTTAGGGCTGGCGCCCAATACCTCGCGACTGTCCATTCGG TTCTGGGCAGTCGATAGCCTTGCGGTATTCACCCAGCATCTGGCCGAGCATTTCCGGGATATGCACCTTG AGCCTCTGCCCTGGAAGACGGAGCCGGCCATCTGGCGCTTGCTCTATGCTACCGCGCCCAGTCGTGACG GCAGAGCCAAGACCGAAGACGTACTCCCACAACTGGCCGGTGAAATGACCCGCGCCATCCTGACCGGC AGCCGCTATCCGCGCAGTTTGCTAGCCAACCTGATCATGCGCATGCGTGCCGACGGCGACGTCTCTGGC ATACGCGTCGCGCTGTGCAAGGCCGTGCTCGCTCGCGAGGCACGCCTGAGCGGCAAAATTCACCAAGA GGAGCTACCTATGAGTCTCGACAAGGACGCCAGCAACCCCGGCTATCGCTTGGGGAGGCTGTTCGCCGT GTTGGAAGGCGCCCAGCGCGCAGCCCTGGGCGACAGGGTCAATGCCACTATCCGTGACCGCTACTACG GTGCCGCGTCCAGCACGCCAGCCACGGTTTTCCCGATACTGCTGCGCAACACACAAAACCACTTGGCCA AGCTGCGCAAGGAGAAGCCCGGACTAGCAGTGAACCTAGAGCGCGATATAGGCGAAATCATTGACGGT ATGCAGAGCCAATTCCCGCGTTGCCTGCGCCTGGAGGACCAGGGACGCTTTGCTATTGGTTACTACCAA CAGGCCCAGGCCCGTTTCAACCGTGGCCCCGATTCCGTCGAGTAA
Cas7c	78	ATGACCGCCATCTCCAACCGCTACGAGTTCGTTTACCTCTTTGATGTCAGCAATGGCAATCCCAATGGCG ACCCGGATGCTGGCAACATGCCGCGTCTCGATCCGGAAACCAACCAGGGGTTGGTCACTGACGTTTGCC TCAAGCGCAAGATCCGCAACTACGTCAGCCTGGAGCAGGAAAGTGCCCCCGGCTATGCCATCTATATGC AGGAAAAATCCGTGCTGAATAACCAGCACAAACAGGCCTACGAGGCGCTCGGTATCGAGTCAGAGGCA AAGAAACTGCCCAAGGACGAAGCCAAGGCGCGCGAACTGACCTCTTGGATGTGCAAGAACTTCTTCGA TGTGCGTGCTTTCGGGGCGGTGATGACCACCGAGATTAATGCCGGCCAGGTGCGTGGACCGATCCAAC TGGCATTCGCCACGTCTATCGACCCGGTATTGCCTATGGAGGTATCCATCACCCGCATGGCGGTGACTAA CGAAAAGGATTTGGAGAAGGAACGCACCATGGGACGCAAGCACATCGTGCCTTACGGCTTGTACCGCG CCCATGGTTTCATCTCTGCCAAGTTGGCCGAGCGAACCGGCTTTTCCGACGACGACTTGGAACTGCTATG GCGCGCTTTGGCCAATATGTTCGAACACGACCGCTCGGCGGCACGTGGCGAGATGGCAGCGCGCAAGT TGATCGTCTTCAAGCATGAGCATGCCATGGGCAATGCACCCGCCCATGTGCTGTTCGGCAGCGTTAAGG TCGAGCGAGTCGAGGGGGACGCAGTTACACCAGCACGCGGTTTCCAGGATTACCGTGTCAGCATCGAT GCGGAAGCTCTGCCTCAGGGCGTGAGCGTGCGCGAGTACCTCTAG

Protein	SEQ ID	Sequence
Cas3	79	MDAEASDTHFFAHSTLKADRSDWQPLVEHLQAVARLAGEKAAFFGGGELAALAGLLHDLGKYTDEFQRRI AGDAIRVDHSTRGAILAVERYGALGQLLAYGIAGHHAGLANGREAGERTALVDRLKGVGLPRLLEGWCVEI VLPERLQPPPLKARLERGFFQLAFLGRMLFSCLVDADYLDTEAFYHRVEGRRSLREQARPTLAELRAALDRH LTEFKGDTPVNRVRGEILAGVRGKASELPGLFSLTVPTGGGKTLASLAFALDHALAHGLRRVIYVIPFTSIVEQ NAAVFRRALGALGEEAVLEHHSAFVDDRRQSLEAKKKLNLAMENWDAPIVVTTAVQFFESLFADRPAQCR KLHNIAGSVVILDEAQTLPLKLLRPCVAALDELALNYRCSPVLCTATQPALQSPDFIGGLQDVRELAPEPQRL FRELVRVRIRTLGPLEDAALTEQIARREQVLCIVNNRRQARALYESLAELPGARHLTTLMCAKHRSSVLAEVR QMLKKGEPCRLVATSLIEAGVDVDFPVVLRAEAGLDSIAQAAGRCNREGKRPLAESEVLVFAAANSDWAP PEELKQFAQAAREVMRLHPDDCLSMAAIERYFRILYWQKGAEELDAGNLLGLIERGRLDGLPYETLATKFR MIDSLQLPVIIPFDDEARAALRELEFADGCAAIARRLQPYLVQMPRKGYQALREAGAIQAAAGTRYGEQFM ALVNPDLYHHQFGLHWDNPAFVSSERLCW*
Cas5c	80	MAYGIRLMVWGERACFTRPEMKVERVSYDAITPSAARGILEAIHWKPAIRWVVDRIQVLKPIRFESIRRNE VGGKLSAVSVGKAMKAGRTNGLVNLVEEDRQQRATTLLRDVSYVIEAHFEMTDRAGADDTVGKHLDIFN RRARKGQCFHTPCLGVREFPASFRLLEEGSAEPEVDAFLRGERDLGWMLHDIDFADGMTPHFFRALMRD GLIEVPAFRAAEDKA*
Cas8c	81	MILSALNDYYQRLLERGEANISPFGYSQEKISYALLLSAQGELLDVQDIRLLSGKKPQPRLMSVPQPEKRTSGI KSNVLWDKTSYVLGVSAKGGERTQQEHESFKTLHRQILVGEGDPGLQALLQFLDCWQPEQFKPPLFSEAM

		LDSNLVFRLDGQQRYLHETPAALALRTRLLADGDSREGLCLVCGQRQPLARLHPAVKGVNGAQSSGASIVS FNLDAFSSYGKSQGENAPVSEQAAFAYTTVLNHLLRRDEHNRQRLQIGDASVVFWAQADTPAQVAAAES TFWNLLEPPADDGQEAEKLRGVLDAVATGRPLHELDSLMEEGTRIFVLGLAPNTSRLSIRFWAVDSLAVFT QHLAEHFRDMHLEPLPWKTEPAIWRLLYATAPSRDGRAKTEDVLPQLAGEMTRAILTGSRYPRSLLANLIM RMRADGDVSGIRVALCKAVLAREARLSGKIHQEELPMSLDKDASNPGYRLGRLFAVLEGAQRAALGDRVN ATIRDRYYGAASSTPATVFPILLRNTQNHLAKLRKEKPGLAVNLERDIGEIIDGMQSQFPRCLRLEDQGRFAI GYYQQAQARFNRGPDSVE*
Cas7c	82	MTAISNRYEFVYLFDVSNGNPNGDPDAGNMPRLDPETNQGLVTDVCLKRKIRNYVSLEQESAPGYAIYMQ EKSVLNNQHKQAYEALGIESEAKKLPKDEAKARELTSWMCKNFFDVRAFGAVMTTEINAGQVRGPIQLAF ATSIDPVLPMEVSITRMAVTNEKDLEKERTMGRKHIVPYGLYRAHGFISAKLAERTGFSDDDLELLWRALAN MFEHDRSAARGEMAARKLIVFKHEHAMGNAPAHVLFGSVKVERVEGDAVTPARGFQDYRVSIDAEALPQ GVSVREYL*

[00383] While preferred embodiments of the present disclosures have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosures. It should be understood that various alternatives to the embodiments of the disclosures described herein may be employed in practicing the disclosures. It is intended that the following claims define the scope of the disclosures and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array comprising one or more spacer sequences complementary to a target nucleotide sequence in a *Pseudomonas* species;

(b) a Cascade polypeptide; and

(c) a Cas3 polypeptide.

2. The bacteriophage of claim 1, wherein the CRISPR array comprises a promoter sequence having at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

3. The bacteriophage of claim 1 or claim 2, wherein the CRISPR array comprises a spacer sequence having at least 90% identity to any one of SEQ ID NOS: 88-116 or 31-74.

4. The bacteriophage of claim 1 or claim 2, wherein the bacteriophage is a modified p1106, p1835, p1772, or p2131 phage.

5. A bacteriophage composition comprising the bacteriophage of claim 1 or claim 2, further comprising a p1695wt bacteriophage and/or a p4430wt bacteriophage.

6. The bacteriophage of claim 1 or claim 2, wherein the Cascade polypeptide forms a Cascade complex of a Type I-C CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-A CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system.

7. The bacteriophage of claim 1 or claim 2, wherein the Cascade complex comprises:

(i) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system);

(ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system);

(iii) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system);

(iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system);

(v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); or

(vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system).

8. The bacteriophage of claim 1 or claim 2, wherein the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system).

9. The bacteriophage of claim 1 or claim 2, wherein the Cas3 polypeptide comprises a sequence at least about 90% identical to SEQ ID NO: 79.

10. The bacteriophage of claim 1 or claim 2, wherein the bacteriophage infects multiple bacterial strains of the *Pseudomonas* species.

11. The bacteriophage of claim 1 or claim 2, wherein the bacteriophage comprises PhiKZvirus, PhiKMV virus, Brunyoghevirus, Samunavirus, Nankokuvirus, Abidjanvirus, Baikalvirus, Beetrevirus, Casadabanvirus, Citexvirus, Cystovirus, Detrevirus, Elvirus, Hollowayvirus, Kochitakasuvirus, Litunavirus, Luzseptimavirus, Nipunavirus, Pakpunavirus, Pamexvirus, Paundecimvirus, Phitrevirus, Primolicivirus, Septimatrevirus, Stubburvirus, Tertilicivirus, Yuavirus, Zicotriavirus or Pbunavirus, or a combination of two or more thereof.

12. A method of killing a *Pseudomonas* species, the method comprising introducing into the target bacterium the nucleic acid sequence encoding a Type I CRISPR-Cas system from the bacteriophage of claim 1 or claim 2, wherein the target nucleotide sequence is present in the *Pseudomonas* species.

13. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the individual the bacteriophage of claim 1 or claim 2, wherein the subject is infected with the *Pseudomonas* species.

14. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the individual a p1695wt bacteriophage and/or a p4430wt bacteriophage.

15. The method of claim 14, wherein the subject is infected with the *Pseudomonas* species.

16. The method of claim 13 or claim 14, wherein the disease or condition is a bacterial infection.

17. The method of claim 16, wherein the bacterial infection is associated with cystic fibrosis or non-cystic fibrosis bronchiectasis.

18. The method of claim 12, 13, or 15, wherein the *Pseudomonas* species is a drug resistant *Pseudomonas* species.

19. The method of claim 18, wherein the drug resistant *Pseudomonas* species is resistant to at least one antibiotic.

20. The method of claim 12, 13 or 15, wherein the *Pseudomonas* species is a multidrug resistant *Pseudomonas* species.

21. The method of claim 18, wherein the multi-drug resistant *Pseudomonas* species is resistant to at least one antibiotic.

22. The method of claim 19 or claim 21, wherein the antibiotic comprises a cephalosporin, a fluoroquinolone, a carbapenem, a colistin, an aminoglycoside, vancomycin, streptomycin, or methicillin.

23. The method of claim 12, 13 or 15, wherein the *Pseudomonas* species is *Pseudomonas aeruginosa.*

24. The method claim 12, 13 or 15, wherein the bacteriophage is an obligate lytic bacteriophage or a temperate bacteriophage that is rendered lytic.

25. The method of claim 24, wherein the *Pseudomonas* species is killed by lytic activity of the bacteriophage and/or activity of the CRISPR-Cas system.

26. The method of claim 24 or claim 25, wherein the lytic activity of the bacteriophage and the activity of the CRISPR-Cas system are synergistic.

27. A nucleic acid comprising SEQ ID NO: 83, or a sequence at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 83.

28. A nucleic acid comprising SEQ ID NO: 25, or a sequence at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 25.

29. A bacteriophage comprising the nucleic acid of claim 27 or claim 28.

30. A bacteriophage comprising at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to p1106e003, p1772e005, p1835e002, p2131e002, or two or more phage thereof, wherein the bacteriophage is a recombinant.

31. The bacteriophage of claim 29 or claim 30, comprising

(a) a CRISPR array;

(b) a Cascade polypeptide comprising one or more spacer sequences complementary to one or more target nucleotide sequence in a *Pseudomonas* species; and

(c) a Cas3 polypeptide.

32. The bacteriophage of claim 31, wherein the one or more spacer sequences comprise at least one of SEQ ID NOs: 12, 16, and 20.

33. A bacteriophage comprising a nucleic acid sequence encoding a Type I CRISPR-Cas system comprising:

(a) a CRISPR array comprising one or more spacer sequences complementary to one or more target nucleotide sequences in a *Pseudomonas* species, wherein the one or more spacer sequences comprise at least one of SEQ ID NOs: 12, 16, and 20;

(b) a Cascade polypeptide; and

(c) a Cas3 polypeptide.

34. The bacteriophage of claim 32 or claim 33, wherein the CRISPR array comprises SEQ ID NO: 12.

35. The bacteriophage of claim 32 or claim 33, wherein the CRISPR array comprises SEQ ID NO: 16.

36. The bacteriophage of claim 32 or claim 33, wherein the CRISPR array comprises SEQ ID NO: 20.

37. The bacteriophage of claim 32 or claim 33, comprising SEQ ID NOS: 12, 16, and 20.

38. The bacteriophage of any one of claims 31-37, wherein the CRISPR array comprises a promoter sequence having at least about 90% sequence identity to any one of SEQ ID NOs: 1-11.

39. The bacteriophage of any one of claims 31-38, wherein the Cascade polypeptide forms a Cascade complex of a Type I-C CRISPR-Cas system, a Type I-B CRISPR-Cas system, a Type I-A CRISPR-Cas system, a Type I-D CRISPR-Cas system, a Type I-E CRISPR-Cas system, or a Type I-F CRISPR-Cas system.

40. The bacteriophage of claim 39, wherein the Cascade complex comprises:

(i) a Cas5d polypeptide, a Cas8c polypeptide, and a Cas7 polypeptide (Type I-C CRISPR-Cas system);

(ii) a Cas6b polypeptide, a Cas8b polypeptide, a Cas7 polypeptide, and a Cas5 polypeptide (Type I-B CRISPR-Cas system);

(iii) a Cas7 polypeptide, a Cas8a1 polypeptide or a Cas8a2 polypeptide, a Cas5 polypeptide, a Csa5 polypeptide, and a Cas6a polypeptide, wherein the Cas3 polypeptide comprises a Cas3' polypeptide and a Cas3" polypeptide having no nuclease activity (Type I-A CRISPR-Cas system);

(iv) a Cas10d polypeptide, a Csc2 polypeptide, a Csc1 polypeptide, a Cas6d polypeptide (Type I-D CRISPR-Cas system);

(v) a Cse1 polypeptide, a Cse2 polypeptide, a Cas7 polypeptide, a Cas5 polypeptide, and a Cas6e polypeptide (Type I-E CRISPR-Cas system); or

(vi) a Csy1 polypeptide, a Csy2 polypeptide, a Csy3 polypeptide, and a Csy4 polypeptide (Type I-F CRISPR-Cas system).

41. The bacteriophage of claim 40, wherein the Cascade complex comprises a Cas5d polypeptide (optionally SEQ ID NO: 80), a Cas8c polypeptide (optionally SEQ ID NO: 81), and a Cas7 polypeptide (optionally SEQ ID NO: 82) (Type I-C CRISPR-Cas system).

42. The bacteriophage of any one of claims 29-41, comprising SEQ ID NO: 83, or a sequence at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 83.

43. The bacteriophage of any one of claims 29-42, comprising SEQ ID NO: 25, or a sequence at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 25.

44. The bacteriophage of any one of claims 29-43, wherein the bacteriophage comprises at least 85% or 90% identity to p1106e003, p1772e005, p1835e002, p2131e002, or two or more phage thereof.

45. The bacteriophage of any one of claims 29-44 comprising:

(a) a first bacteriophage comprising at least 80% sequence identity with p1106e003;

(b) a second bacteriophage comprising at least 80% sequence identity with p1835e002;

(c) a third bacteriophage comprising at least 80% sequence identity with p1772e005; and

(d) a fourth bacteriophage comprising at least 80% sequence identity with p2131e002.

46. The bacteriophage of claim 45, further comprising a fifth bacteriophage comprising at least 80% sequence identity with p1695.

47. The bacteriophage of claim 45, further comprising a fifth bacteriophage comprising at least 80% sequence identity with p4430.

48. The bacteriophage of claim 47, further comprising a sixth bacteriophage comprising at least 80% sequence identity with p1695.

49. A method of killing a *Pseudomonas* target bacterium, the method comprising administering to a subject in need thereof the nucleic acid of claim 27 or claim 28, or the bacteriophage of any one of claims 29-48.

50. A method of treating a disease or condition in a subject in need thereof, the method comprising administering to the subject the nucleic acid of claim 27 or claim 28, or the bacteriophage of any one of claims 29-48.

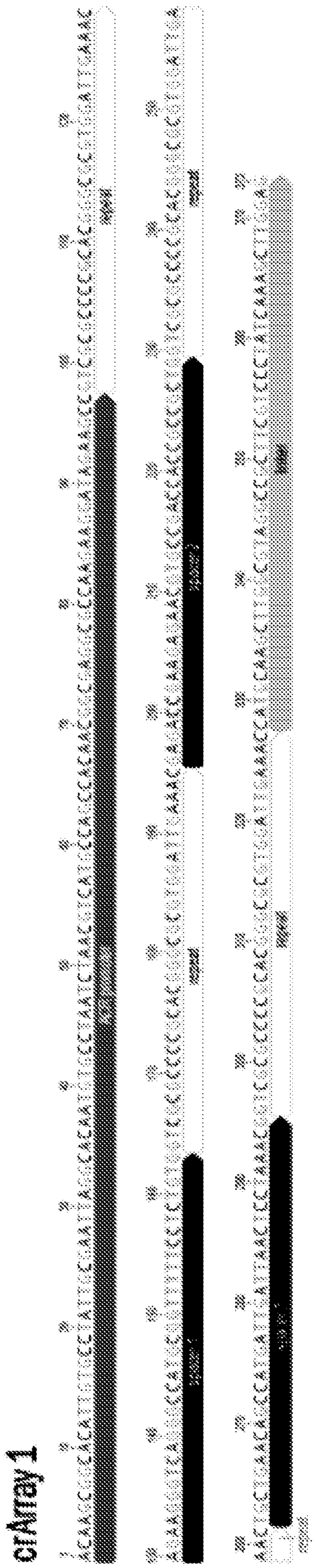


Fig. 1A

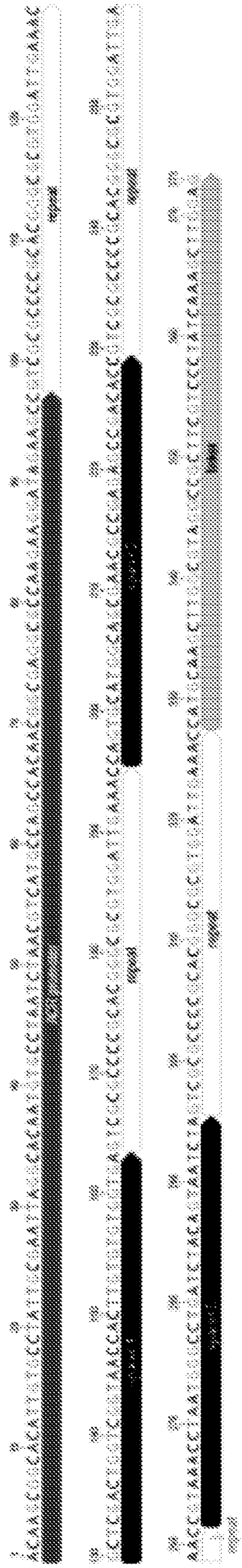


Fig. 1B

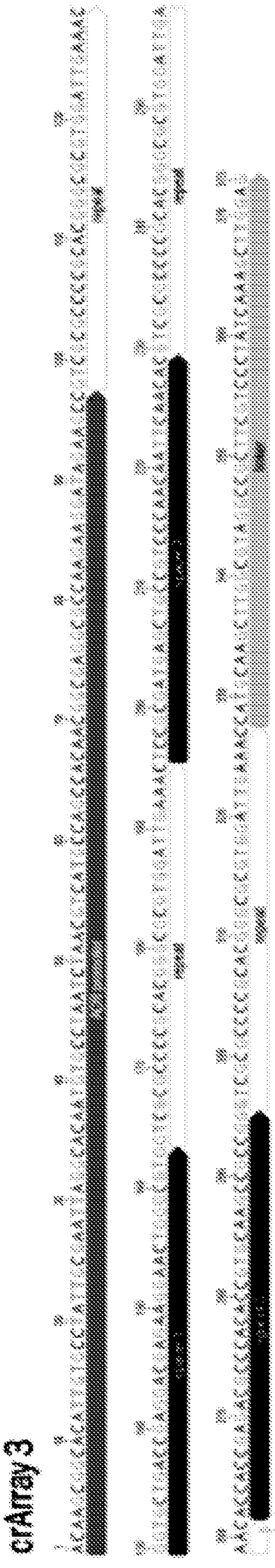


Fig. 1C

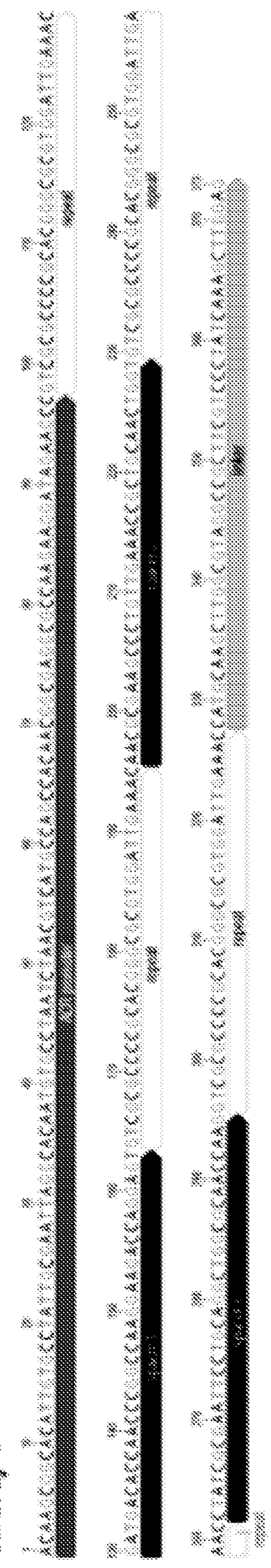


Fig. 1D

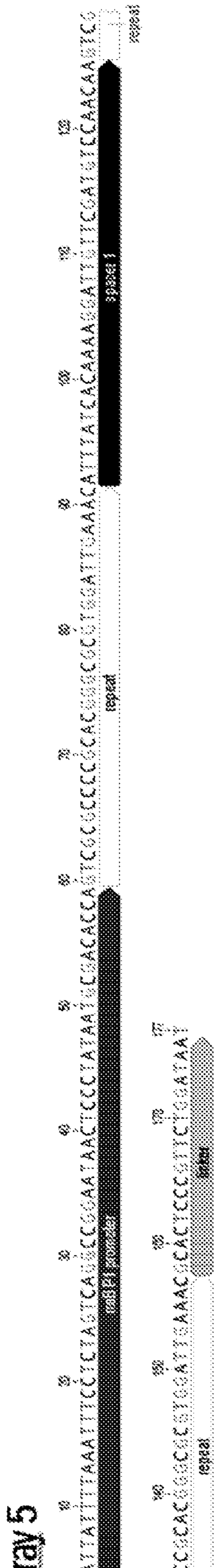


Fig. 1E

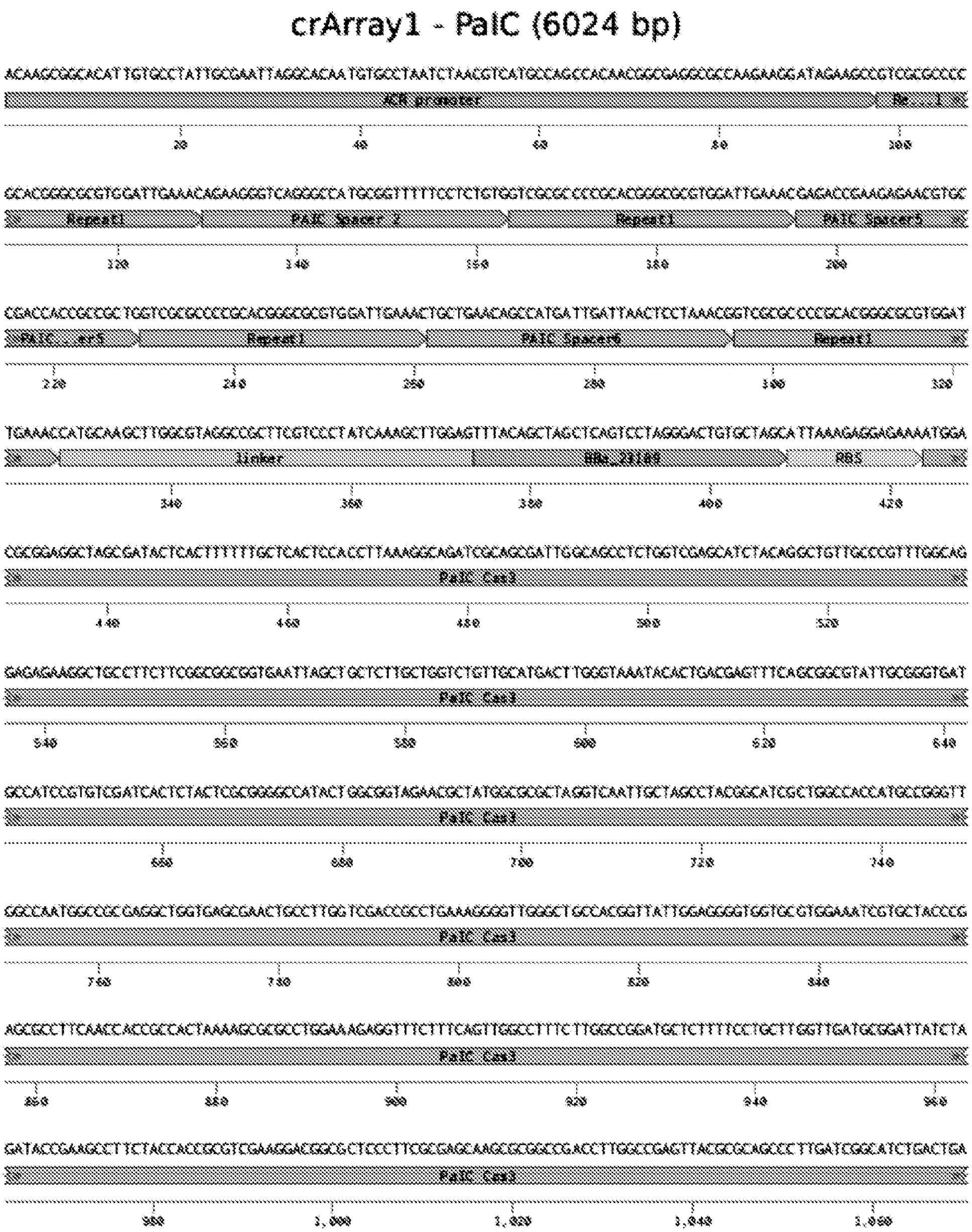

crArray1 - PaIC (6024 bp)
ACR promoter
Repeat1
PAIC Spacer 2
Repeat1
PAIC Spacer5
PAIC Spacer6
Repeat1
Linker
RBS
PaIC Cas3

Fig. 1F

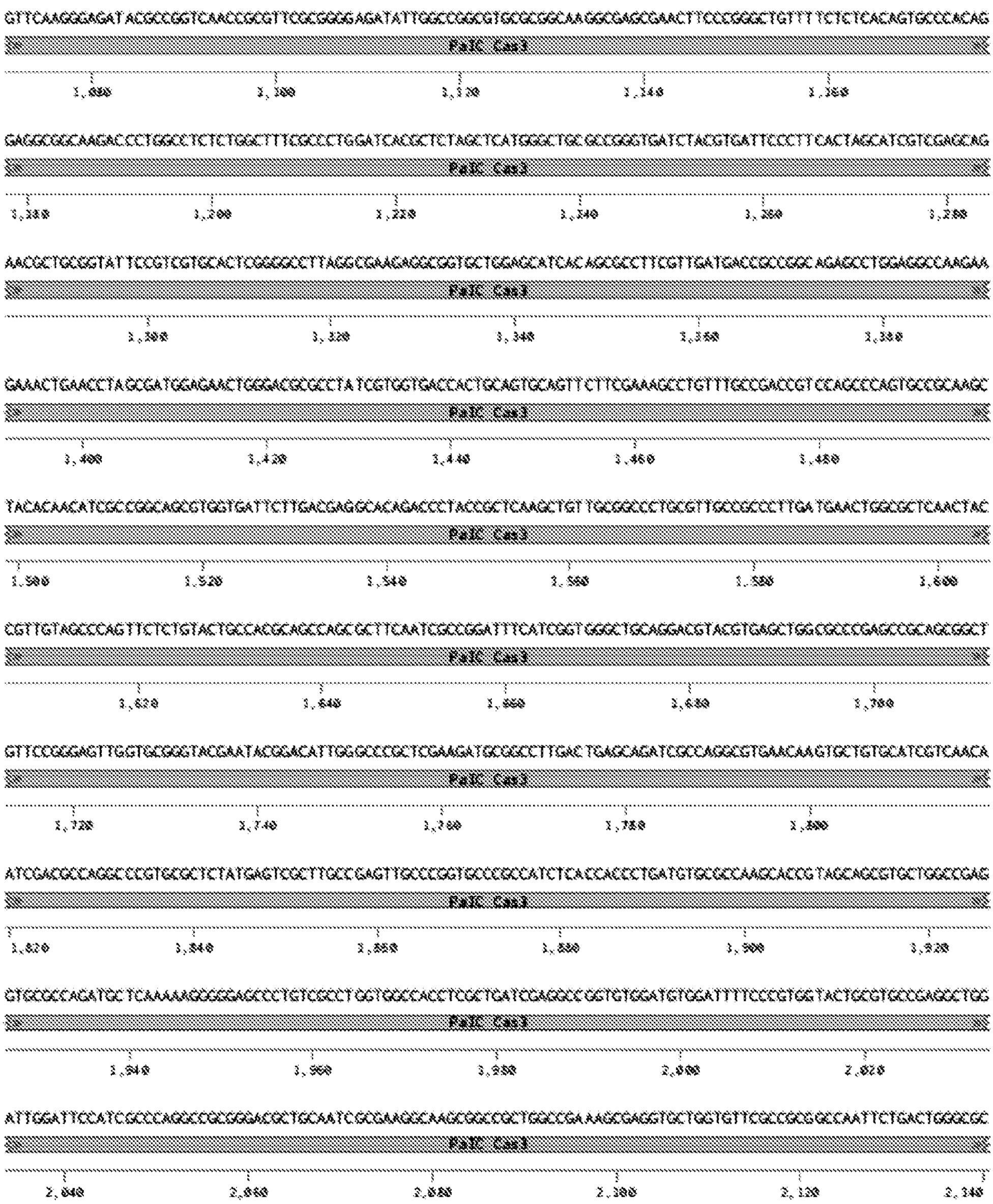

GTTCAAGGGAGATACGCCGGTCAACCGCGTTCGCGGGGAGATATTGGCCGGCGTGCGCGGCAAGGCGAGCGAACTTCCCGGGCTGTTTTCTCTCACAGTGCCCACAG
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1,100
1,120
1,140
1,160
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PaIC Cas3
1,180
1,200
1,220
1,240
1,260
1,280
AACGCTGCGGTATTCCGTCGTGCACTCGGGGCCTTAGGCGAAGAGGCGGTGCTGGAGCATCACAGCGCCTTCGTTGATGACCGCCGGCAGAGCCTGGAGGCCAAGAA
PaIC Cas3
1,300
1,320
1,340
1,360
1,380
GAAACTGAACCTAGCGATGGAGAACTGGGACGCGCCTATCGTGGTGACCACTGCAGTGCAGTTCTTCGAAAGCCTGTTTGCCGACCGTCCAGCCCAGTGCCGCAAGC
PaIC Cas3
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1,420
1,440
1,460
1,480
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PaIC Cas3
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1,540
1,560
1,580
1,600
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PaIC Cas3
1,620
1,640
1,660
1,680
1,700
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PaIC Cas3
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1,740
1,760
1,780
1,800
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PaIC Cas3
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1,840
1,860
1,880
1,900
1,920
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PaIC Cas3
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1,960
1,980
2,000
2,020
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Fig. 1G

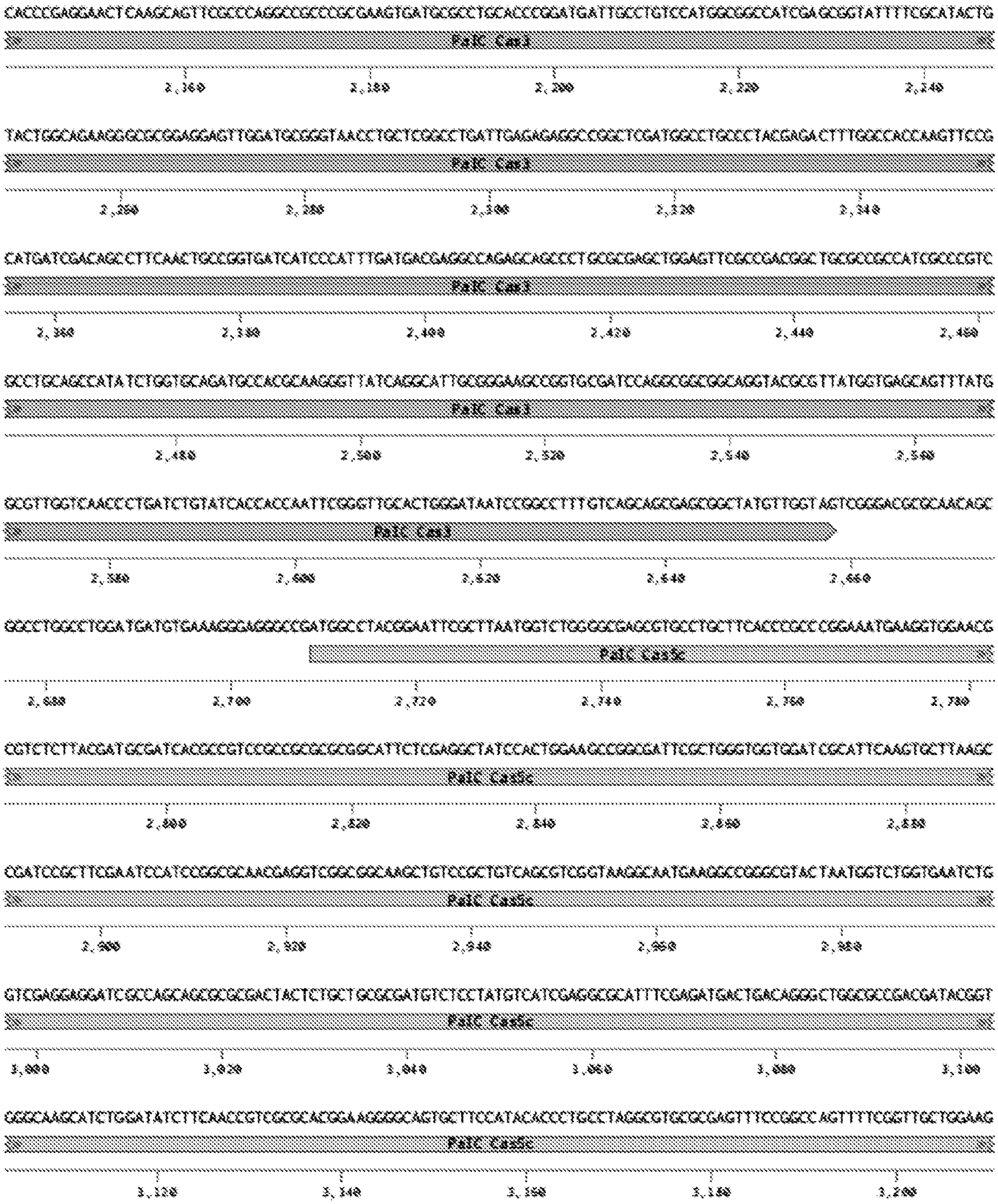

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PaIC Cas3
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2,380
2,400
2,420
2,440
TACTGGCAGAAGGCCGCGGAGGAGTTGGATGCGGGTAACCTGCTCGGCCTGATTGAGAGAGGCCGGCTCGATGGCCTGCCCTACGAGACTTTGGCCACCAAGTTCCG
PaIC Cas3
2,360
2,380
2,400
2,420
2,440
CATGATCGACAGCCTTCAACTGCCGGTGATCATCCCATTTGATGACGAGGCCAGAGCAGCCCTGCGCGAGCTGGAGTTCGCCGACGGCTGCGCCGCCATCGCCCGTC
PaIC Cas3
2,360
2,380
2,400
2,420
2,440
2,460
GCCTGCAGCCATATCTGGTGCAGATGCCACGCAAGGGTTATCAGGCATTGCGGGAAGCCGGTGCGATCCAGCGCGCCGGCAGGTACGCGTTATGGTGAGCAGTTTATG
PaIC Cas3
2,460
2,500
2,520
2,540
2,560
GCGTTGGTCAACCCTGATCTGTATCACCACCAATTCGGGTTGCACTGGGATAATCCGGCCTTTGTCAGCAGCGAGCGGCTATGTTGGTAGTCGGGACGCGCAACAGC
PaIC Cas3
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2,600
2,620
2,640
2,660
GGCCTGGCCTGGATGATGTGAAAGGGAGGGCCGATGGCCTACGGAATTCGCTTAATGGTCTGGGGCGAGCGTGCCTGCTTCACCCGCCCGGAAATGAAGGTGGAACG
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2,700
2,720
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2,780
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2,820
2,840
2,860
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PaIC Cas5c
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2,940
2,960
2,980
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PaIC Cas5c
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3,020
3,040
3,060
3,080
3,100
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Fig. 1H

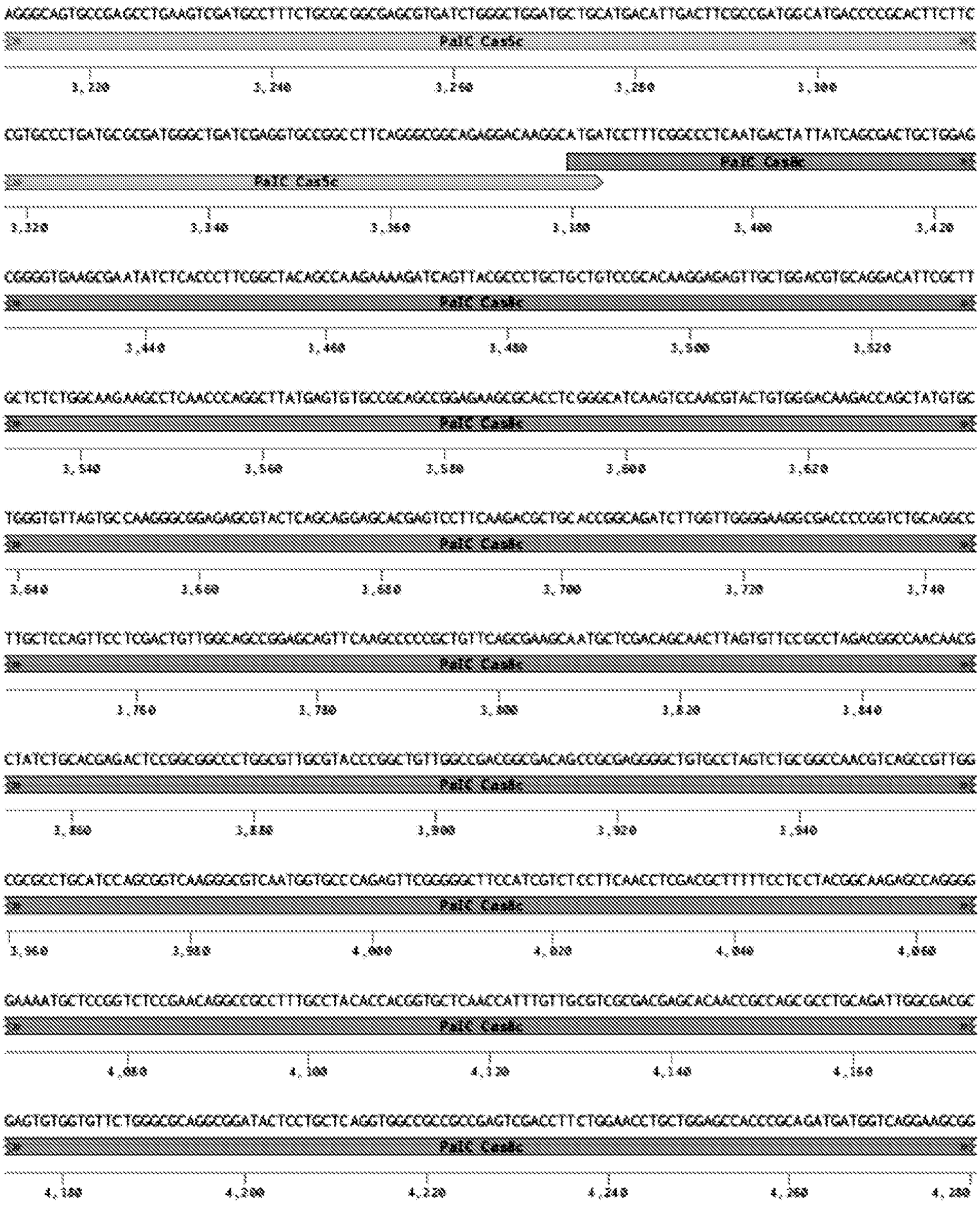

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PaIC Cas5c
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3,240
3,260
3,280
3,300
CGTGCCCTGATGCGCGATGGGCTGATCGAGGTGCCGGCCTTCAGGCGGCAGAGGACAAGGCATGATCCTTTCGGCCCTCAATGACTATTATCAGCGACTGCTGGAG
PaIC Cas8c
PaIC Cas5c
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3,340
3,360
3,380
3,400
3,420
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PaIC Cas8c
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3,500
3,520
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PaIC Cas8c
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3,560
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3,600
3,620
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PaIC Cas8c
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3,660
3,680
3,700
3,720
3,740
TTGCTCCAGTTCCTCGACTGTTGGCAGCCGGAGCAGTTCAAGCCCCCGCTGTTCAGCGAAGCAATGCTCGACAGCAACTTAGTGTTCCGCCTAGACGGCCAACAACG
PaIC Cas8c
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3,780
3,800
3,820
3,840
CTATCTGCACGAGACTCCGGCGGCCCTGGCGTTGCGTACCCGGCTGTTGGCCGACGGCGACAGCCGCGAGGGGCTGTCCCTAGTCTGCGGCCAACGTCAGCCGTTGG
PaIC Cas8c
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3,900
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3,940
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PaIC Cas8c
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Fig. 1I

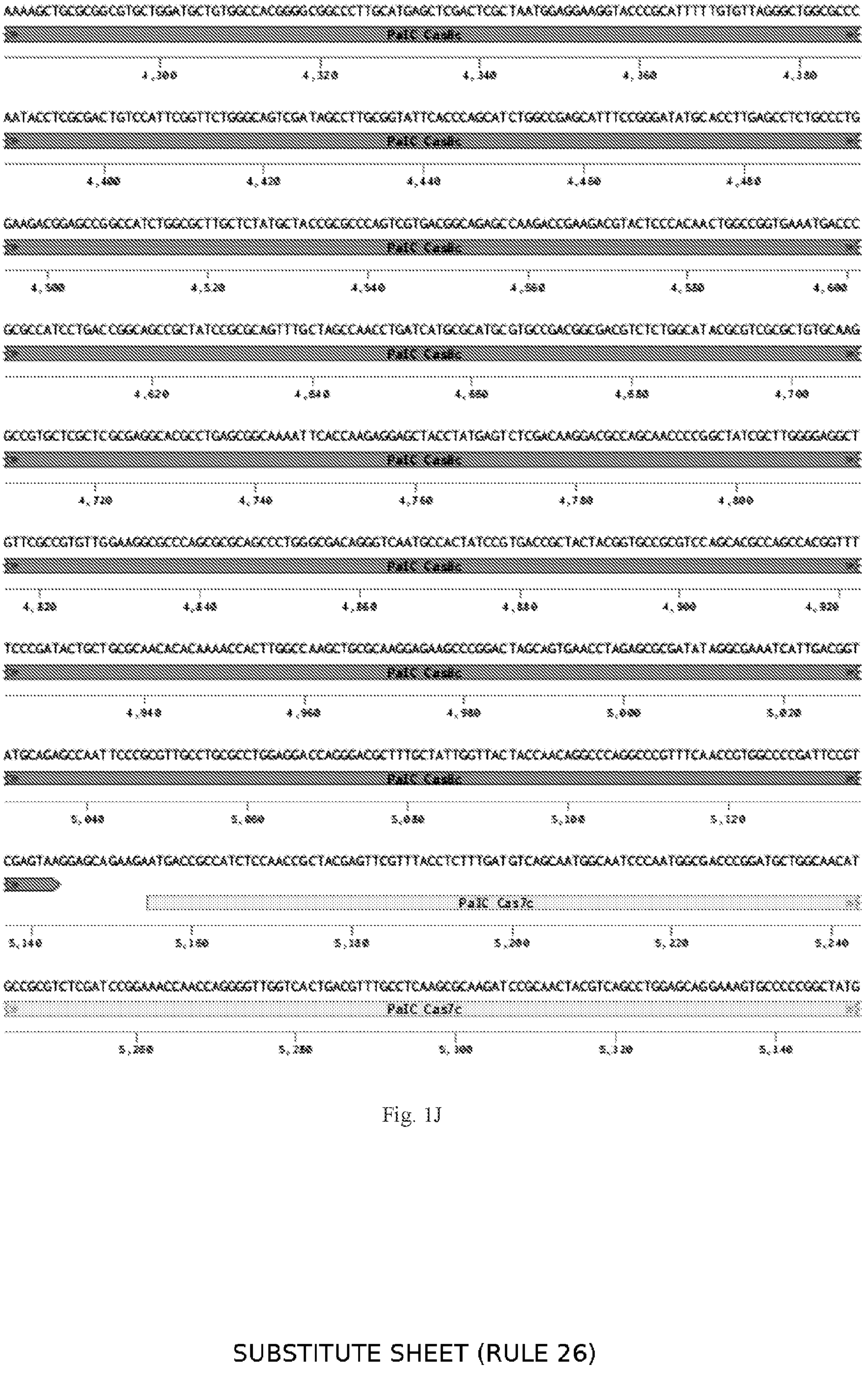

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4,340
4,360
4,380
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4,480
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PaIC Cas9c
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4,540
4,560
4,580
4,600
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PaIC Cas9c
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4,640
4,660
4,680
4,700
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4,740
4,760
4,780
4,800
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4,840
4,860
4,880
4,900
4,920
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4,960
4,980
5,000
5,020
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5,080
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5,180
5,200
5,220
5,240
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5,300
5,320
5,340

Fig. 1J

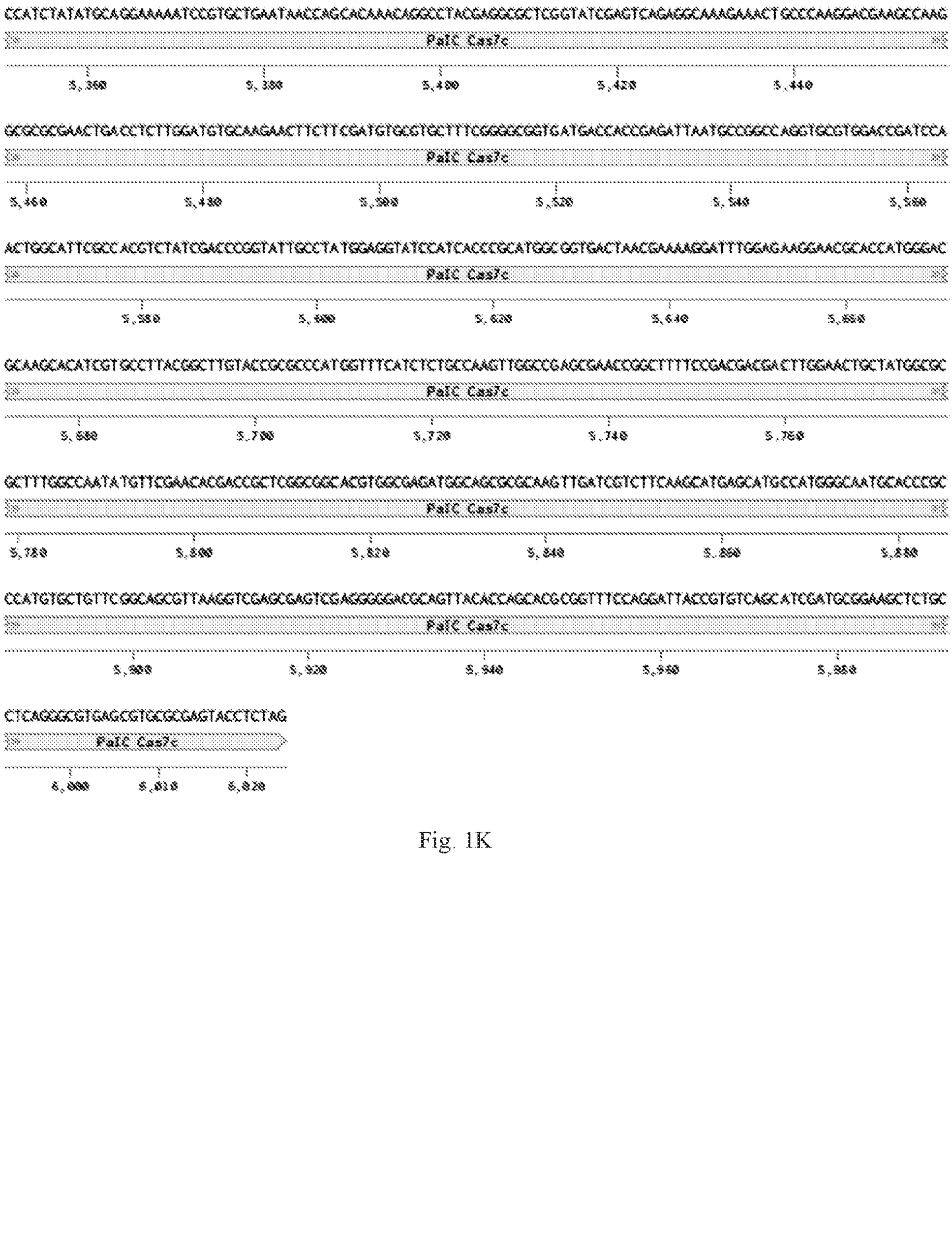

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5,400
5,420
5,440
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FalC Cas7c
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5,480
5,500
5,520
5,540
5,560
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FalC Cas7c
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5,620
5,640
5,660
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FalC Cas7c
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5,720
5,740
5,760
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FalC Cas7c
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5,860
5,880
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FalC Cas7c
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5,920
5,940
5,960
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FalC Cas7c
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6,010
6,020

Fig. 1K

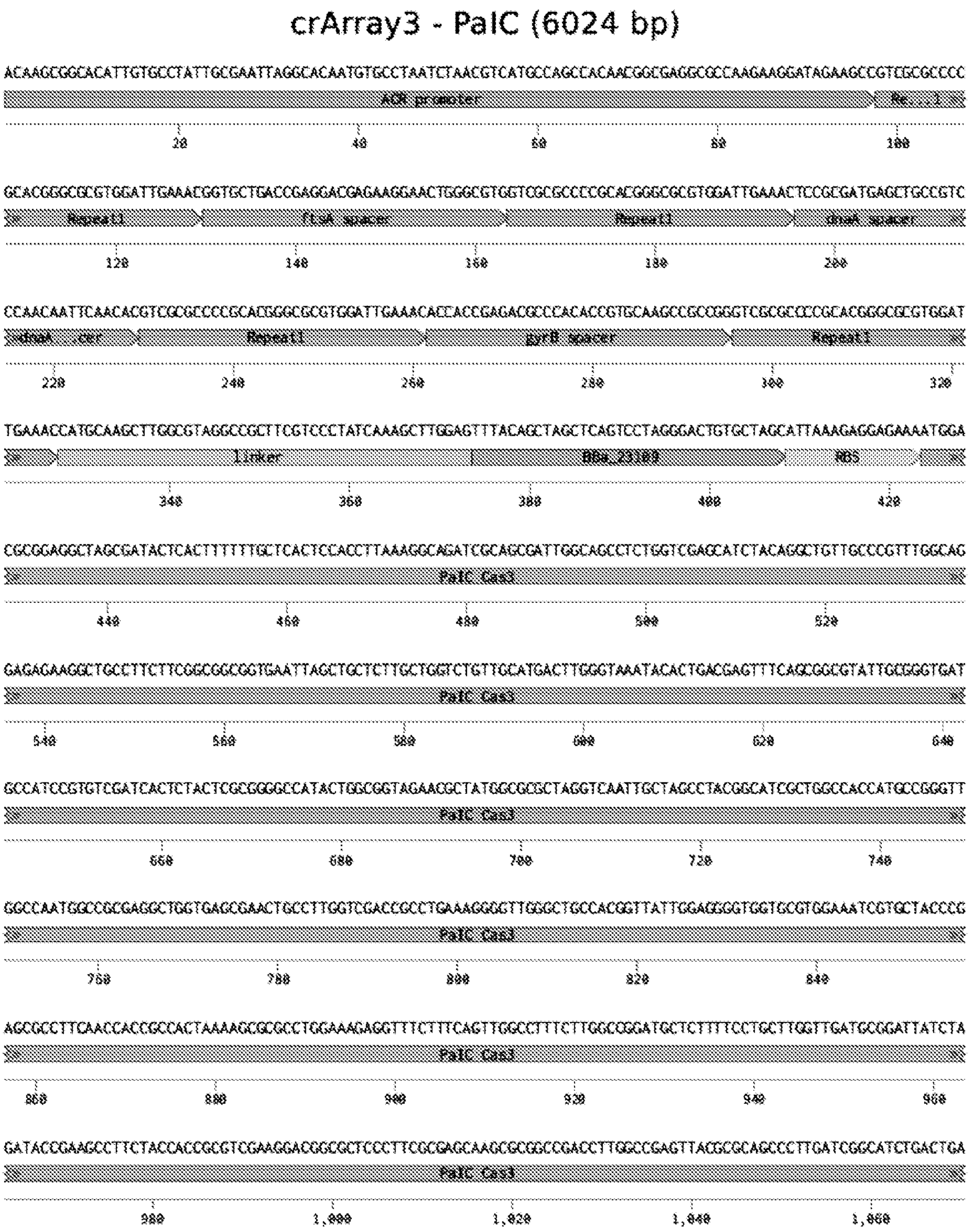

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60
80
100
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Repeat1
fisA spacer
Repeat1
dnaA spacer
120
140
160
180
200
CCAACAATTCAACACGTCGCGCCCCGCACGGGCGCGTGGATTGAAACACCACCGAGACGCCCACACCGTGCAAGCCGCCGGGTCGCGCCCCGCACGGGCGCGTGGAT
dnaA cer
Repeat1
gyrB spacer
Repeat1
220
240
260
280
300
320
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Linker
BBa_23109
HIS
340
360
380
400
420
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PalC Cas3
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460
480
500
520
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PalC Cas3
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560
580
600
620
640
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PalC Cas3
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680
700
720
740
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PalC Cas3
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780
800
820
840
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PalC Cas3
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880
900
920
940
960
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1,020
1,040
1,060

Fig. 1L

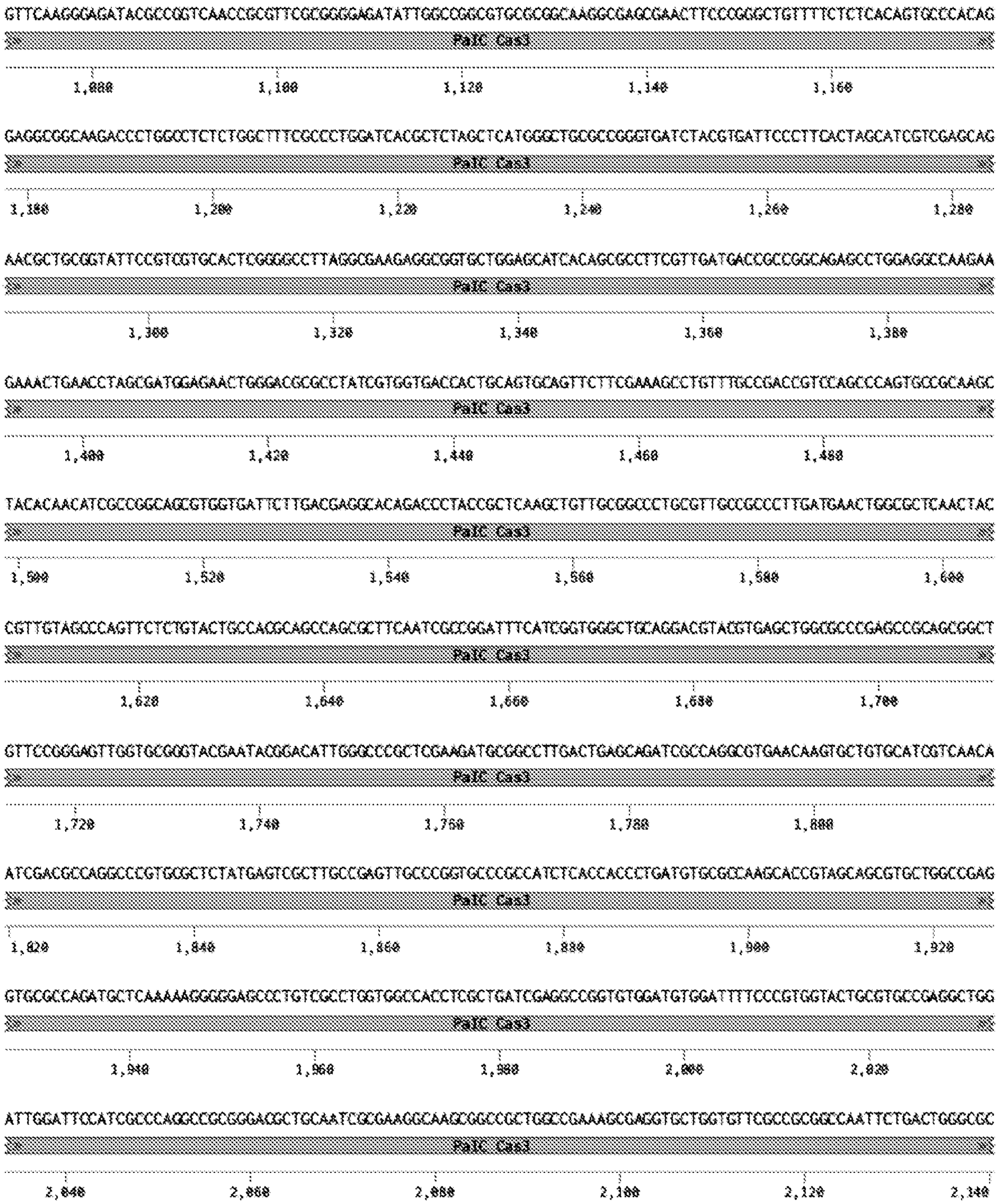

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1,140
1,160
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PaIC Cas3
1,180
1,200
1,220
1,240
1,260
1,280
AACGCTGCGGTATTCCGTCGTGCACTCGGGGCCTTAGGCGAAGAGGCGGTGCTGGAGCATCACAGCGCCTTCGTTGATGACCGCCGGCAGAGCCTGGAGGCCAAGAA
PaIC Cas3
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1,320
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1,360
1,380
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PaIC Cas3
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PaIC Cas3
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1,520
1,540
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1,600
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PaIC Cas3
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1,680
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1,760
1,780
1,800
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1,840
1,860
1,880
1,900
1,920
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1,960
1,980
2,000
2,020
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PaIC Cas3
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2,060
2,080
2,100
2,120
2,140

Fig. 1M

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2,180
2,200
2,220
2,240
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PaIC Cas3
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2,280
2,300
2,320
2,340
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PaIC Cas3
2,360
2,380
2,400
2,420
2,440
2,460
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2,520
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PaIC Cas3
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2,620
2,640
2,660
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PaIC Cas5c
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2,720
2,740
2,760
2,780
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2,820
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2,920
2,940
2,960
2,980
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PaIC Cas5c
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3,020
3,040
3,060
3,080
3,100
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Fig. 1N

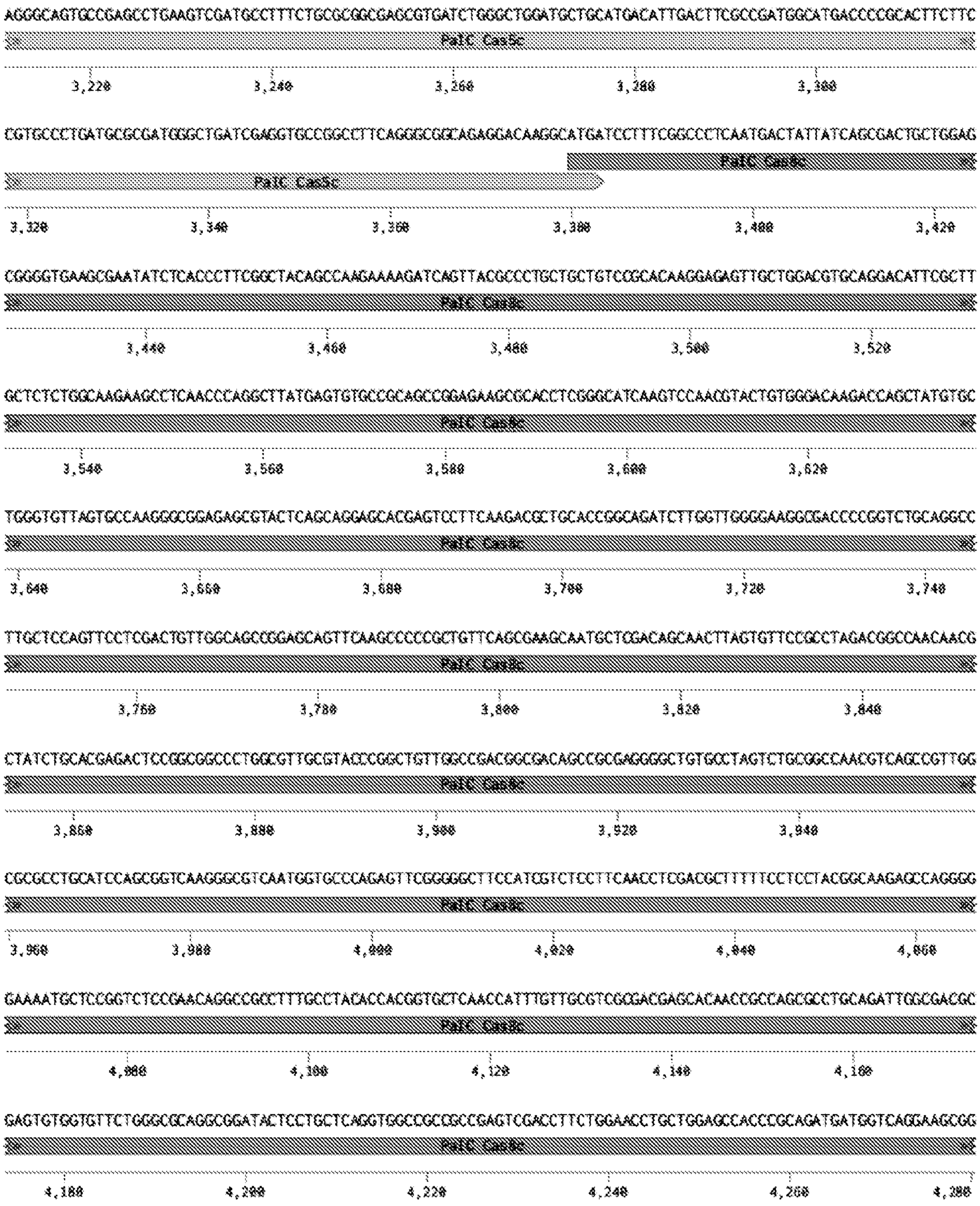

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3,260
3,280
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PaIC Cas6c
PaIC Cas5c
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3,340
3,360
3,380
3,400
3,420
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PaIC Cas8c
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PaIC Cas8c
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3,580
3,600
3,620
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PaIC Cas8c
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3,680
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3,740
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PaIC Cas8c
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3,780
3,800
3,820
3,840
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PaIC Cas8c
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3,900
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3,940
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PaIC Cas8c
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3,980
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4,060
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4,160
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Fig. 10

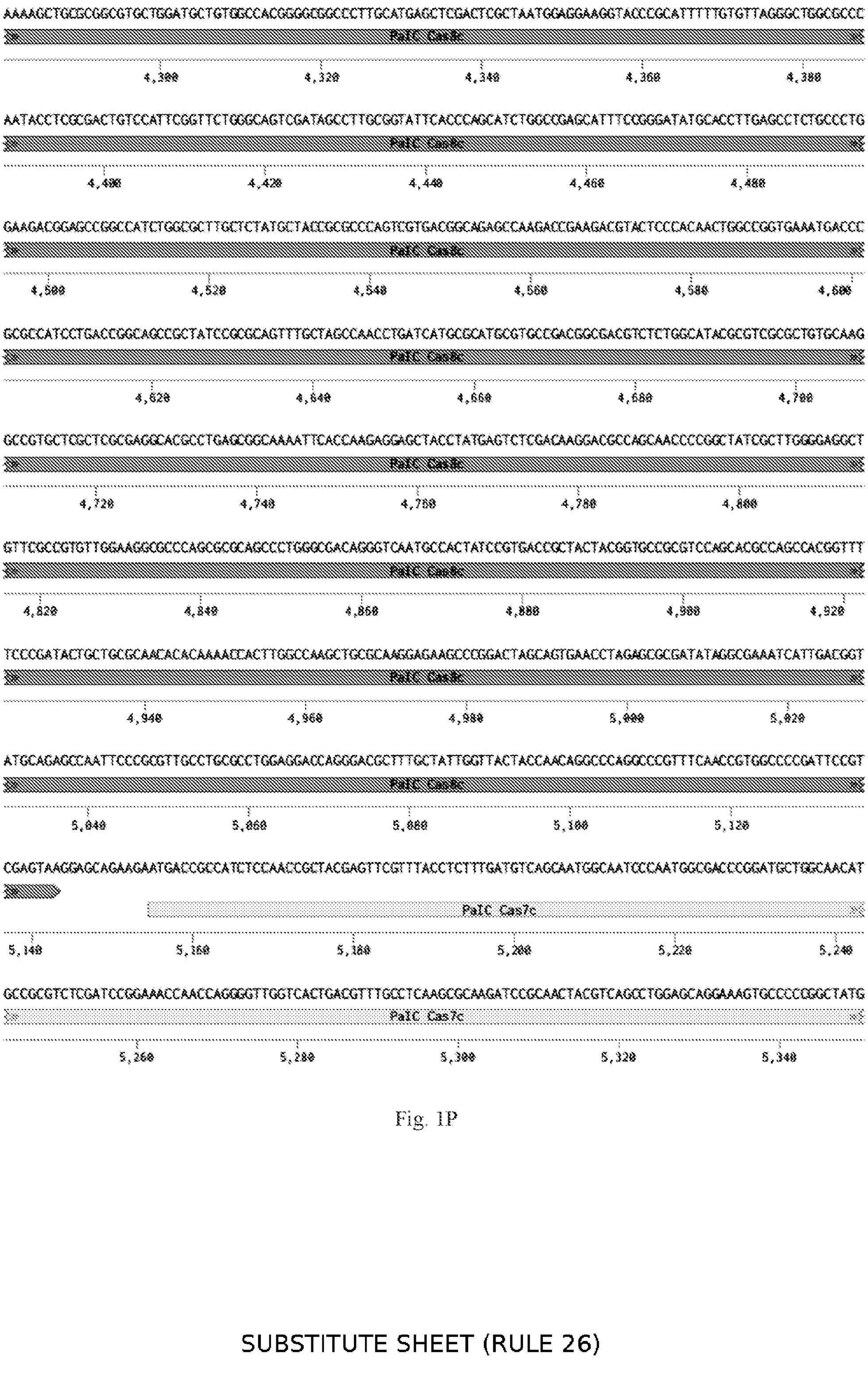

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4,340
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PaIC Cas8c
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PaIC Cas8c
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5,240
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Fig. 1P

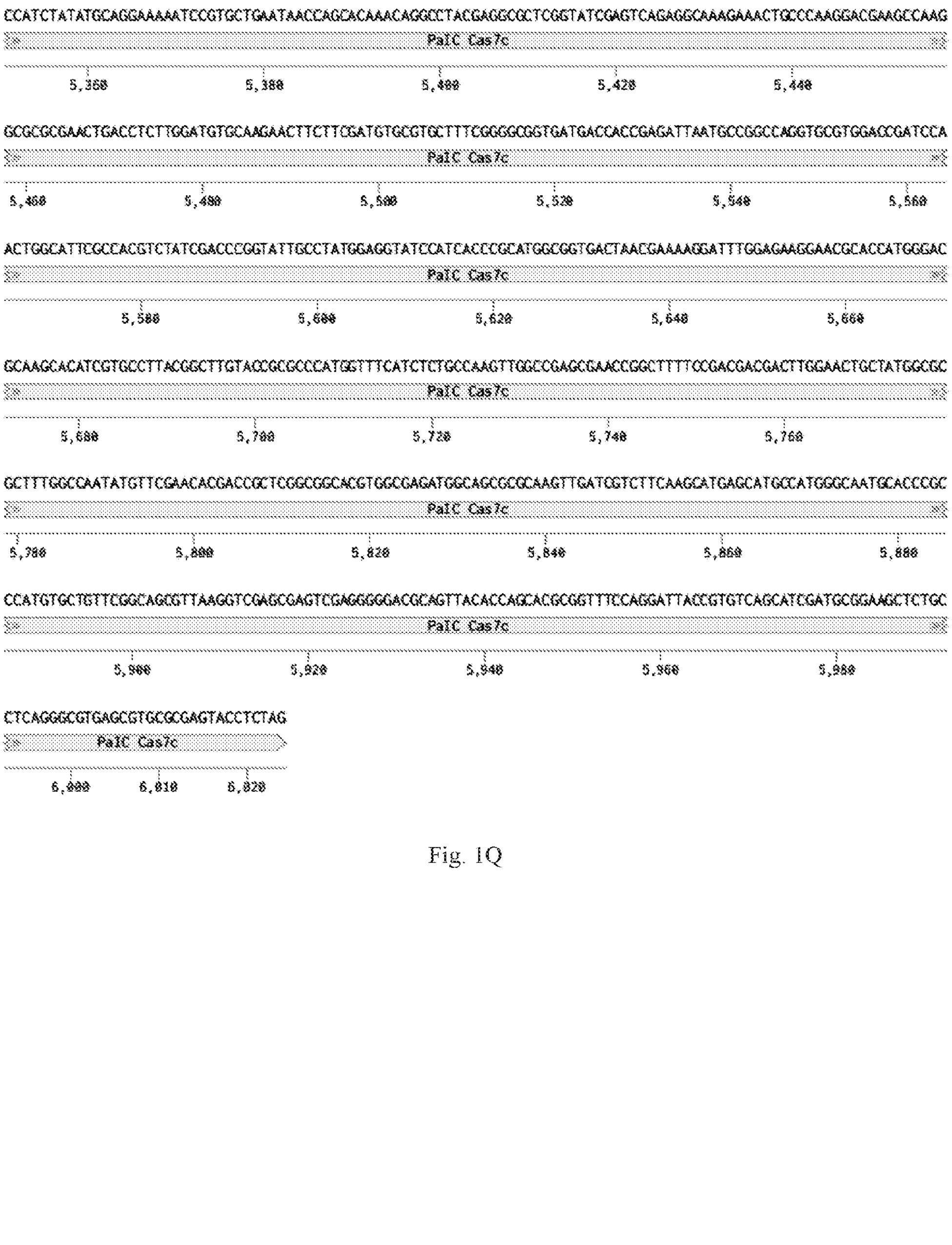
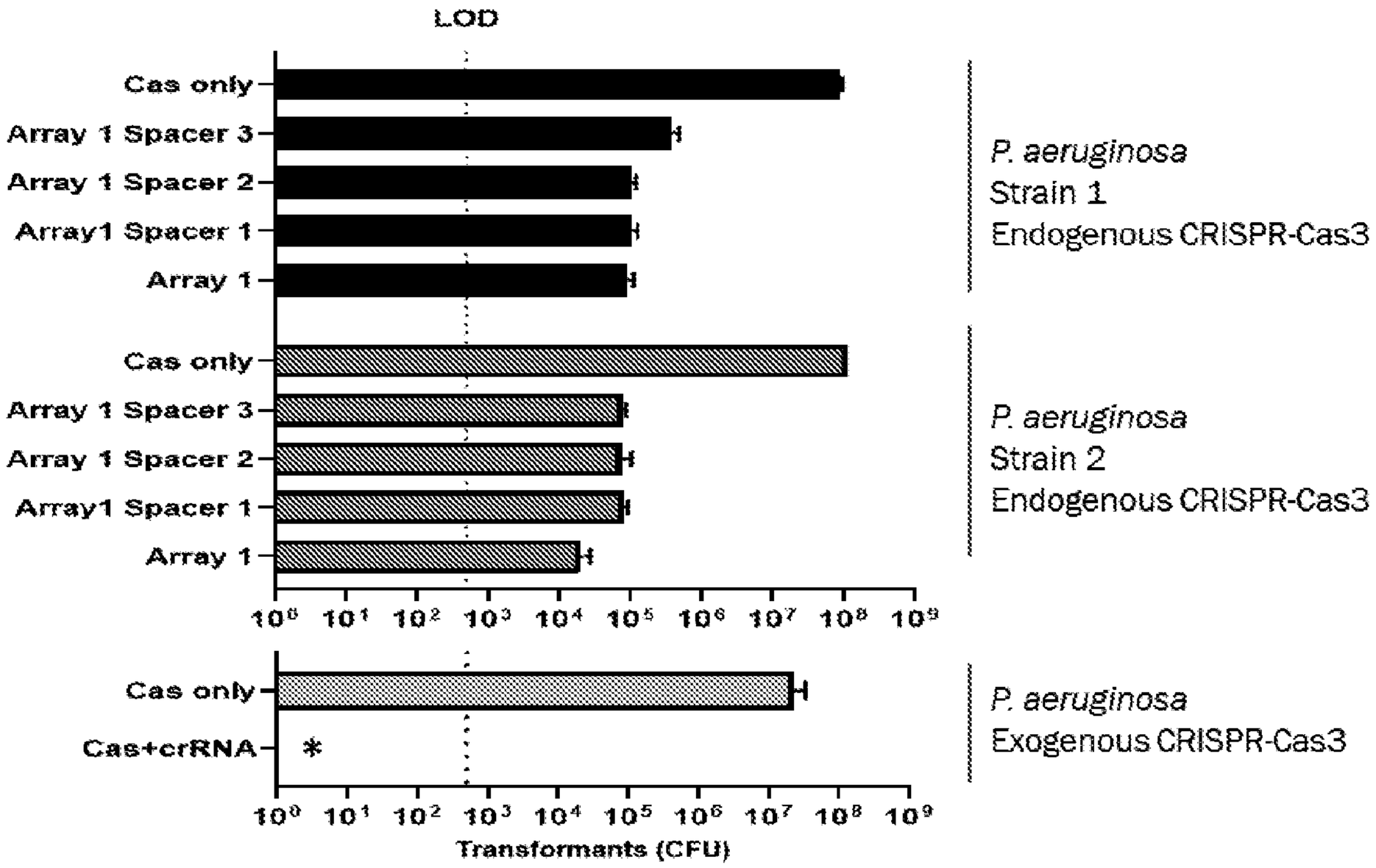

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5,740
5,760
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5,860
5,880
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PaIC Cas7c
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5,940
5,960
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6,010
6,020

Fig. 1Q



*: below LOD

Fig. 2A

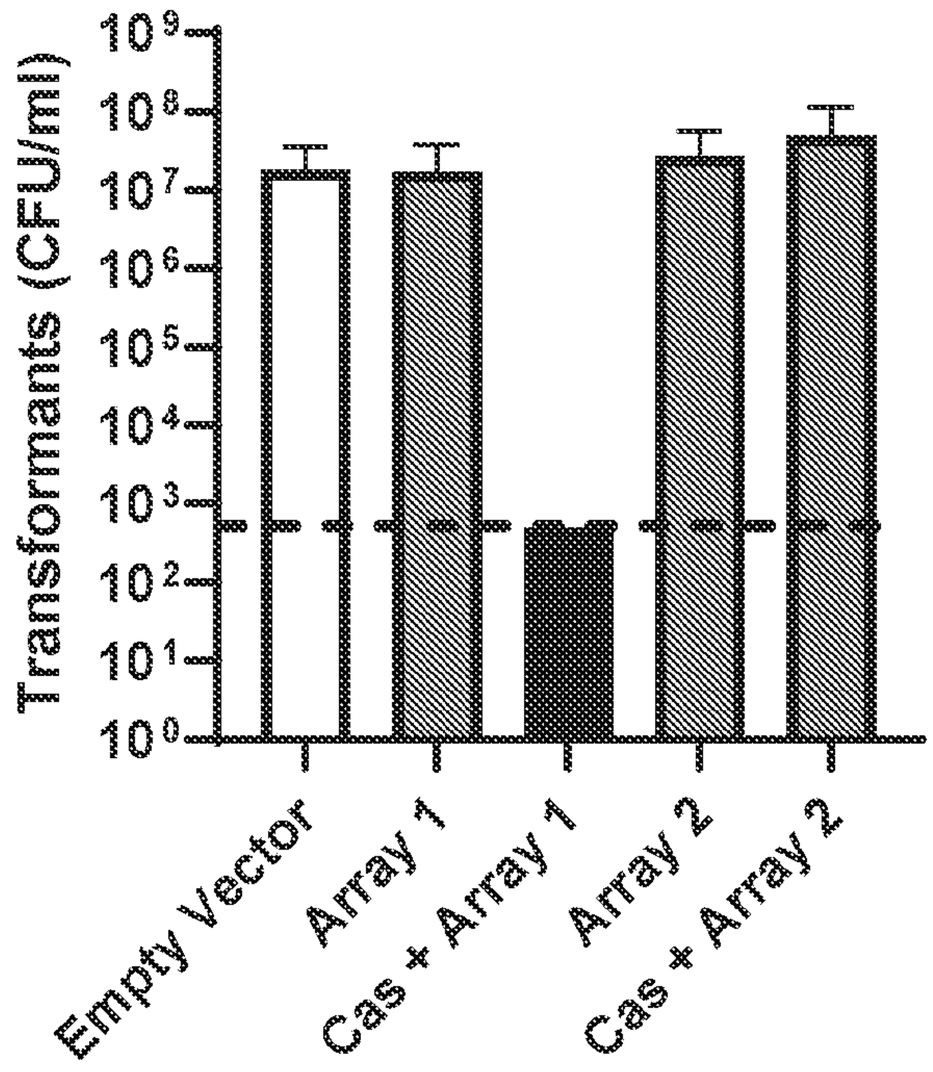


Fig. 2B

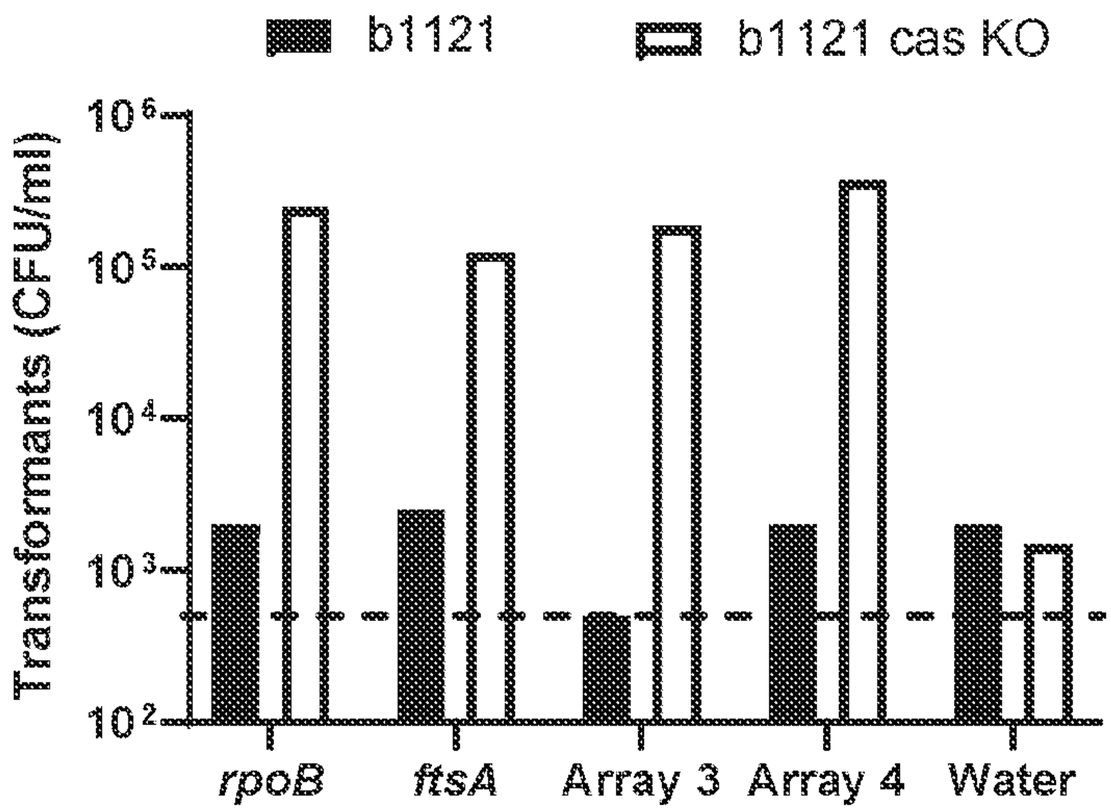

b1121
b1121 cas KO
Transformants (CFU/ml)
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10^5
10^4
10^3
10^2
rpoB
ftsA
Array 3
Array 4
Water

Fig. 2C

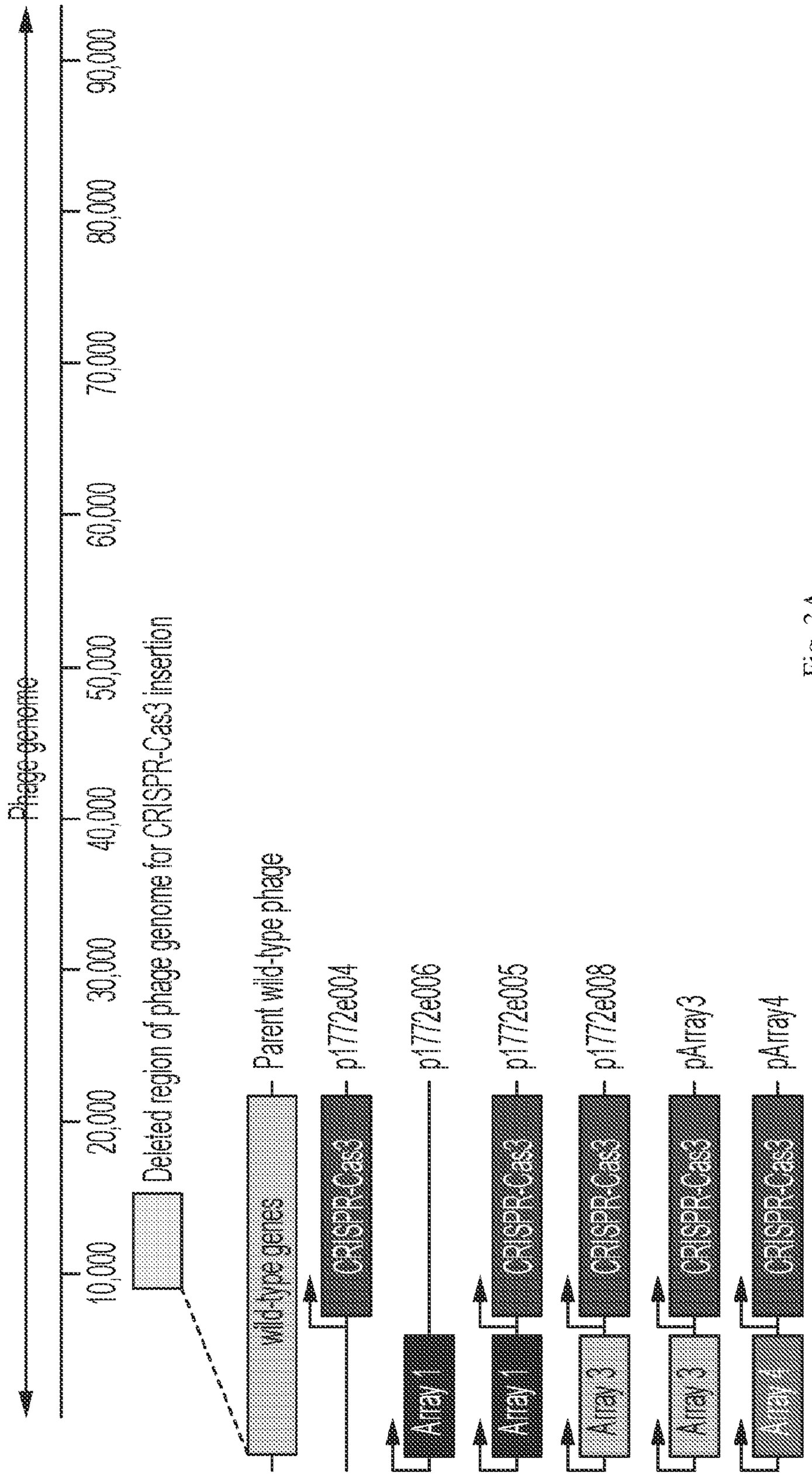

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60,000
50,000
40,000
30,000
20,000
10,000
Phage genome
Deleted region of phage genome for CRISPR-Cas3 insertion
Parent wild-type phage
wild-type genes
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p1772e006
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p1772e008
pArray3
pArray4
CRISPR-Cas3
Array 1
Array 3
Array 4

Fig. 3A

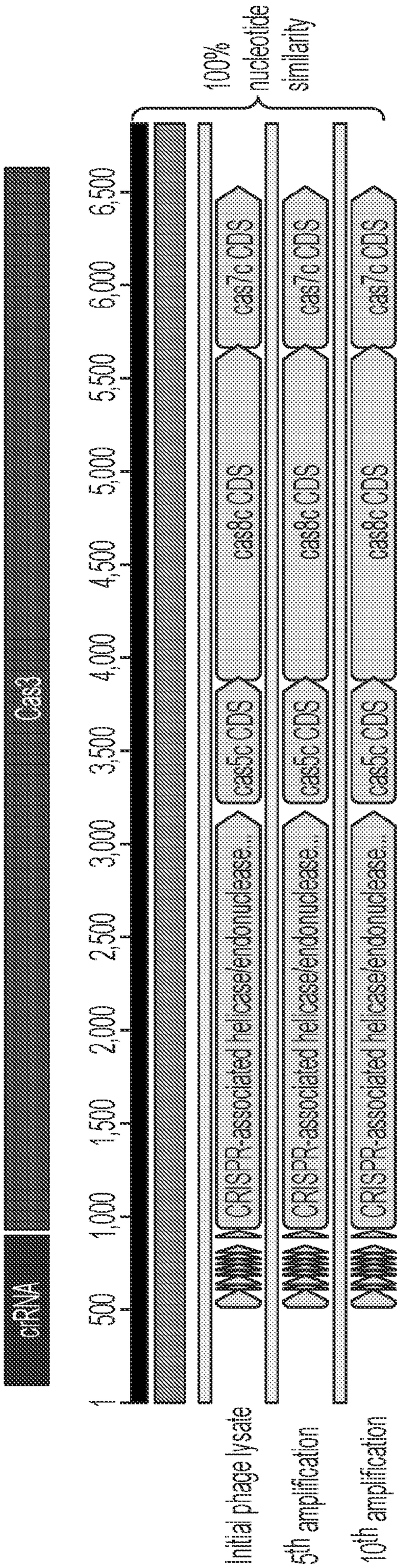

100% nucleotide similarity
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2,000
2,500
3,000
3,500
4,000
4,500
5,000
5,500
6,000
6,500
CRISPR-associated helicase/endonuclease...
cas8c CDS
cas5c CDS
cas7c CDS
initial phage lysate
5th amplification
10th amplification

Fig. 3B

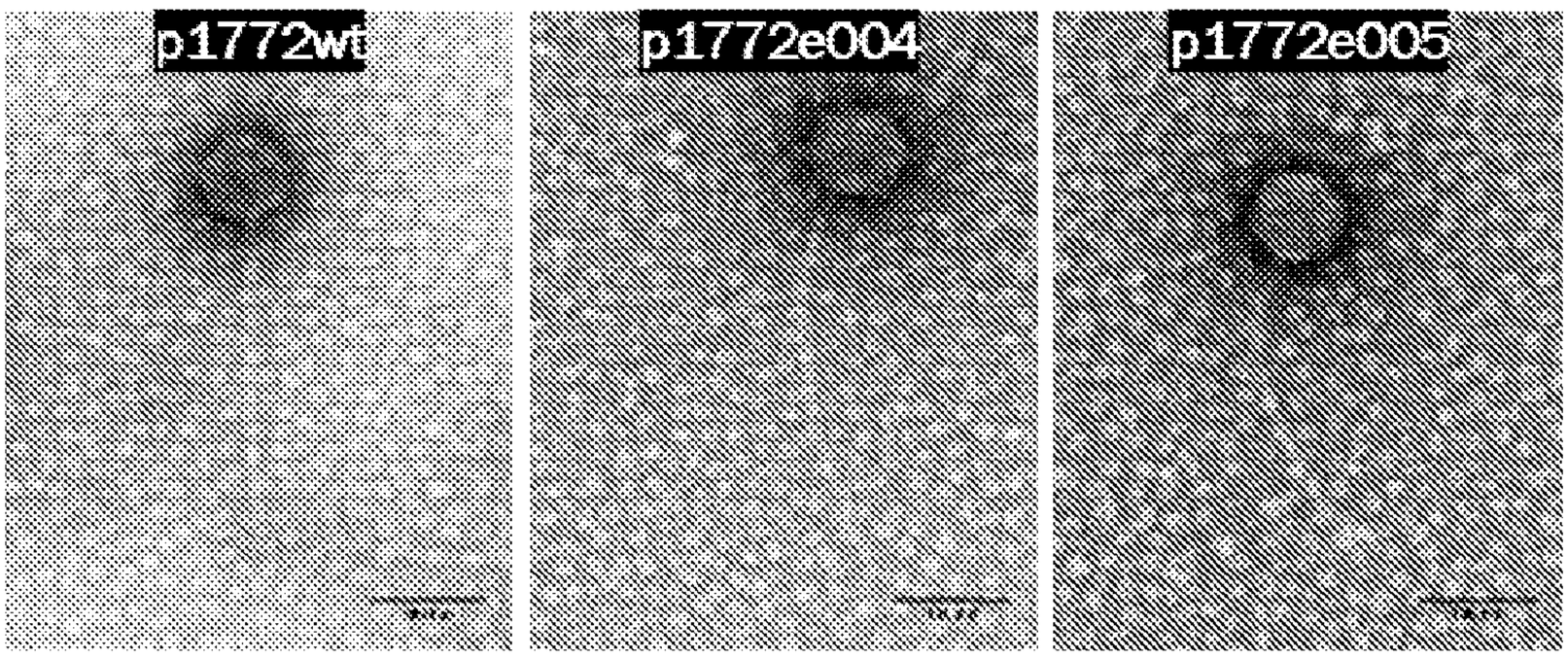

p1772wt
p1772e004
p1772e005
75 nm
72 nm
265 nm
78 nm
76 nm
286 nm
74 nm
73 nm
277 nm
Capsid height
Capsid width
Tail length

Fig. 4

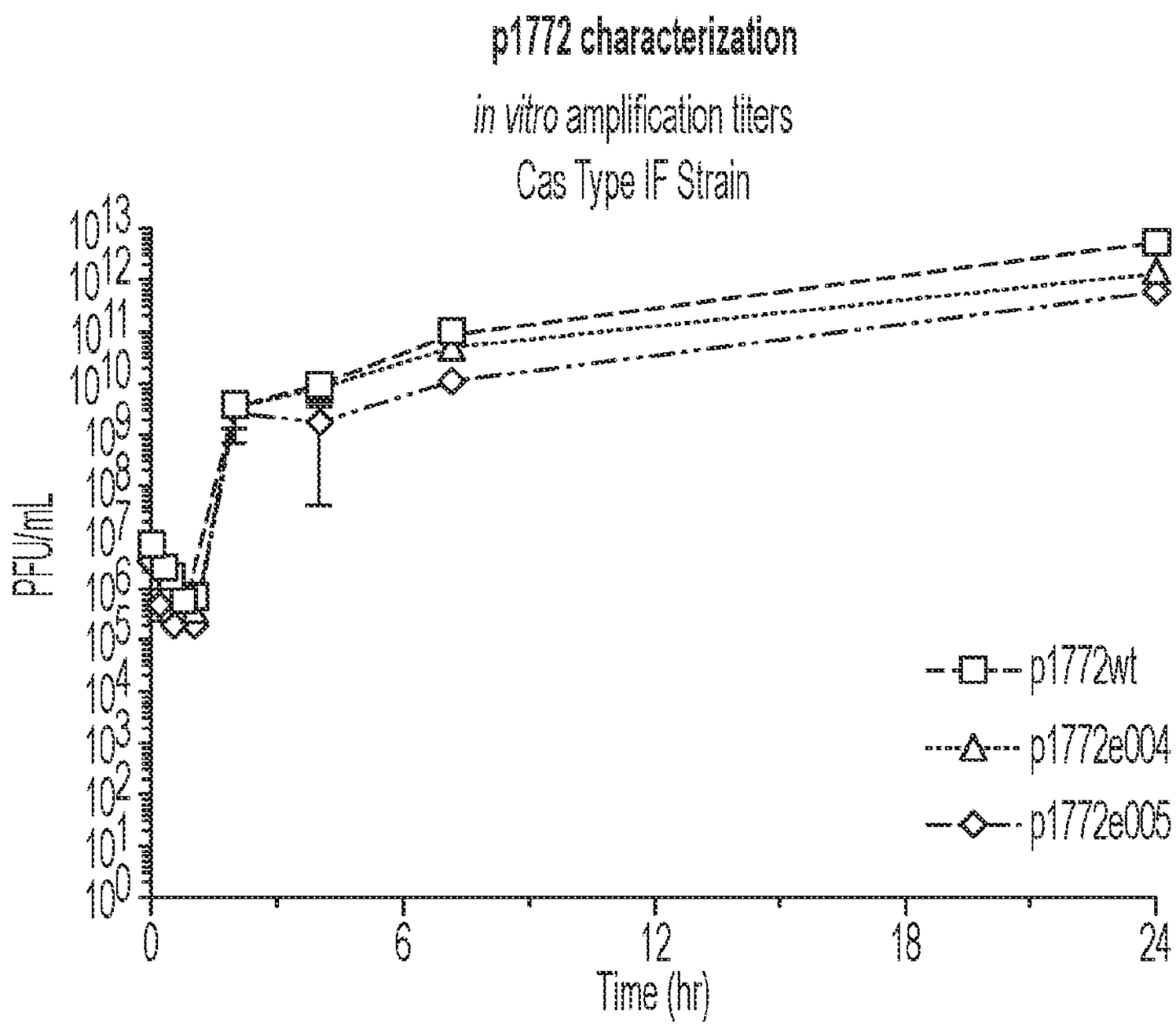

p1772 characterization
in vitro amplification titers
Cas Type IF Strain
PFU/mL
10^13
10^12
10^11
10^10
10^9
10^8
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
6
12
18
24
Time (hr)
p1772wt
p1772e004
p1772e005

Fig. 5A

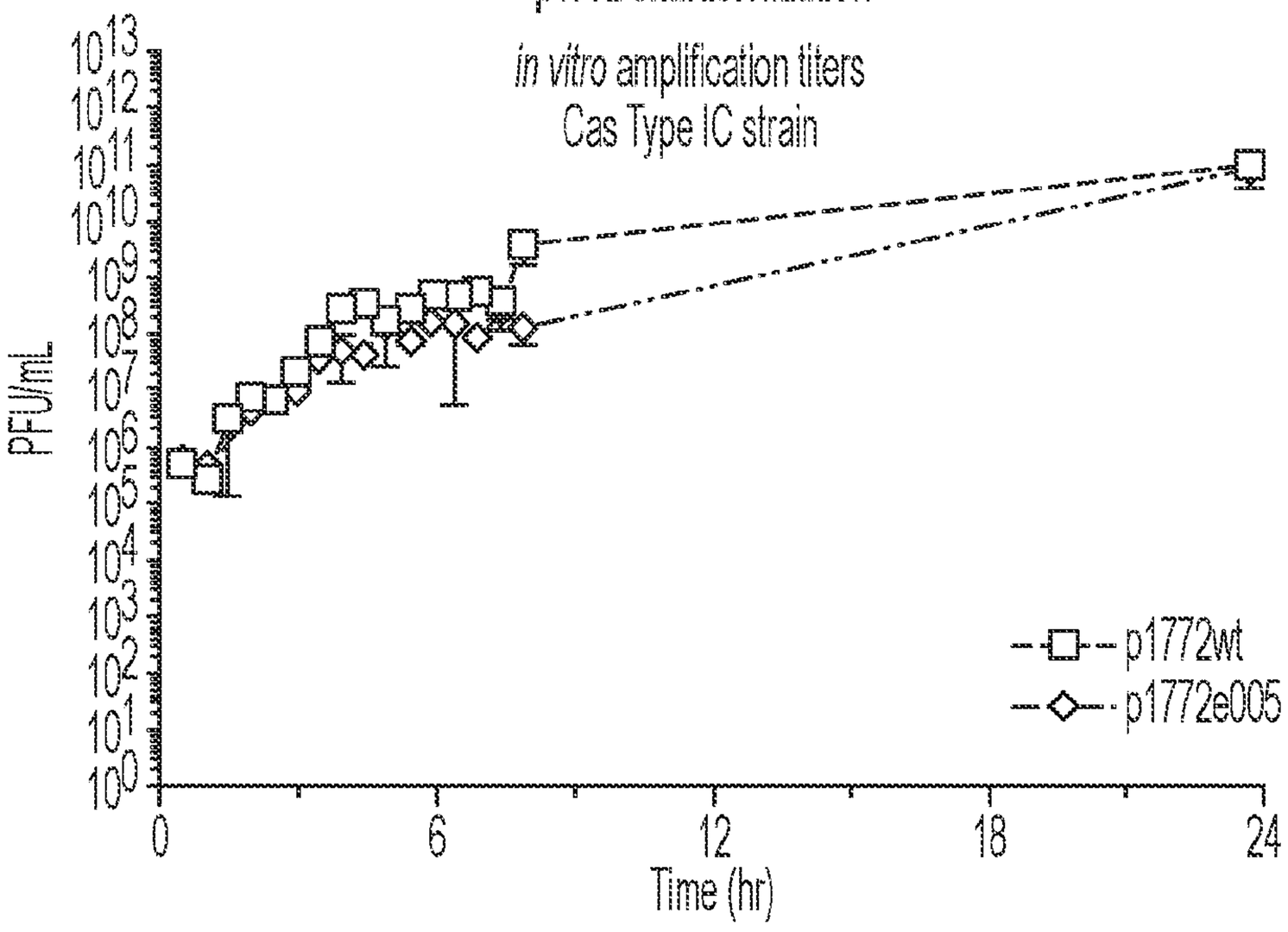

p1772 characterization
in vitro amplification titers
Cas Type IC strain
PFU/mL
Time (hr)
p1772wt
p1772e005

Fig. 5B

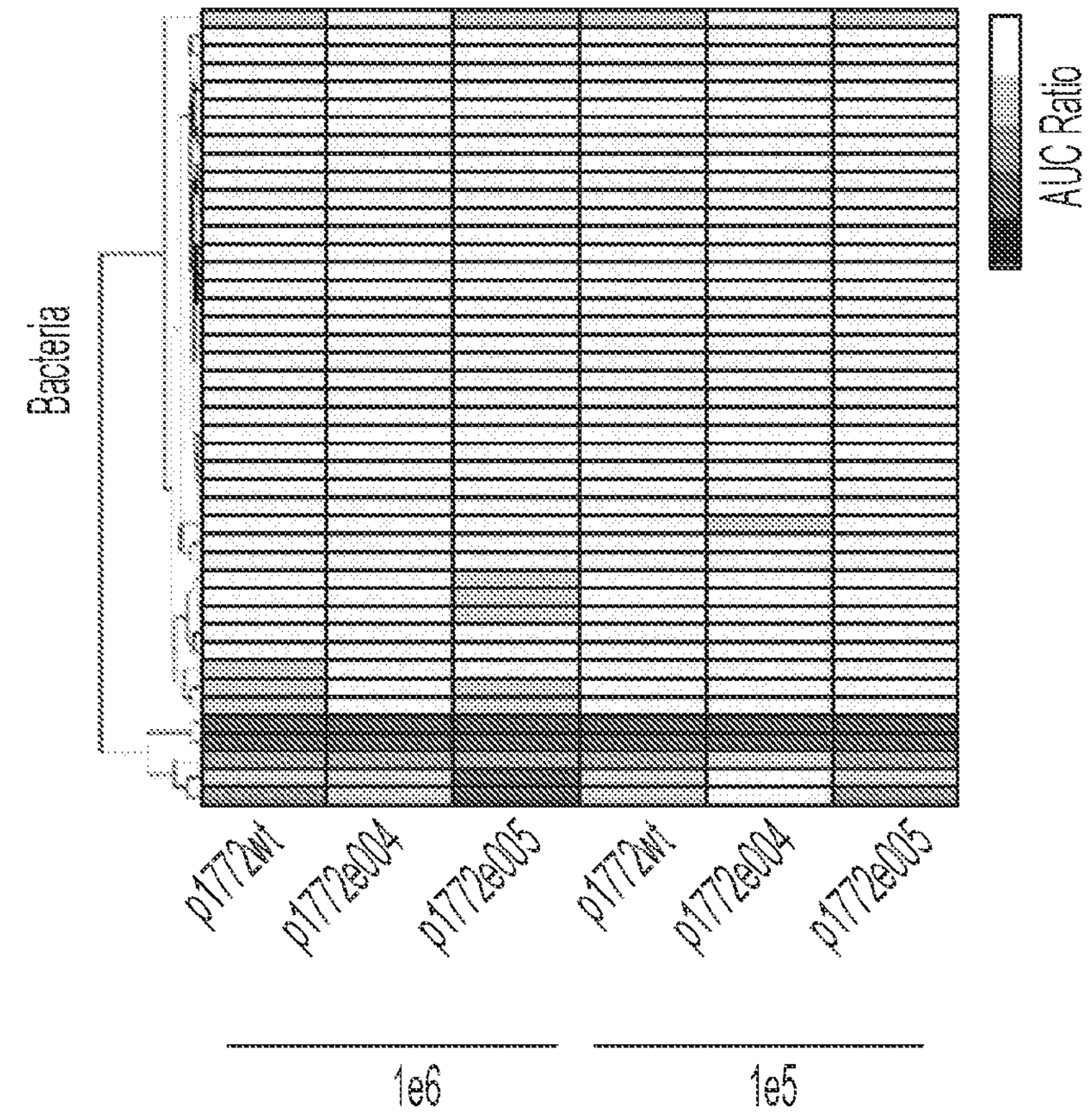

Bacteria
AUC Ratio
p1772wt
p1772e004
p1772e005
p1772wt
p1772e004
p1772e005
1e6
1e5

Fig. 5C

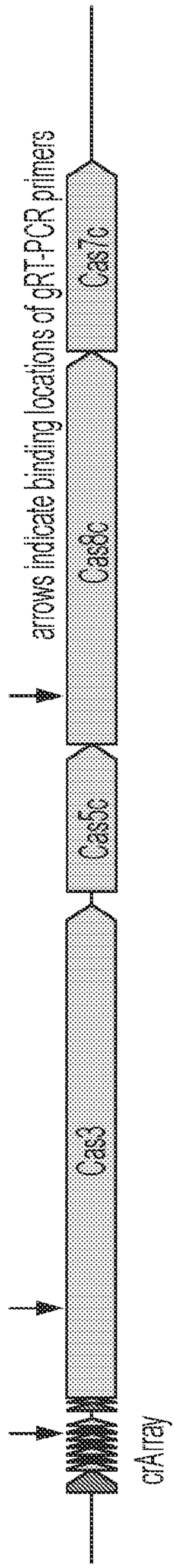

arrows indicate binding locations of qRT-PCR primers
Cas7c
Cas8c
Cas5c
Cas3
crArray

Fig. 6A

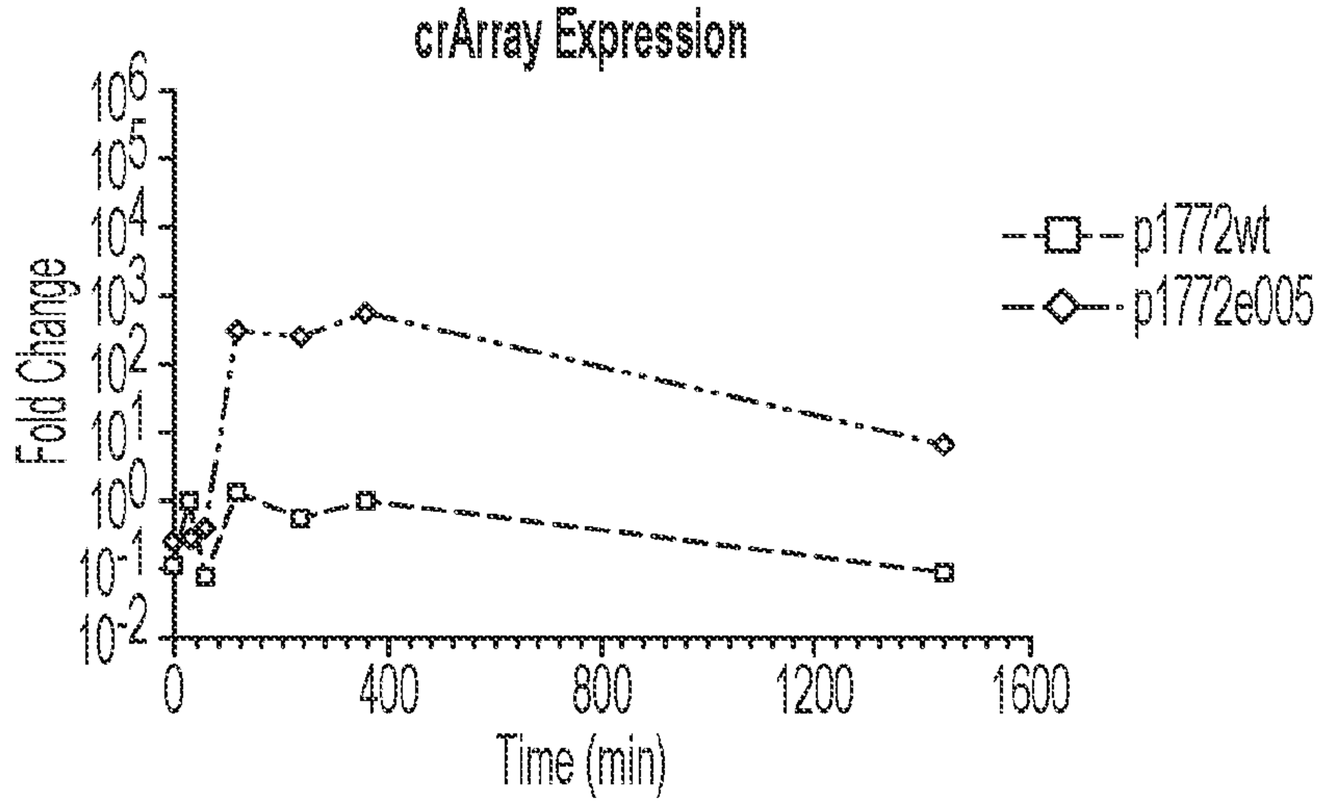


Fig. 6B

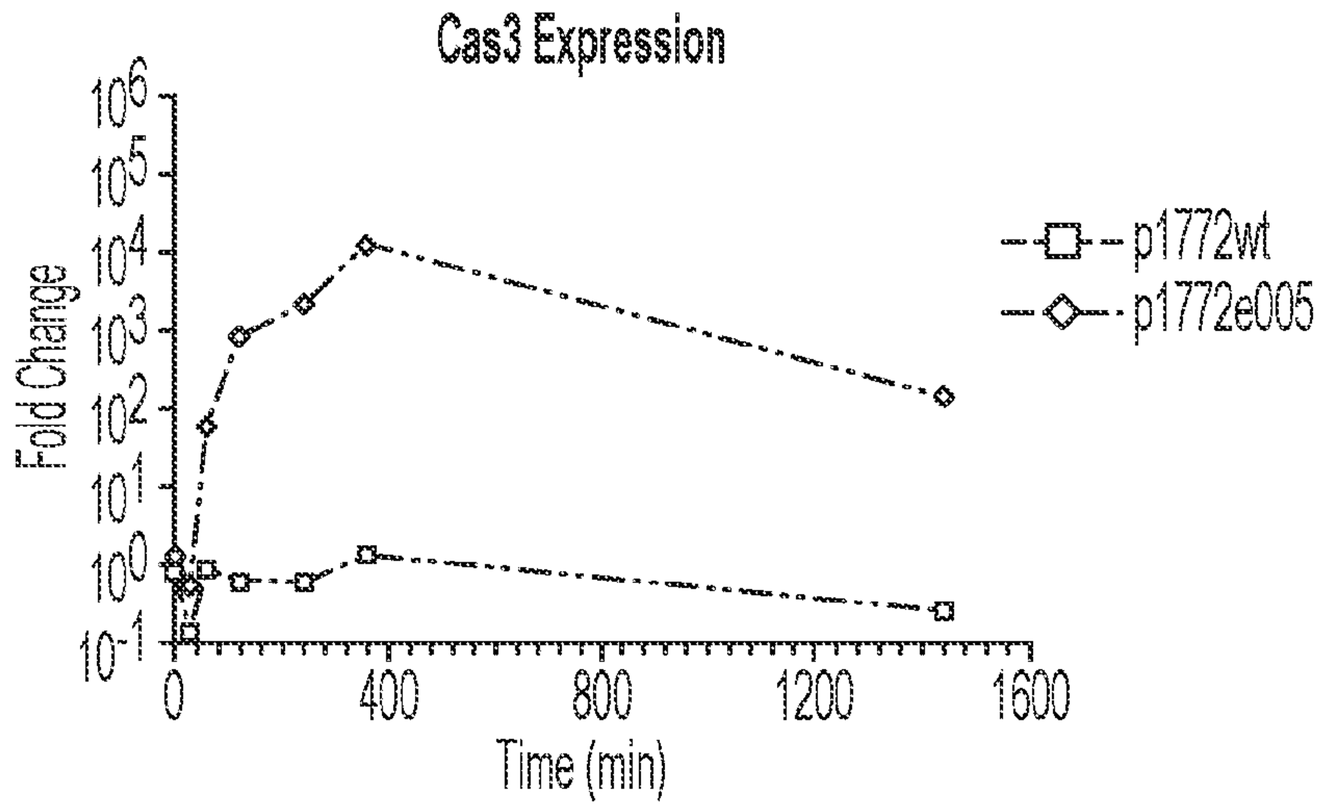


Fig. 6C

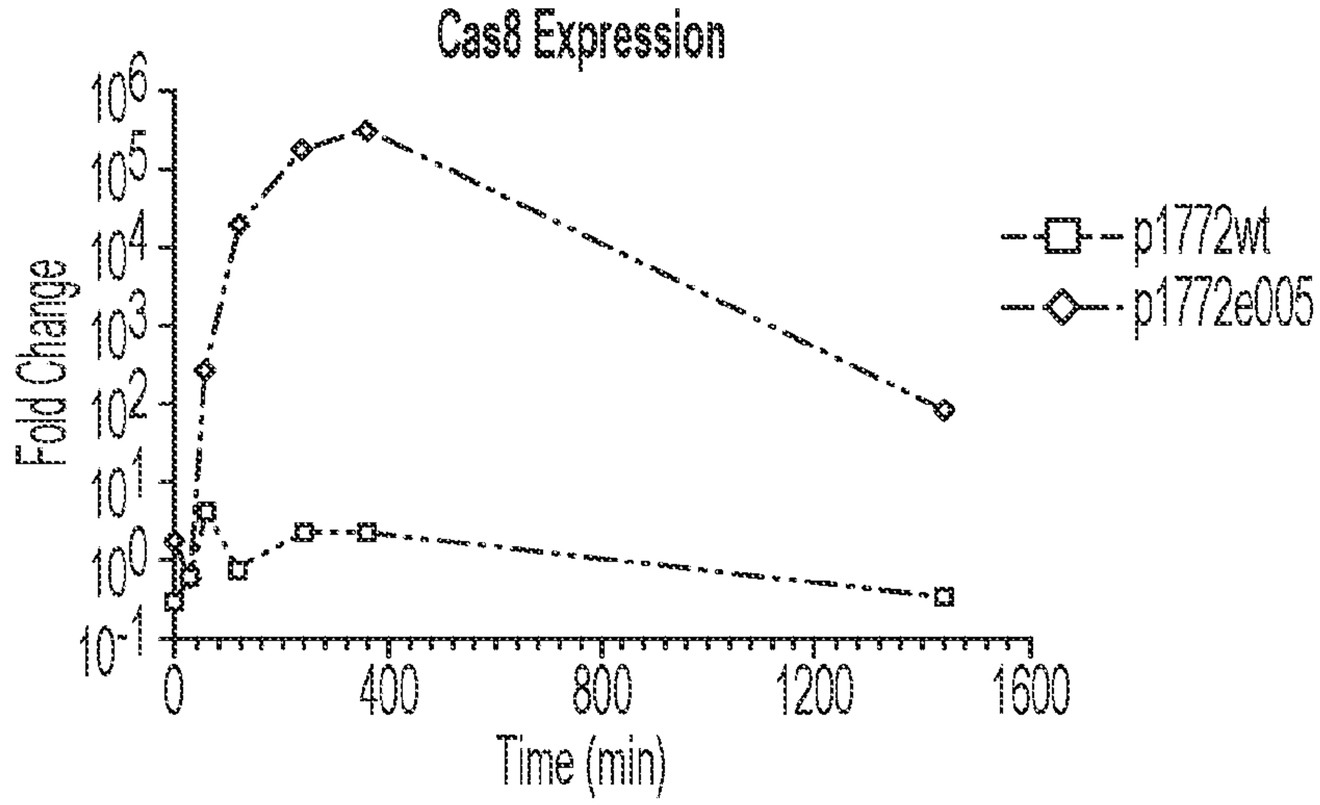


Fig. 6D

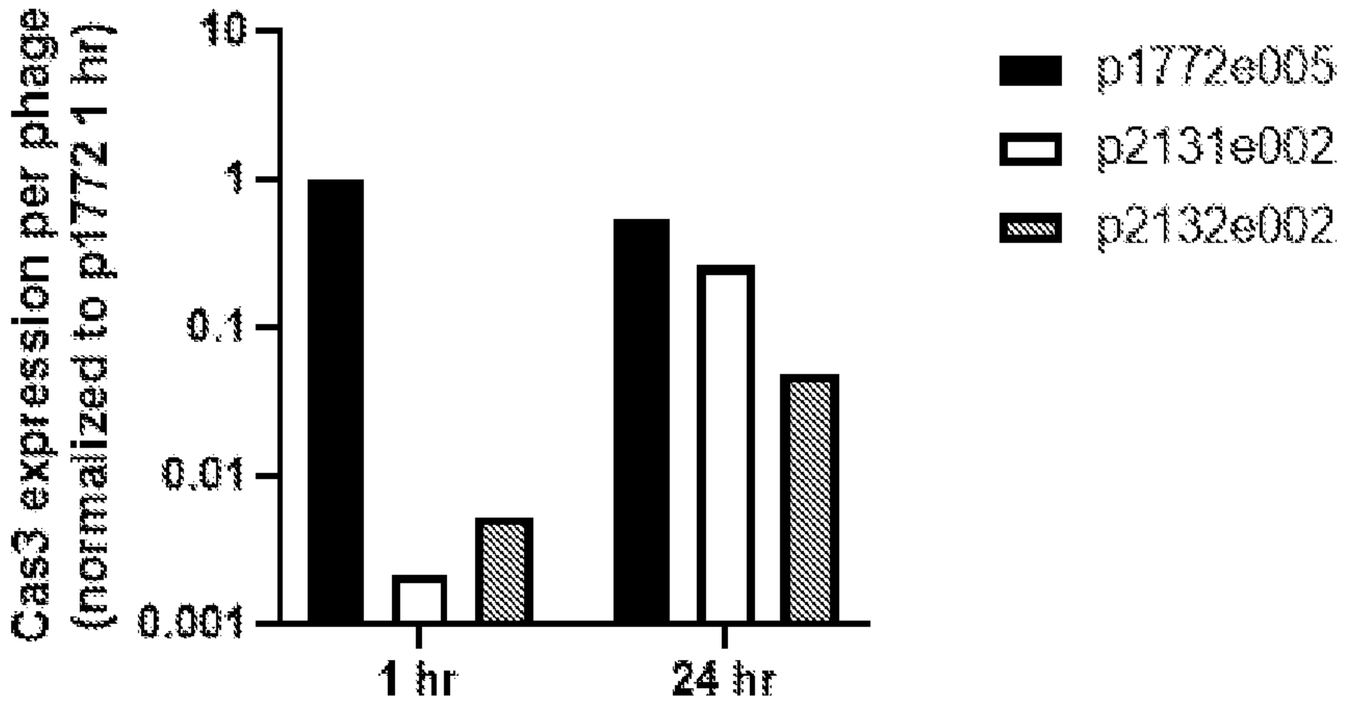

Cas3 expression per phage
(normalized to p1772 1 hr)
10
1
0.1
0.01
0.001
1 hr
24 hr
p1772e005
p2131e002
p2132e002

Fig. 6E

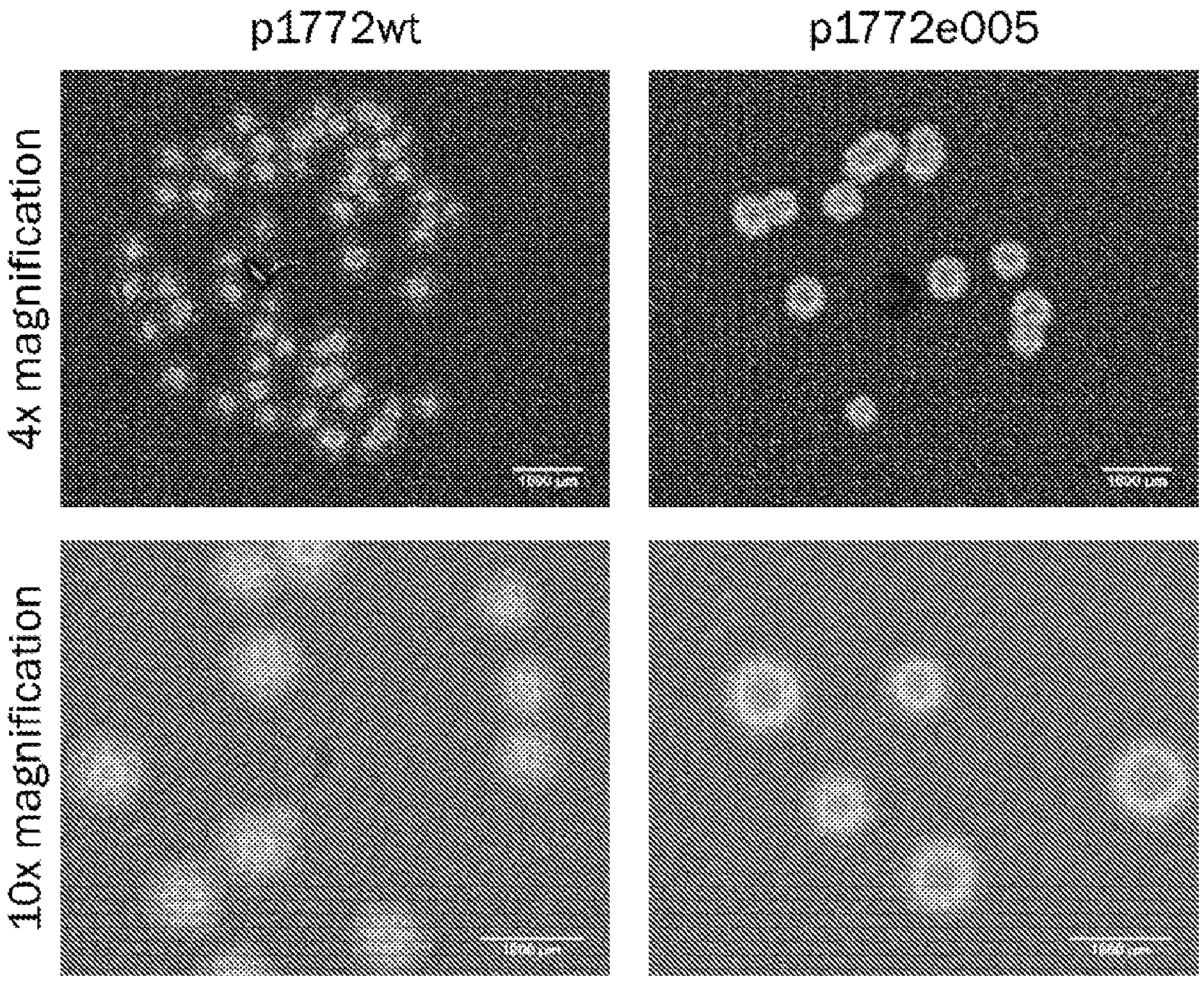

p1772wt
p1772e005
4x magnification
10x magnification

Fig. 7

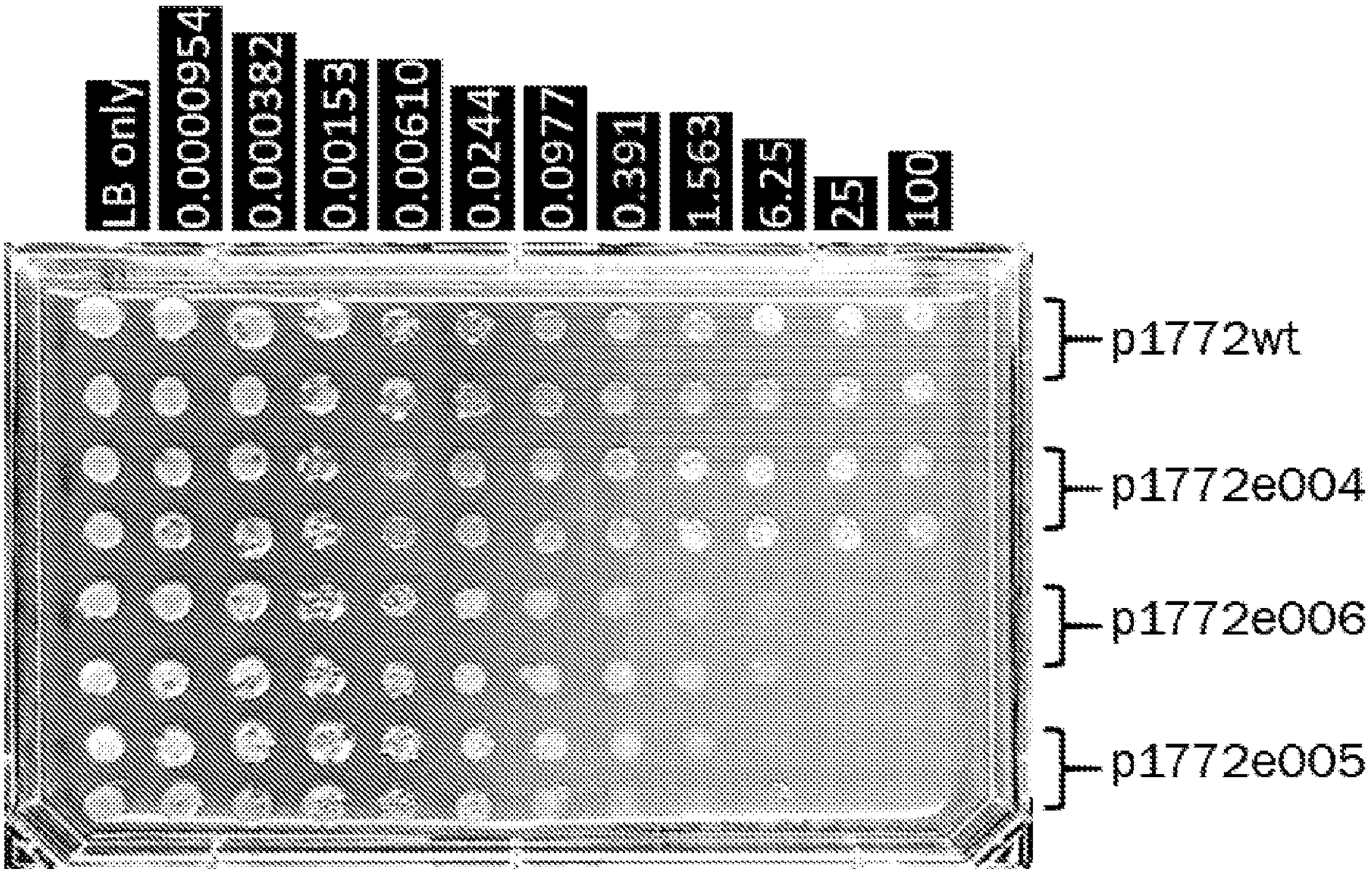

LB only
0.000954
0.00382
0.00153
0.00610
0.0244
0.0977
0.391
1.563
6.25
25
100
p1772wt
p1772e004
p1772e006
p1772e005

Fig. 8A

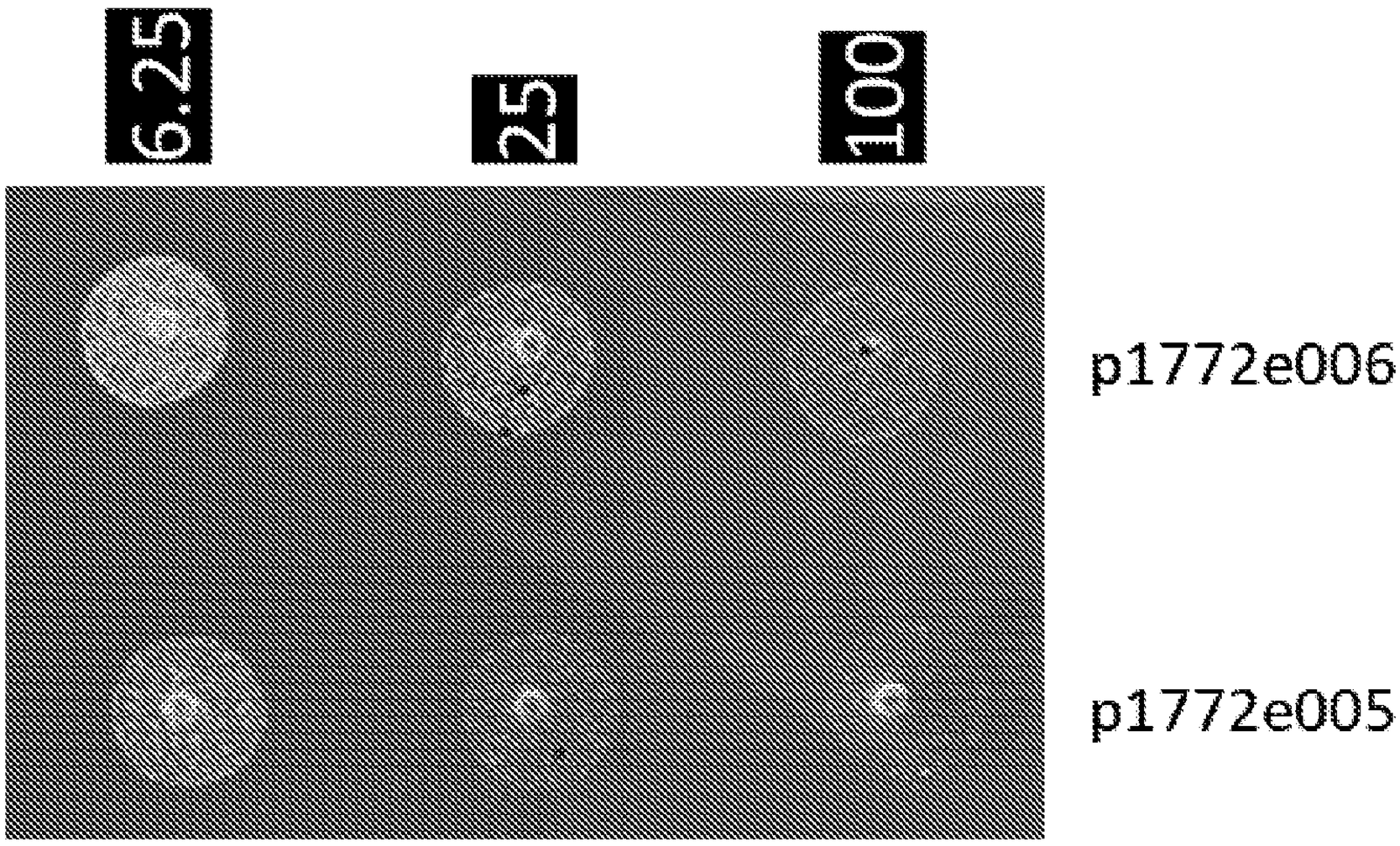

6.25
25
100
p1772e006
p1772e005

Fig. 8B

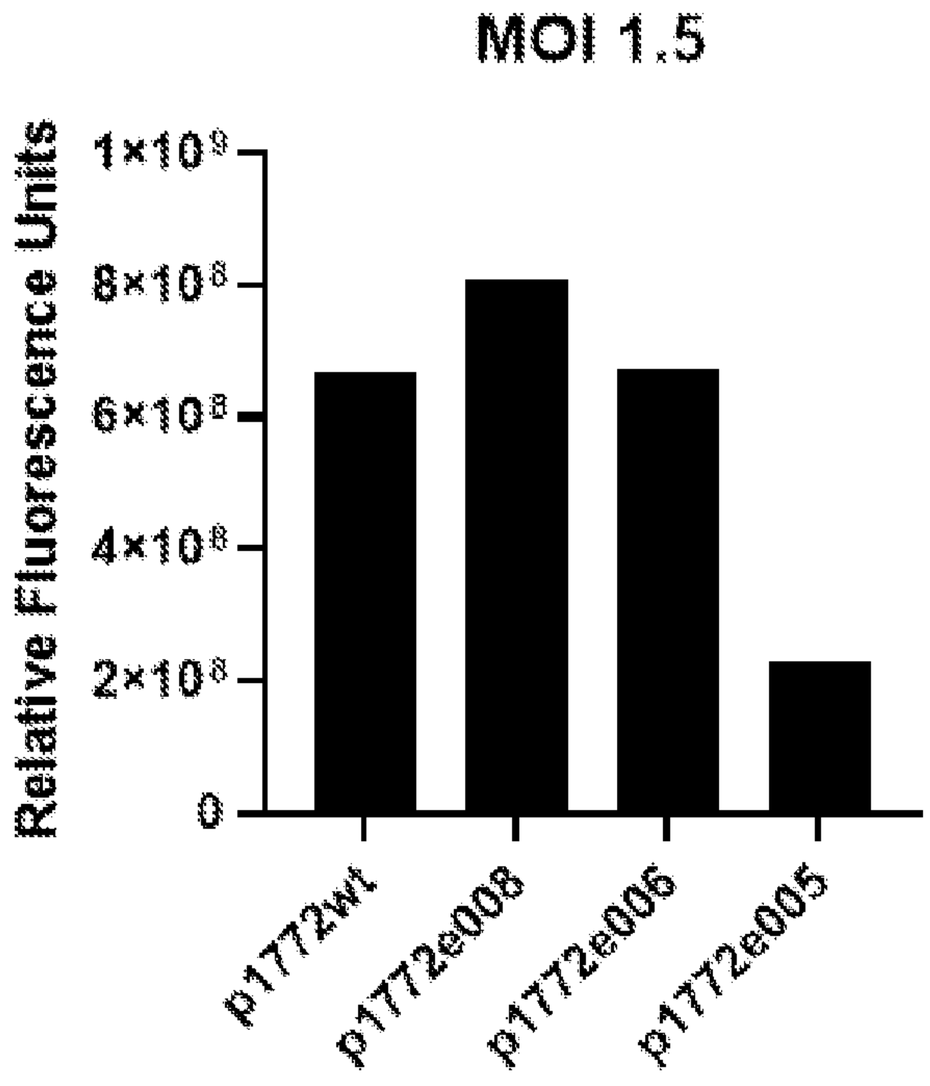

MOI 1.5
Relative Fluorescence Units
1×10^9
8×10^8
6×10^8
4×10^8
2×10^8
0
p1772wt
p1772e008
p1772e006
p1772e005

Fig. 8C

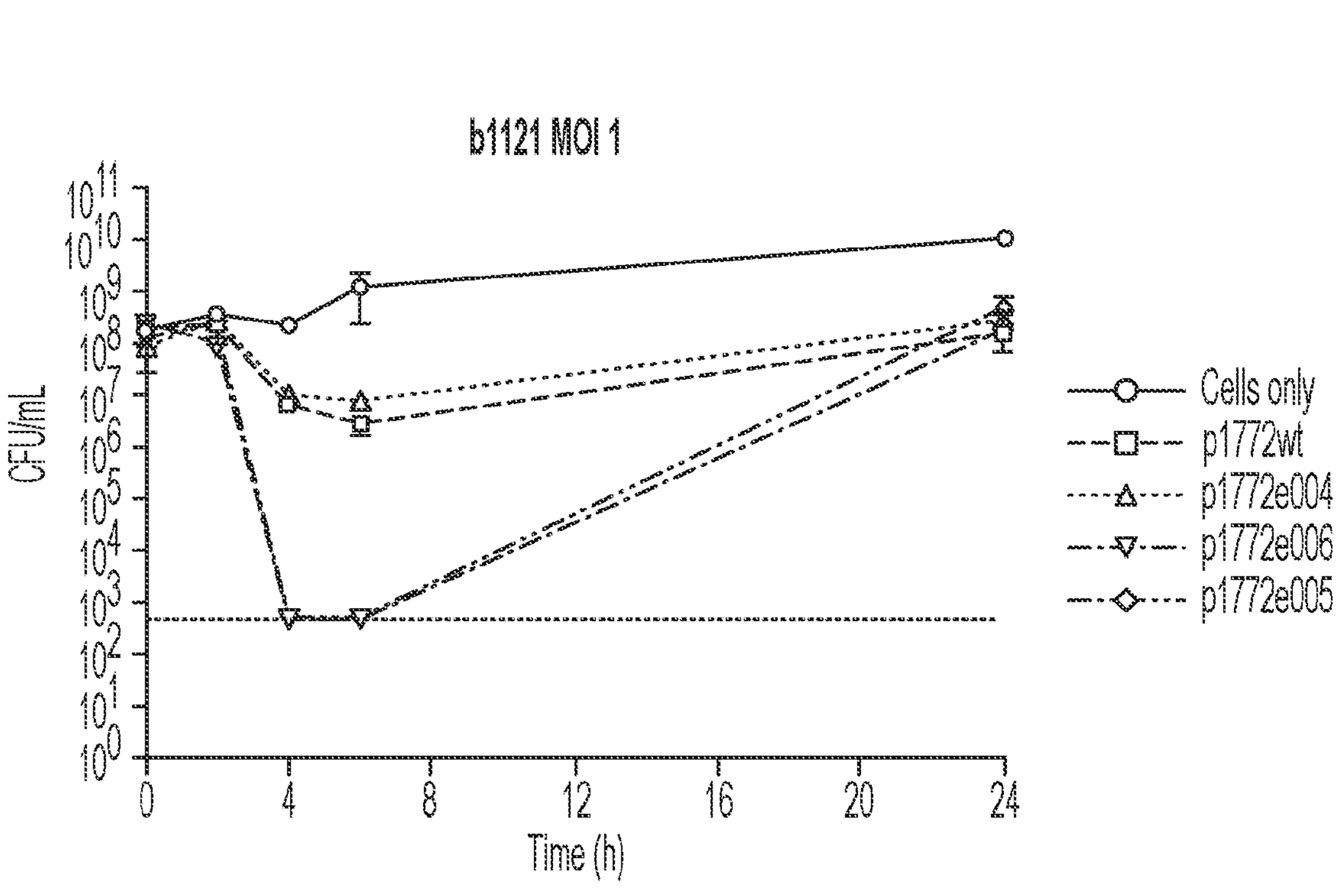

b1121 MOI 1
CFU/mL
Time (h)
Cells only
p1772wt
p1772e004
p1772e006
p1772e005

Fig. 9A

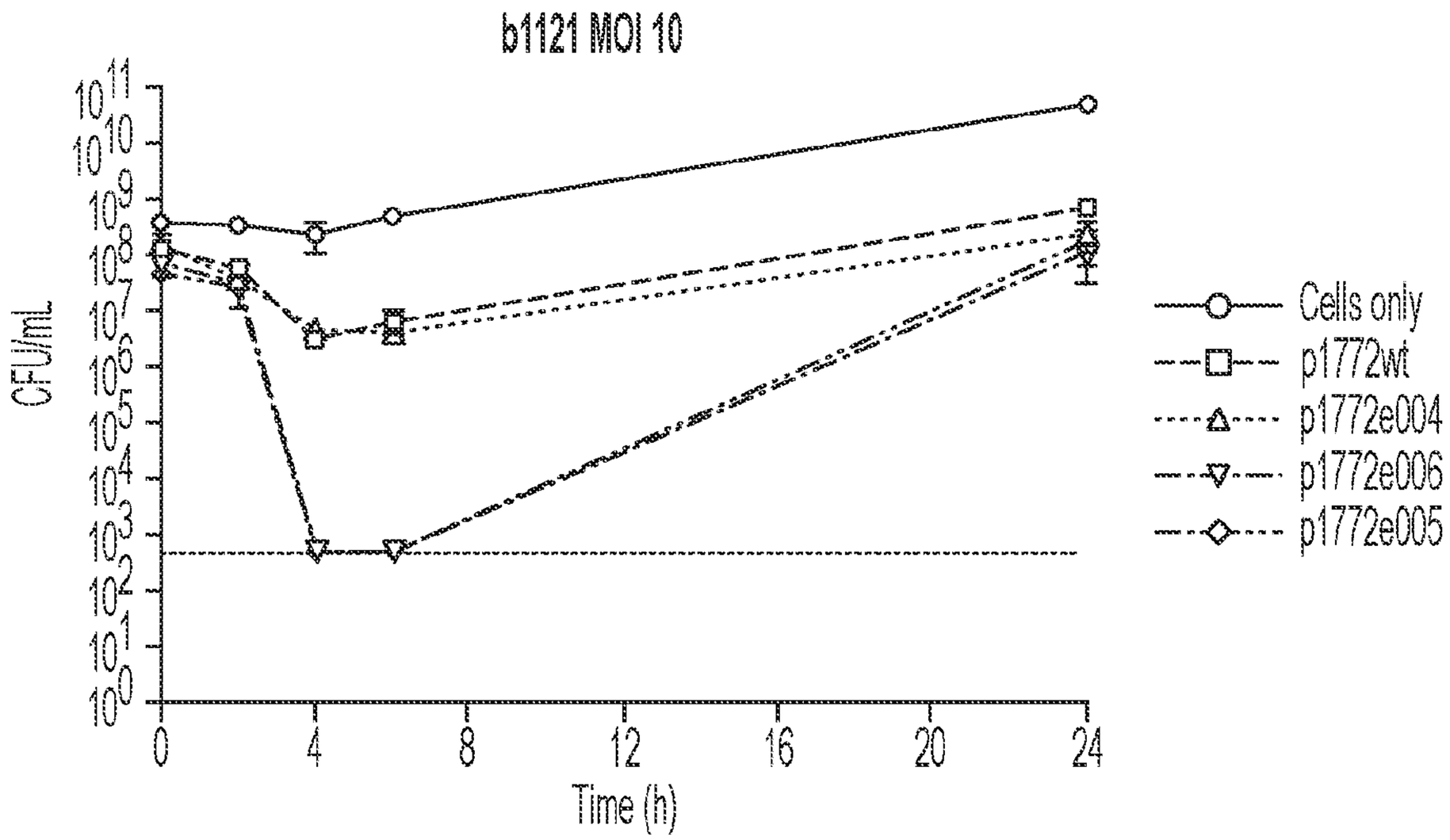

b1121 MOI 10
CFU/mL
Time (h)
Cells only
p1772wt
p1772e004
p1772e006
p1772e005

Fig. 9B

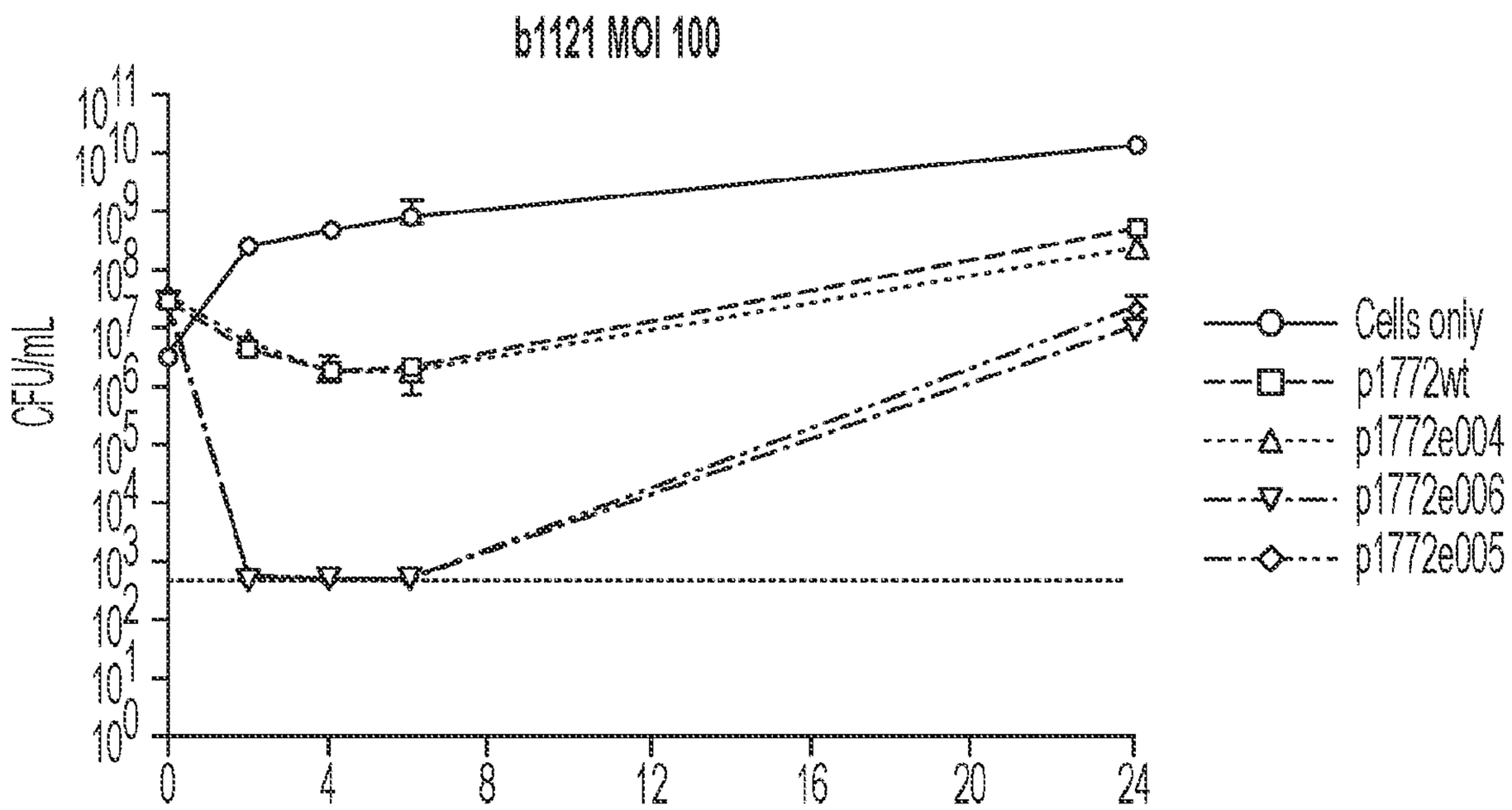

b1121 MOI 100
CFU/mL
Time (h)
Cells only
p1772wt
p1772e004
p1772e006
p1772e005

Fig. 9C

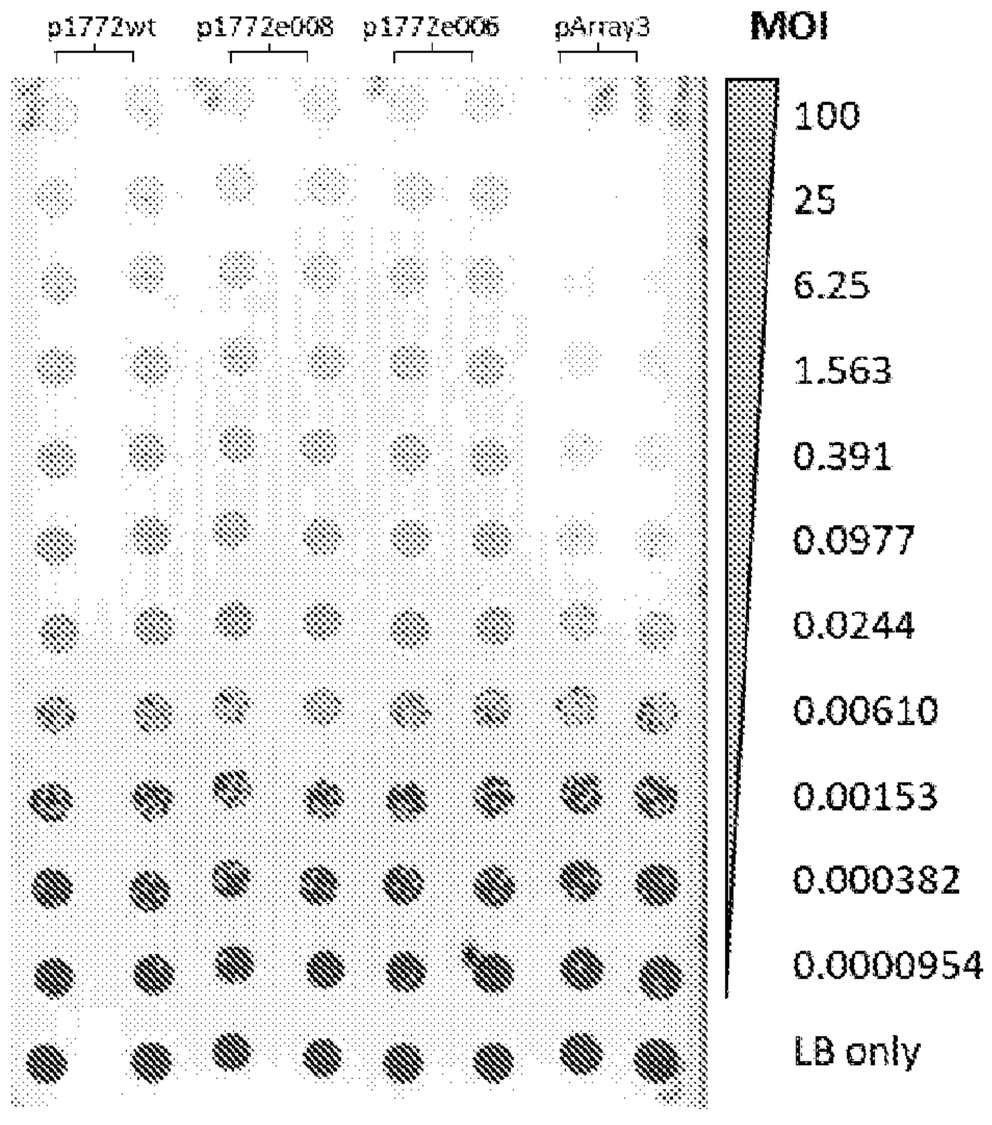


Fig. 10A

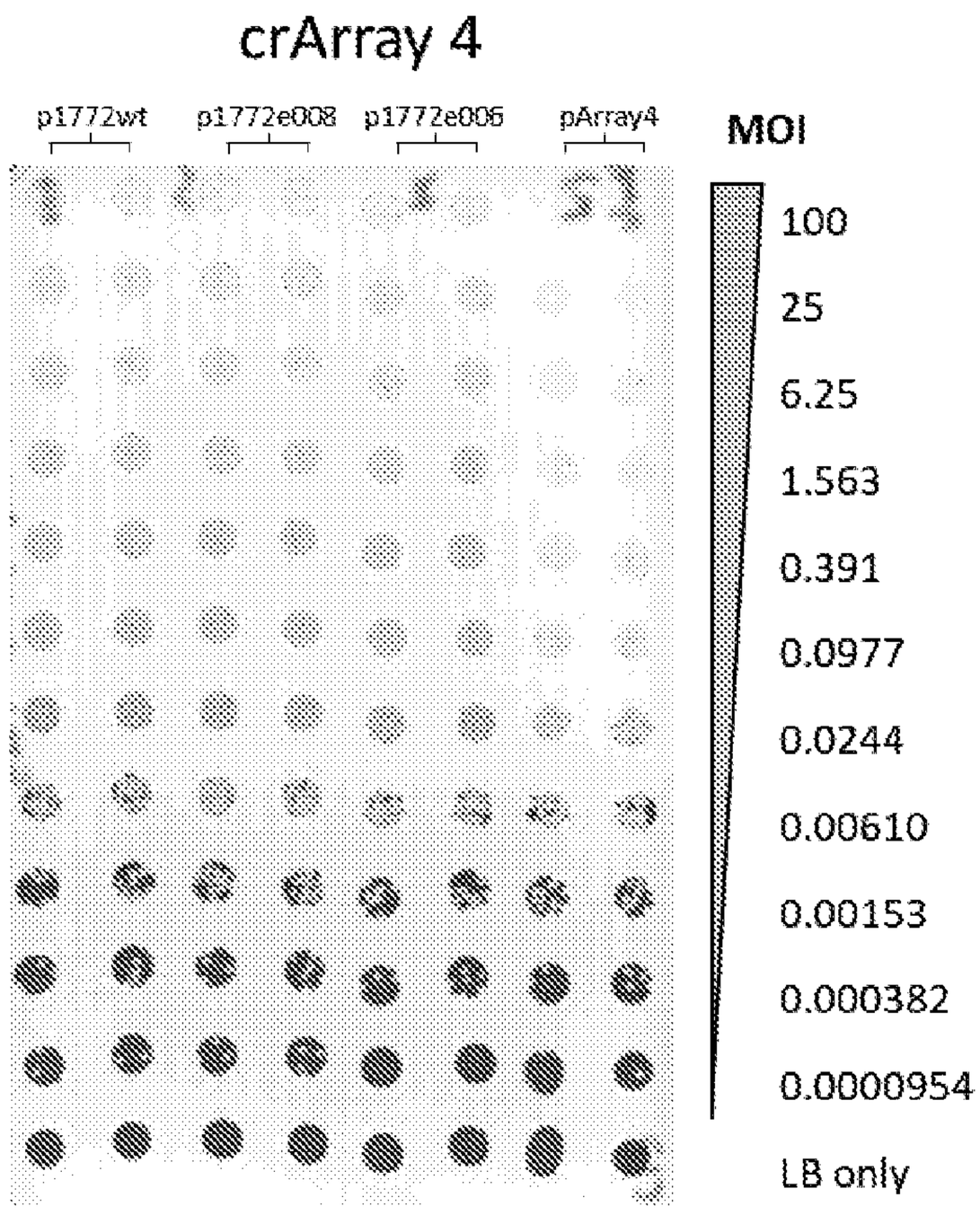


Fig. 10B

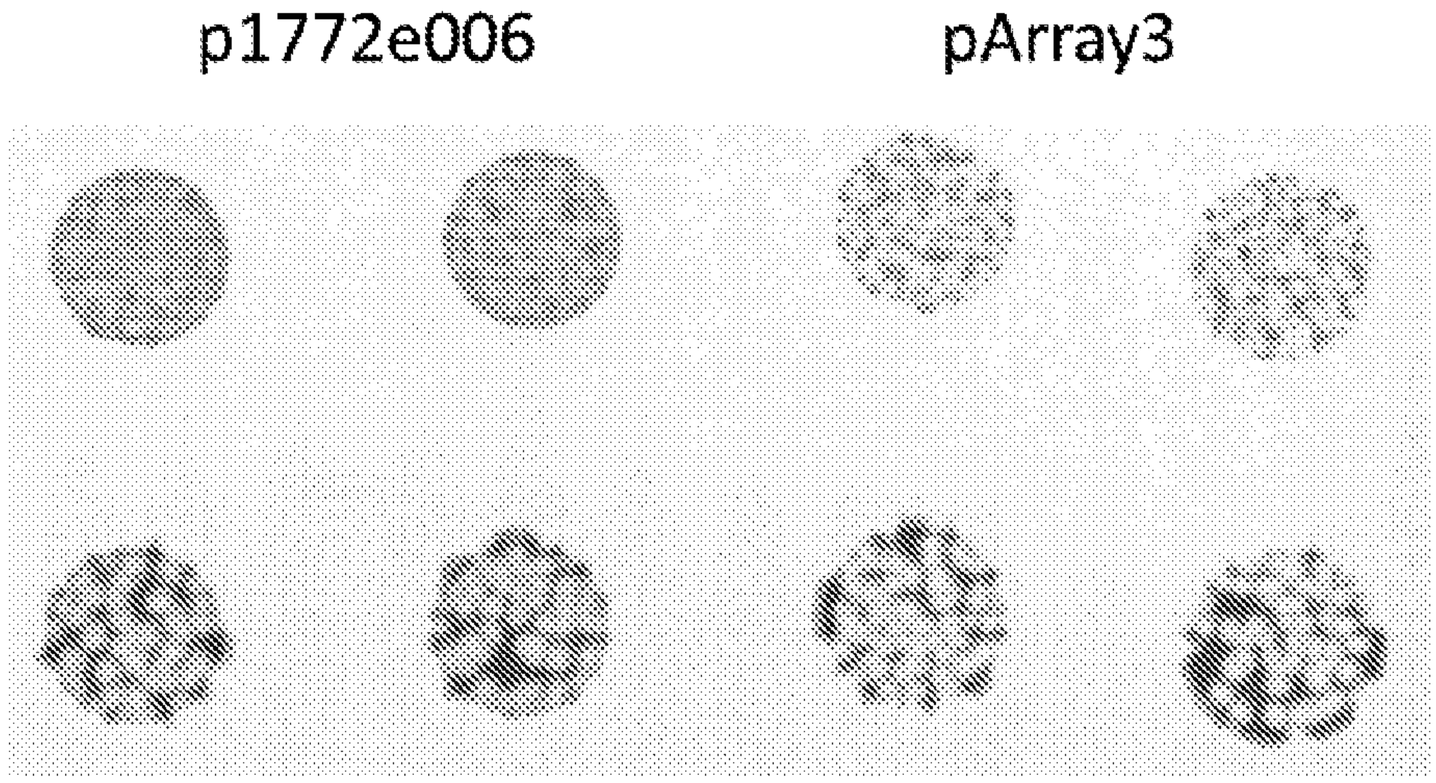


Fig. 10C

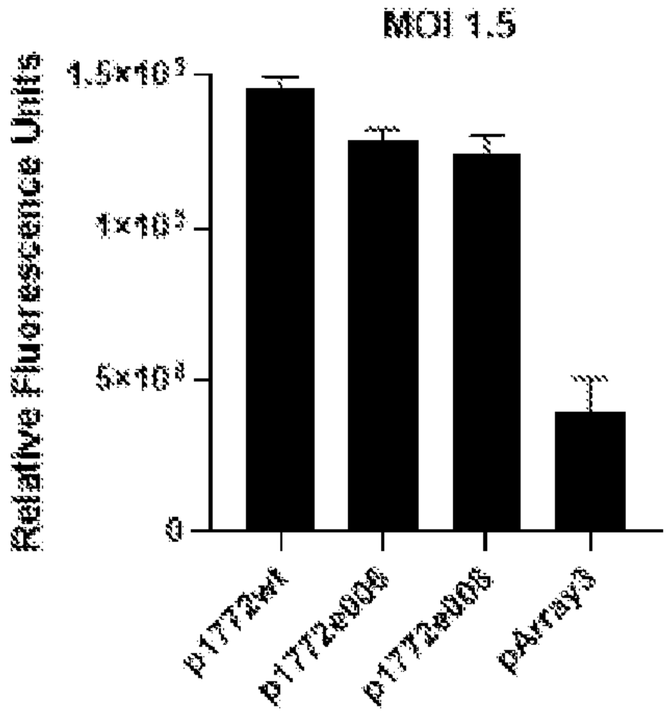


Fig. 10D

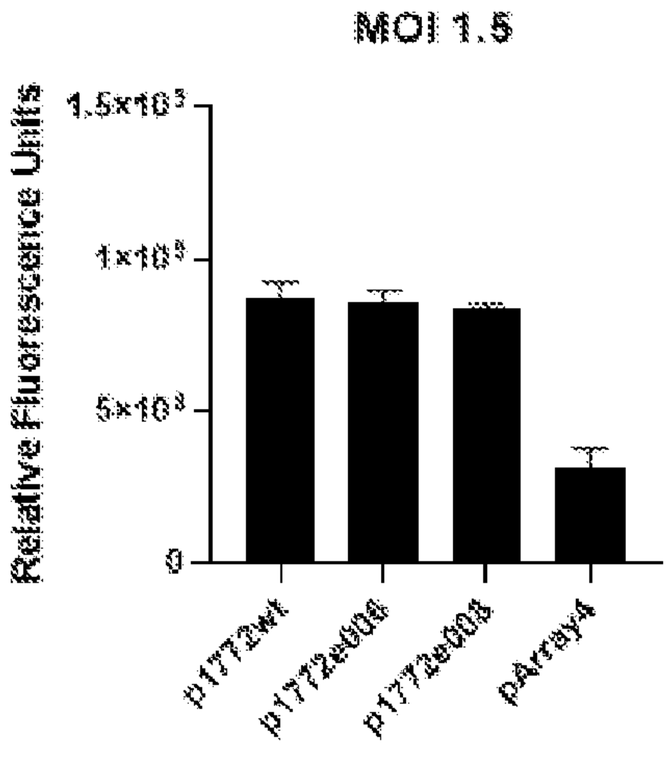


Fig. 10E

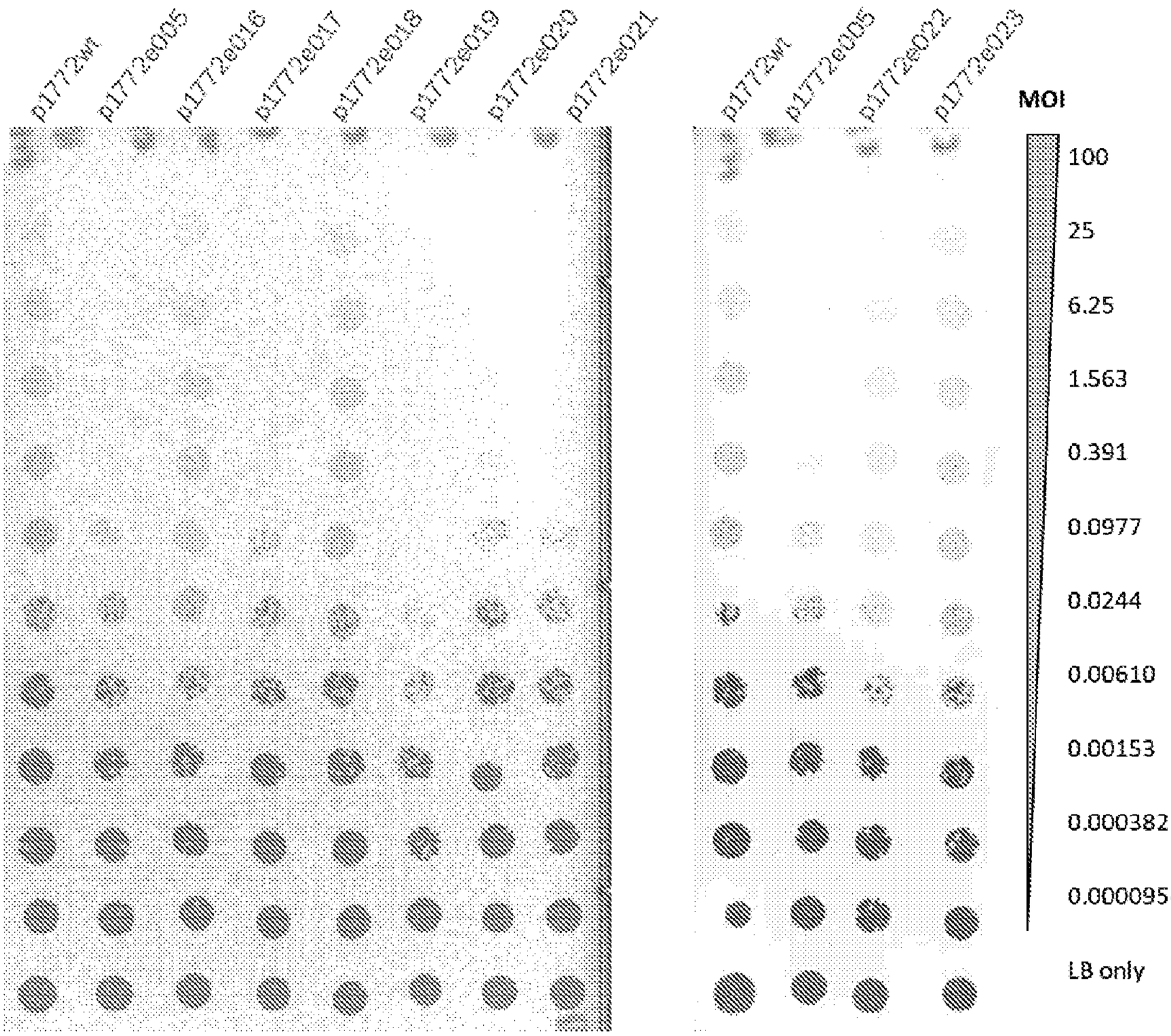

p1772wt
p1772e005
p1772e016
p1772e017
p1772e018
p1772e019
p1772e020
p1772e021
p1772wt
p1772e005
p1772e022
p1772e023
MOI
100
25
6.25
1.563
0.391
0.0977
0.0244
0.00610
0.00153
0.000382
0.0000954
LB only

Fig. 11A

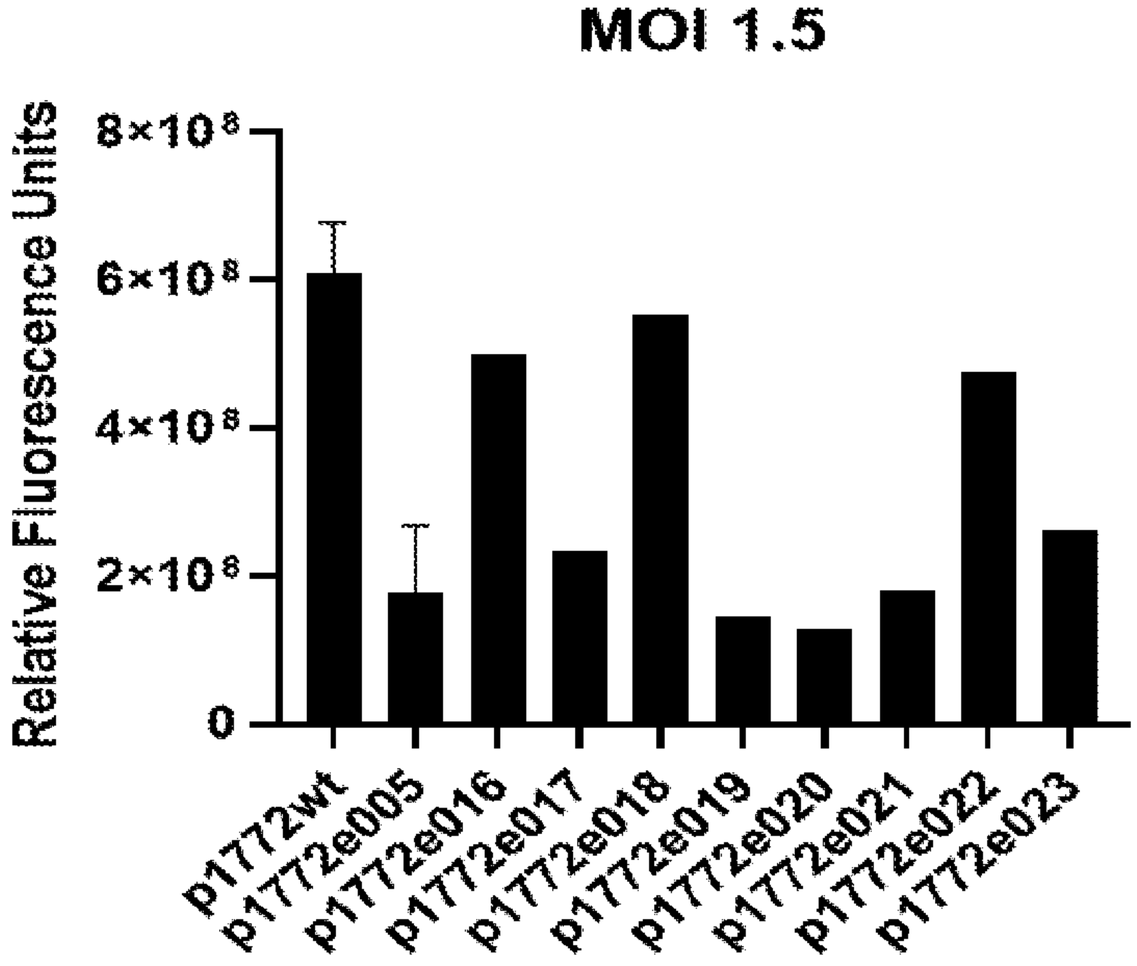


Fig. 11B

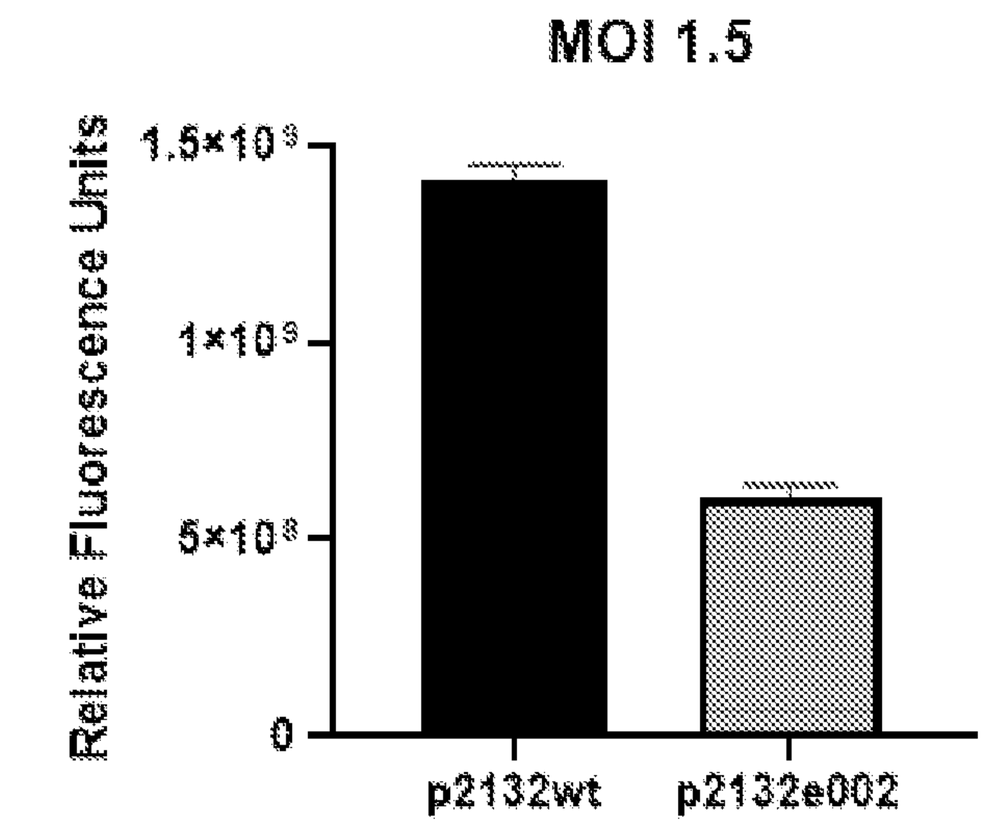


Fig. 12A

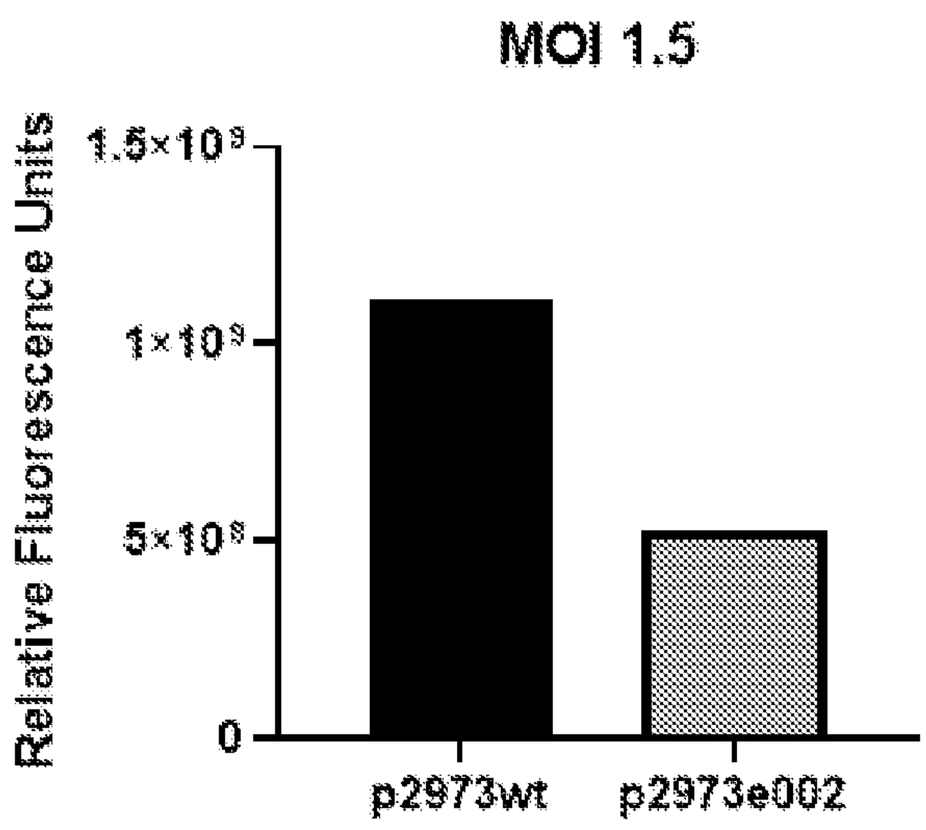

MOI 1.5
Relative Fluorescence Units
1.5×10⁹
1×10⁹
5×10⁸
0
p2973wt
p2973e002

Fig. 12B

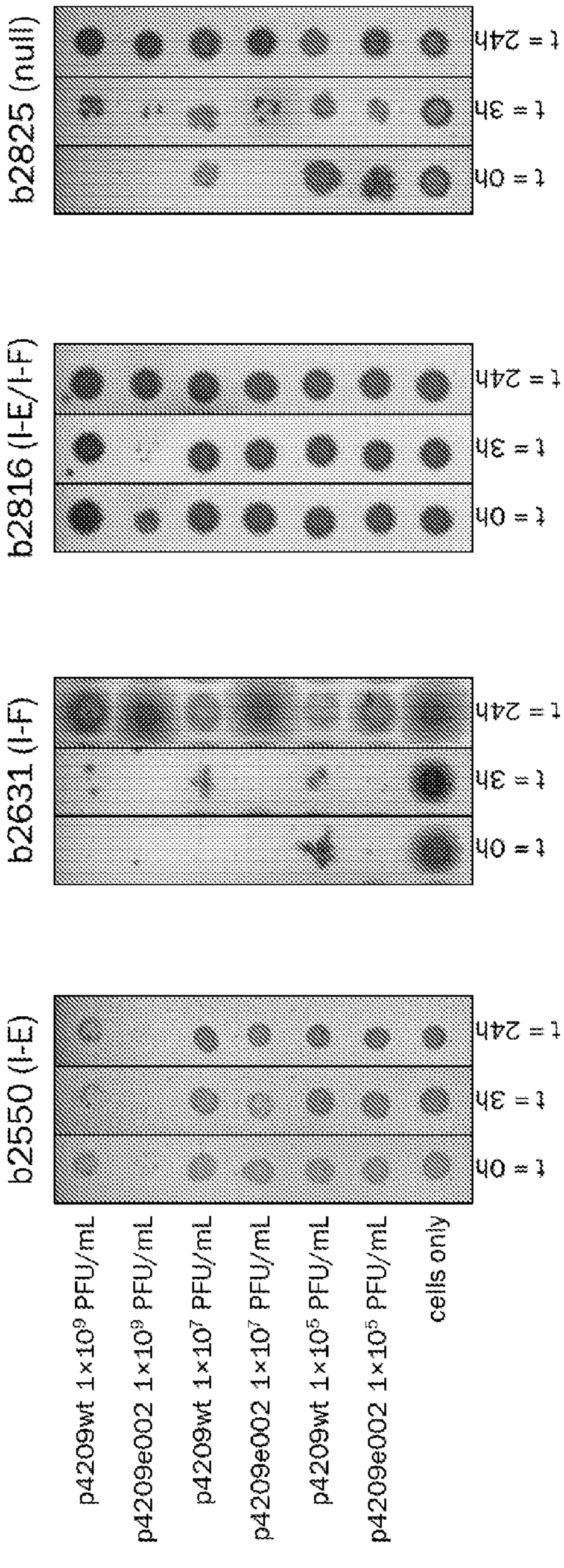

b2825 (null)
b2816 (I-E/I-F)
b2631 (I-F)
b2550 (I-E)
t = 0h
t = 3h
t = 24h
p4209wt 1×10^9 PFU/mL
p4209e002 1×10^9 PFU/mL
p4209wt 1×10^7 PFU/mL
p4209e002 1×10^7 PFU/mL
p4209wt 1×10^5 PFU/mL
p4209e002 1×10^5 PFU/mL
cells only

Fig. 13

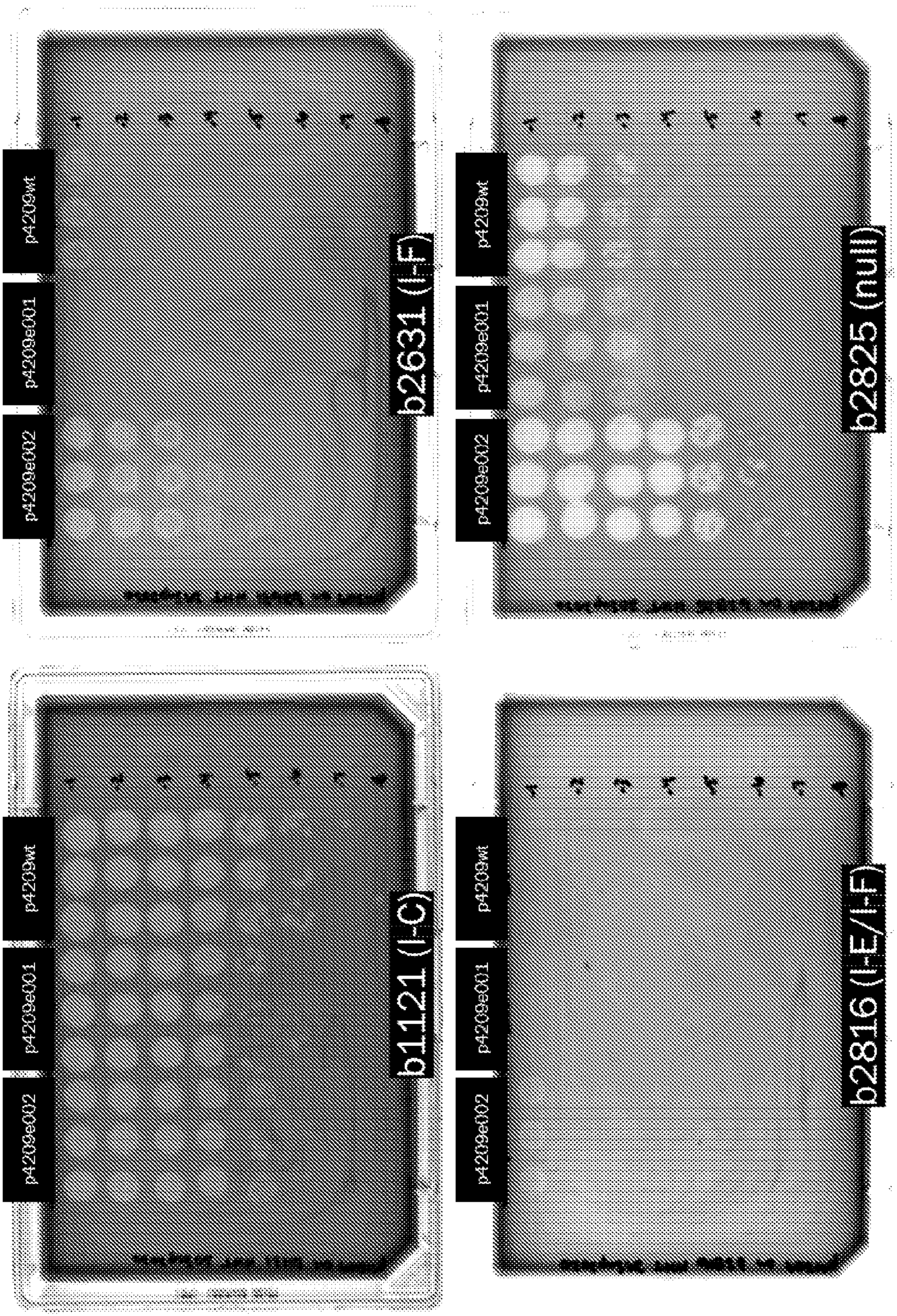
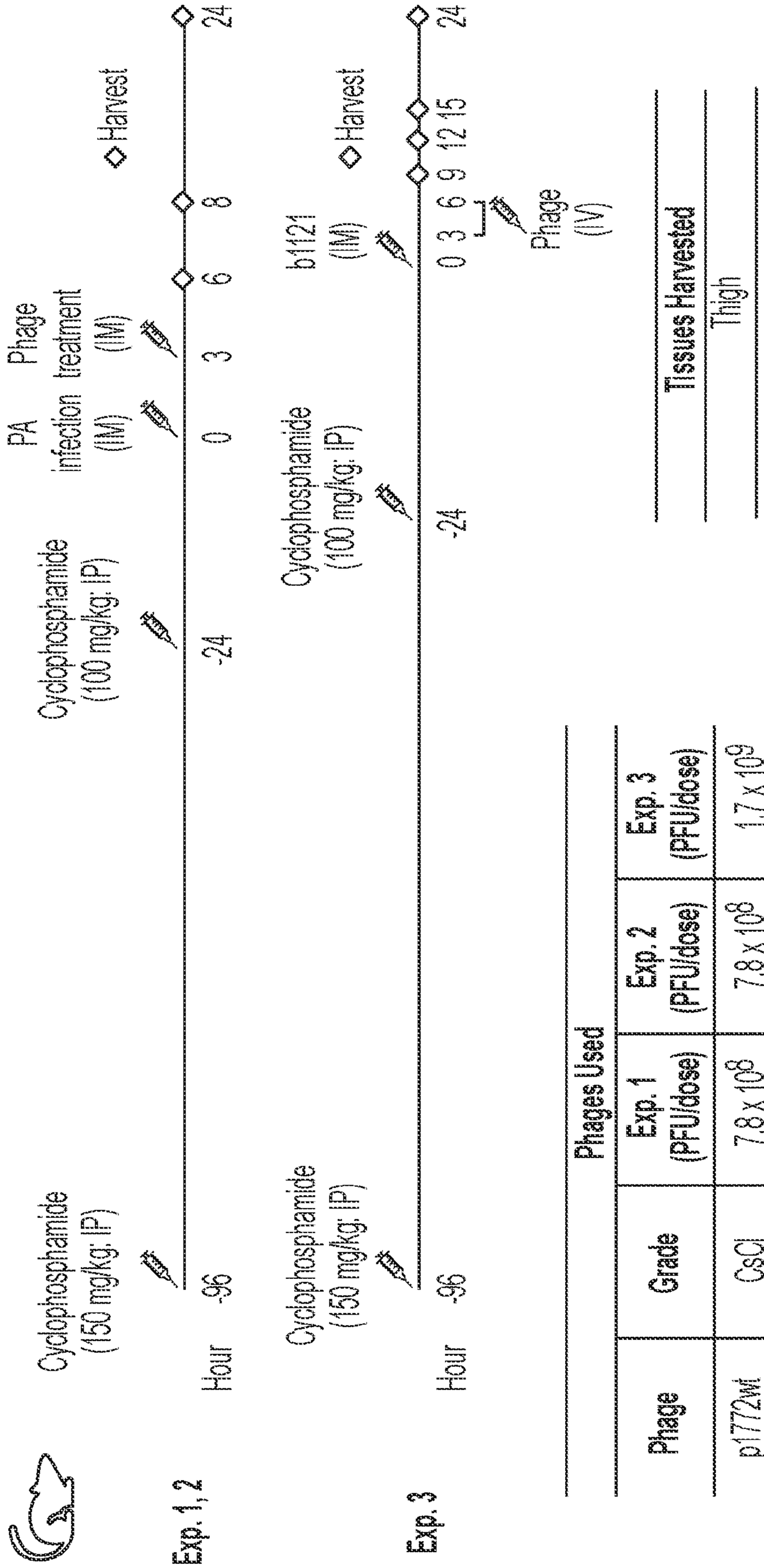

b2631 (I-F)
p4209e002
p4209e001
p4209wt
b2825 (null)
p4209e002
p4209e001
p4209wt
b1121 (I-C)
p4209e002
p4209e001
p4209wt
b2816 (I-E/I-F)
p4209e002
p4209e001
p4209wt

Fig. 14



Phages Used				
Phage	Grade	Exp. 1 (PFU/dose)	Exp. 2 (PFU/dose)	Exp. 3 (PFU/dose)
p1772wt	CsCl	7.8×10^8	7.8×10^8	1.7×10^9
p1772e005	CsCl	1.0×10^9	7.6×10^8	1.2×10^9

Fig. 15A

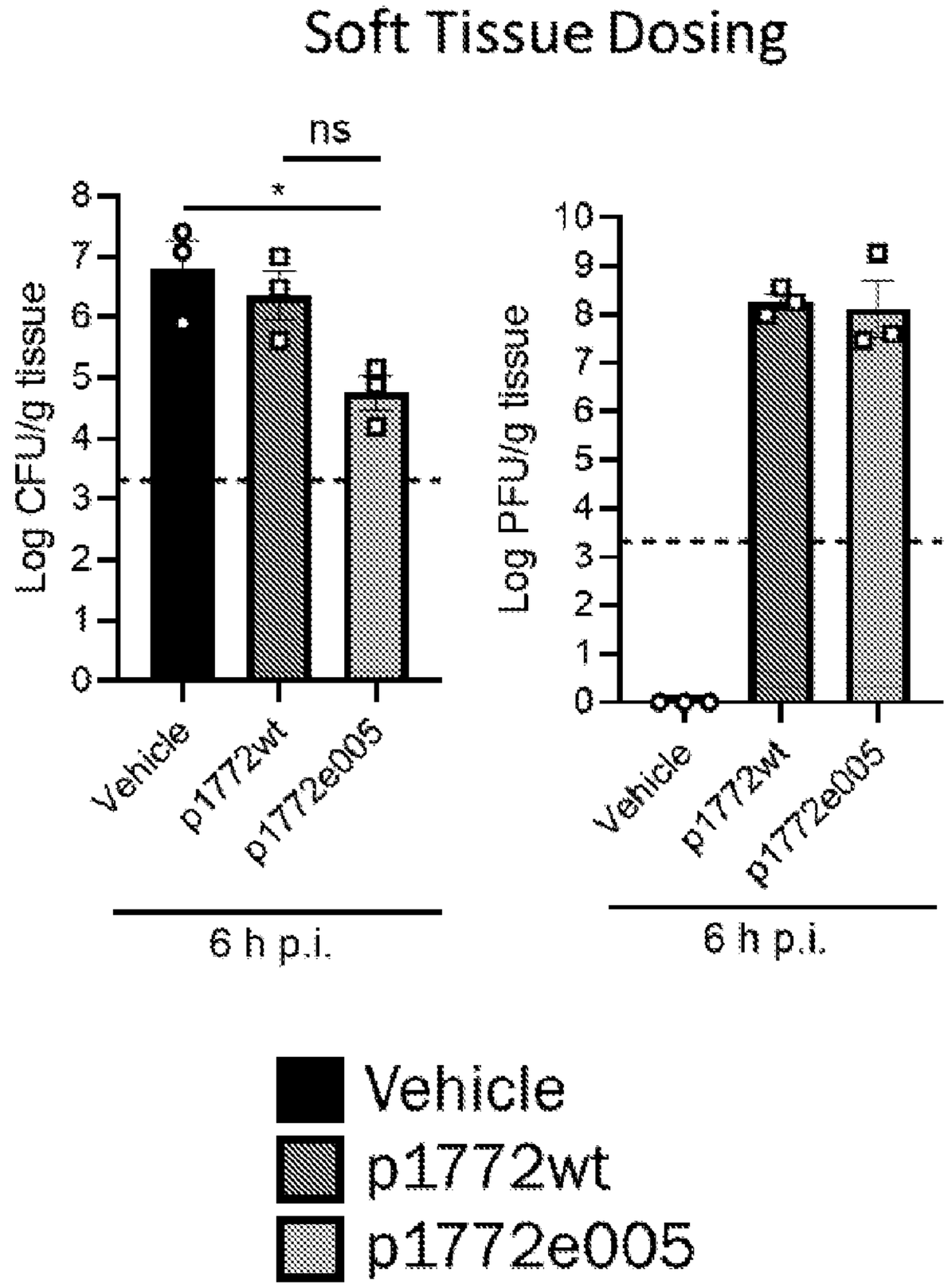

Soft Tissue Dosing
ns
*
Log CFU/g tissue
0
1
2
3
4
5
6
7
8
Vehicle
p1772wt
p1772e005
6 h p.i.
Log PFU/g tissue
0
1
2
3
4
5
6
7
8
9
10
Vehicle
p1772wt
p1772e005
6 h p.i.
Vehicle
p1772wt
p1772e005

Fig. 15B

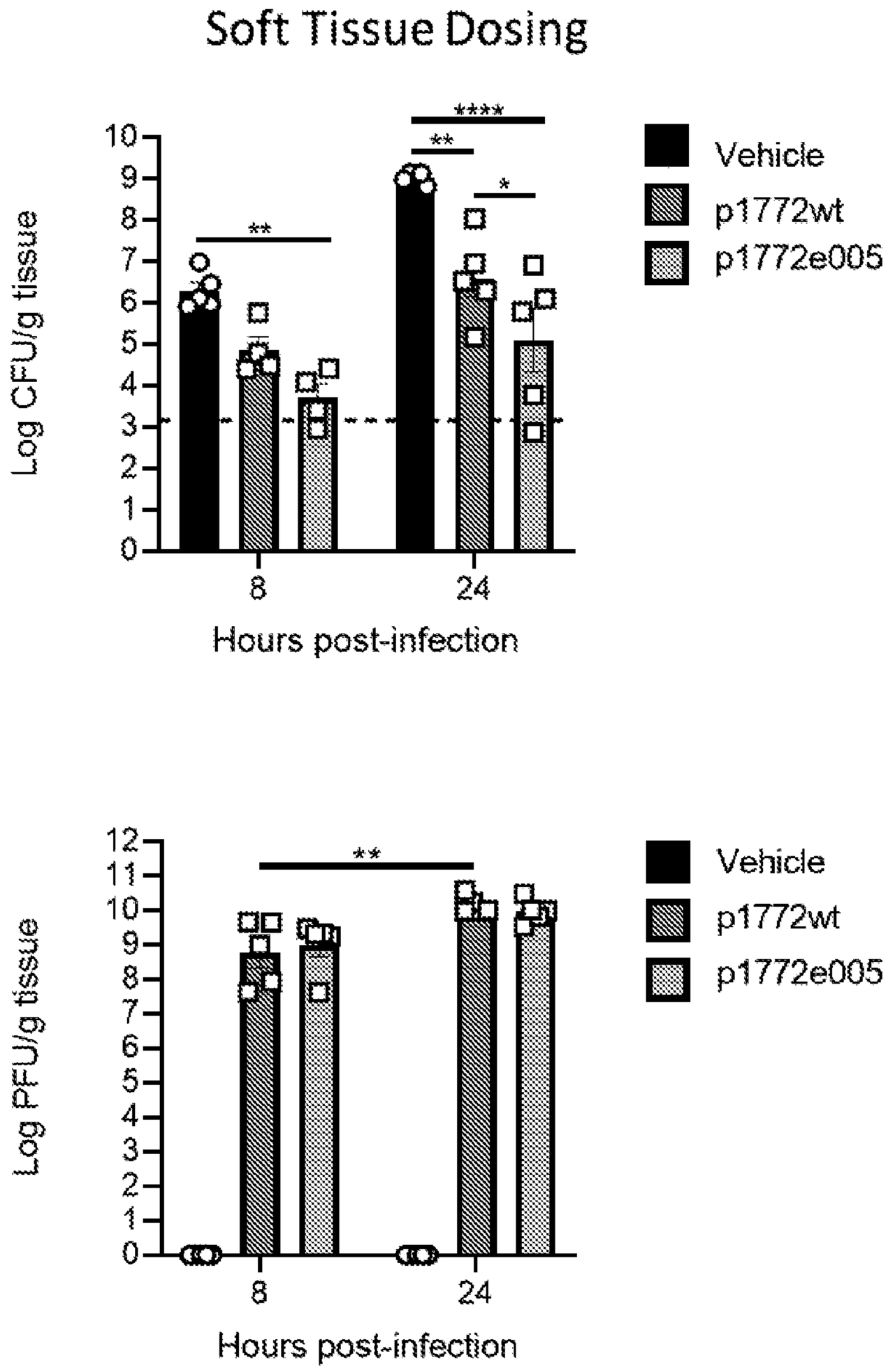

Soft Tissue Dosing
Log CFU/g tissue
10
9
8
7
6
5
4
3
2
1
0
**
**
****
*
8
24
Hours post-infection
Vehicle
p1772wt
p1772e005
Log PFU/g tissue
12
11
10
9
8
7
6
5
4
3
2
1
0
**
8
24
Hours post-infection
Vehicle
p1772wt
p1772e005

Fig. 15C

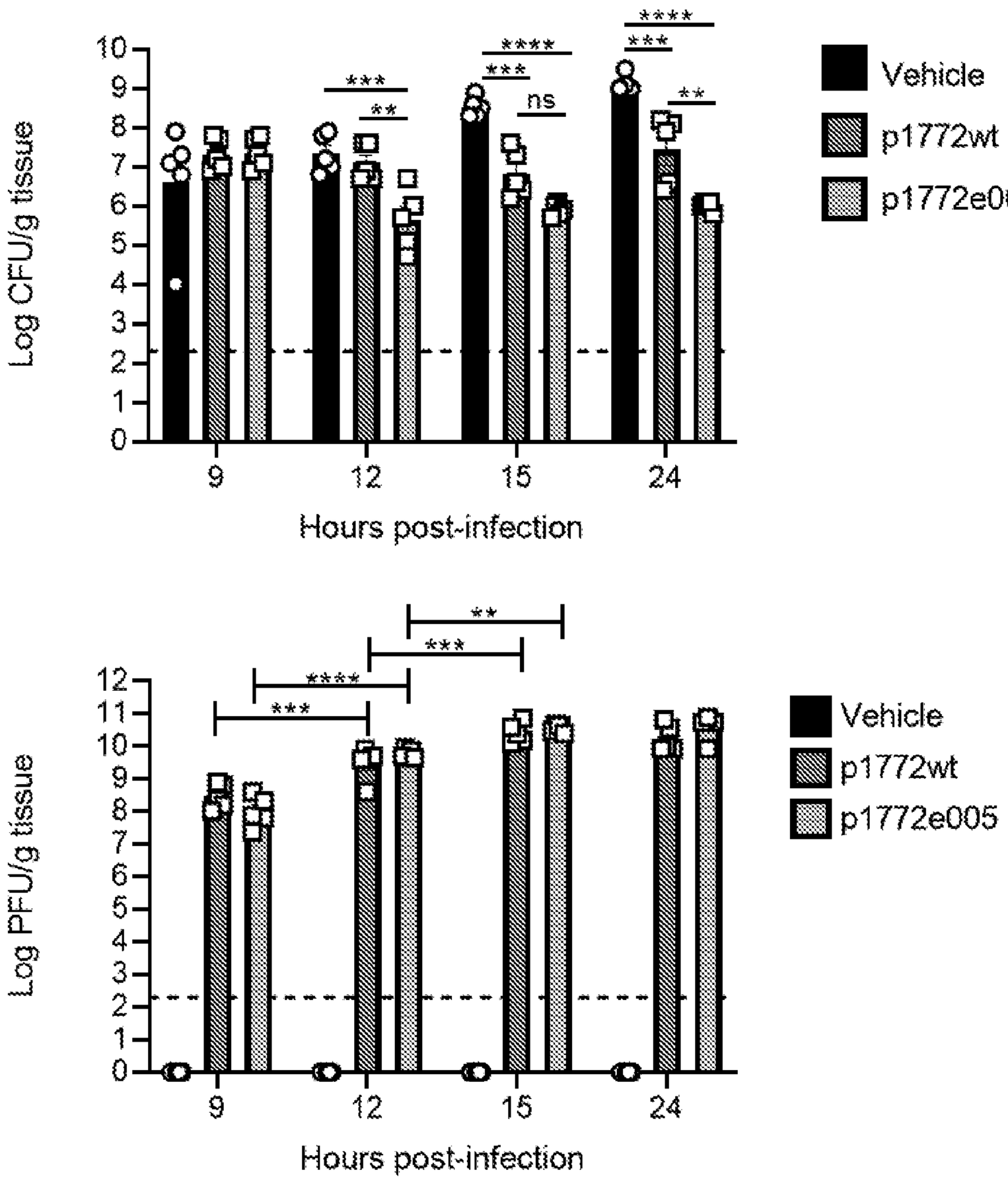
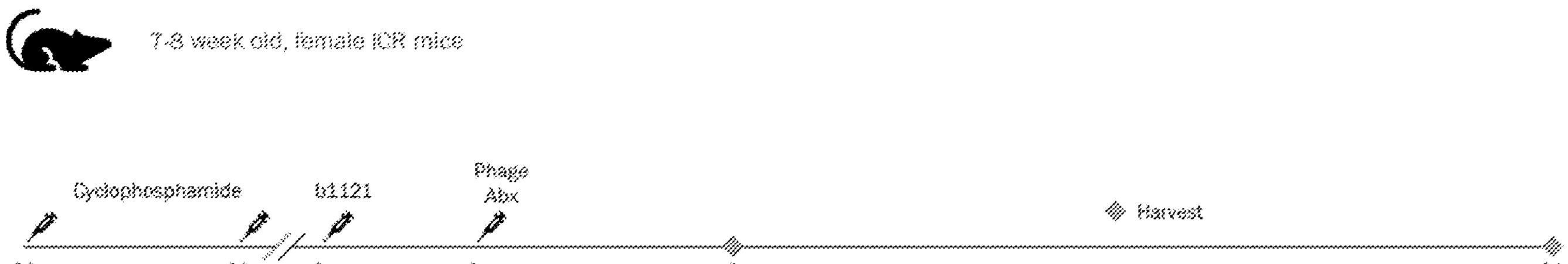

Intravenous Dosing
Log CFU/g tissue
Hours post-infection
Vehicle
p1772wt
p1772e005
***
**
****
***
ns
****
***
**
Log PFU/g tissue
Hours post-infection
Vehicle
p1772wt
p1772e005
**
***
****
***

Fig. 15D

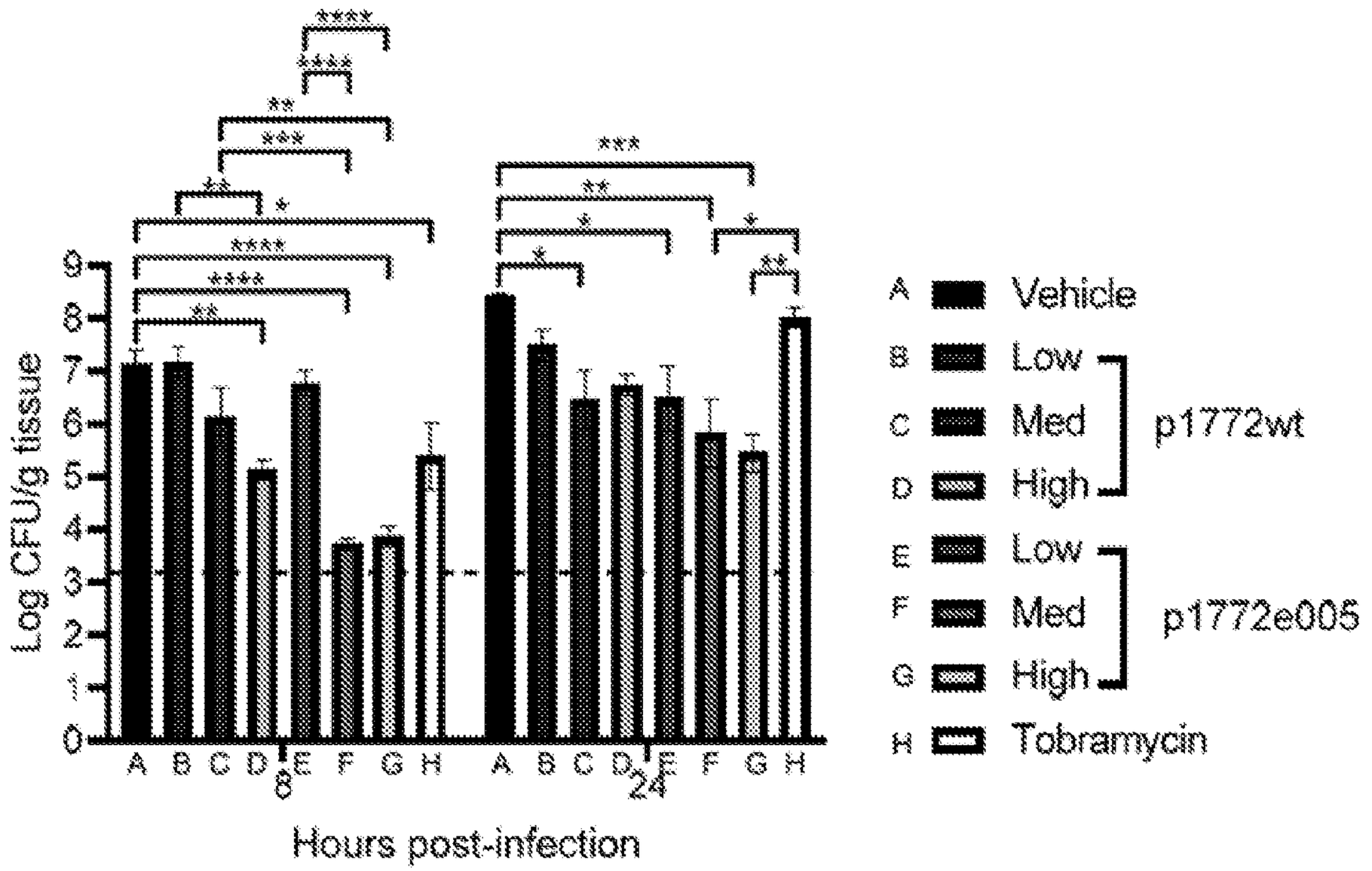


Phages Utilized					
Phage	Grade	High Dose (PFU)	Medium Dose (PFU)	Low Dose (PFU)	Antibiotic Dose
p1772wt	CsCl	6.3×10^{10}	4.9×10^{7}	6.8×10^{4}	
p1772e005	CsCl	4.9×10^{10}	6.5×10^{7}	6.9×10^{4}	
Tobramycin					75 mg/kg/day

Organs/Tissues Harvested
Thigh

Fig. 15E

SUBSTITUTE SHEET (RULE 26)


Log CFU/g tissue
0
1
2
3
4
5
6
7
8
9
A B C D E F G H A B C D E F G H
8
24
Hours post-infection
A Vehicle
B Low
C Med
D High
p1772wt
E Low
F Med
G High
p1772e005
H Tobramycin

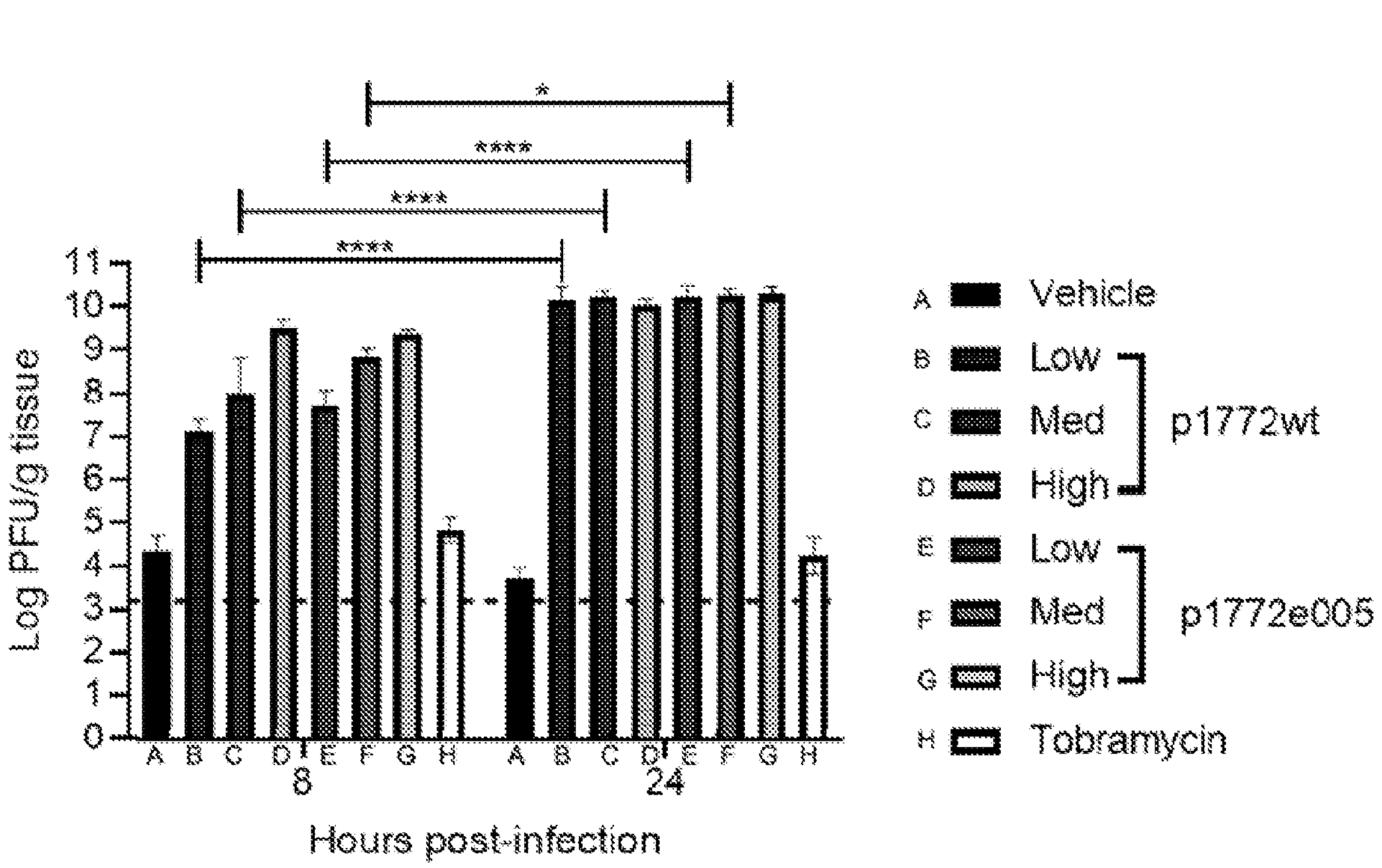

Log PFU/g tissue
0
1
2
3
4
5
6
7
8
9
10
11
A B C D E F G H A B C D E F G H
8
24
Hours post-infection
A Vehicle
B Low
C Med
D High
p1772wt
E Low
F Med
G High
p1772e005
H Tobramycin

Fig. 15F

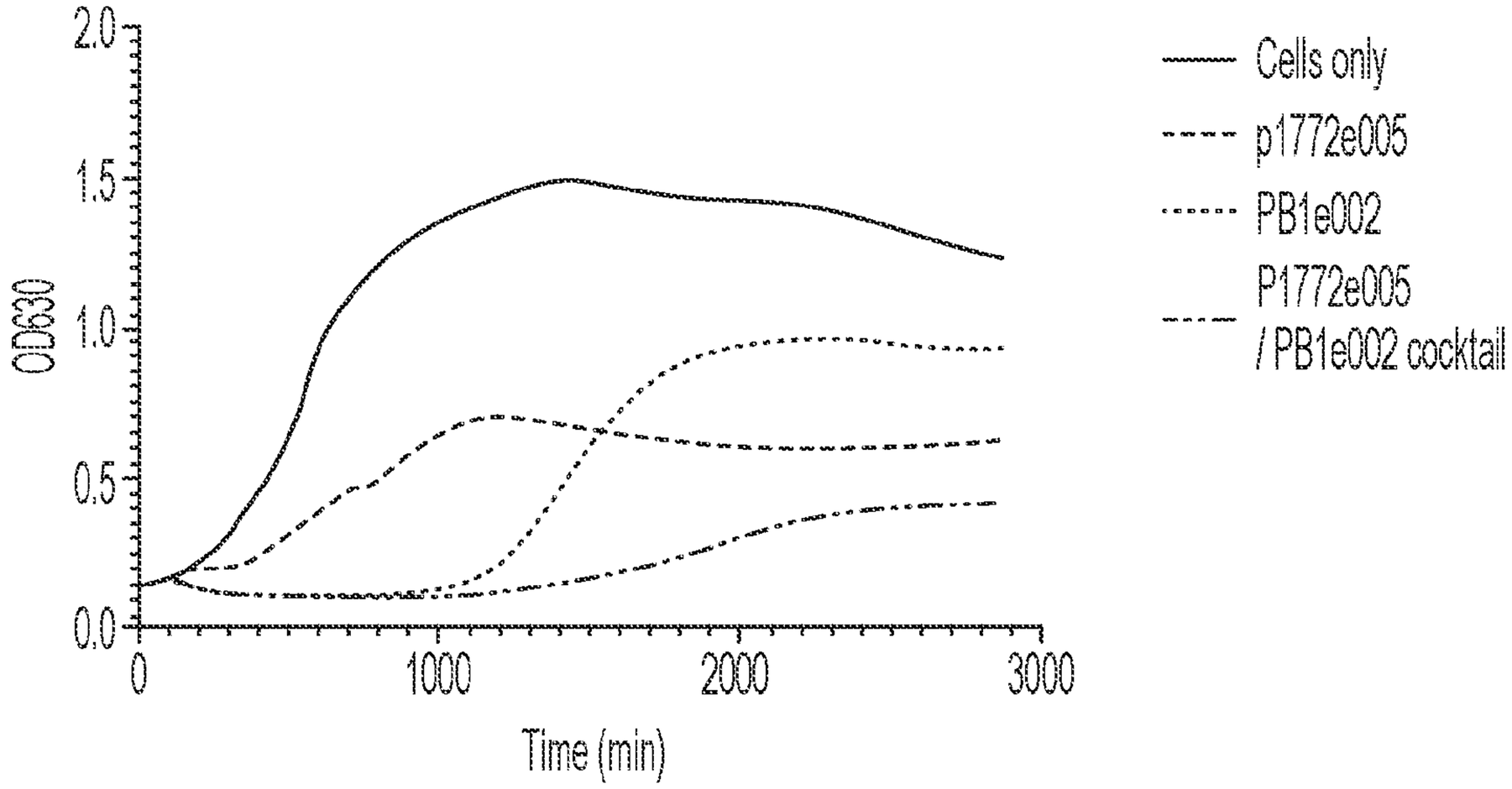

OD630
2.0
1.5
1.0
0.5
0.0
0
1000
2000
3000
Time (min)
Cells only
p1772e005
PB1e002
P1772e005 / PB1e002 cocktail

Fig. 16

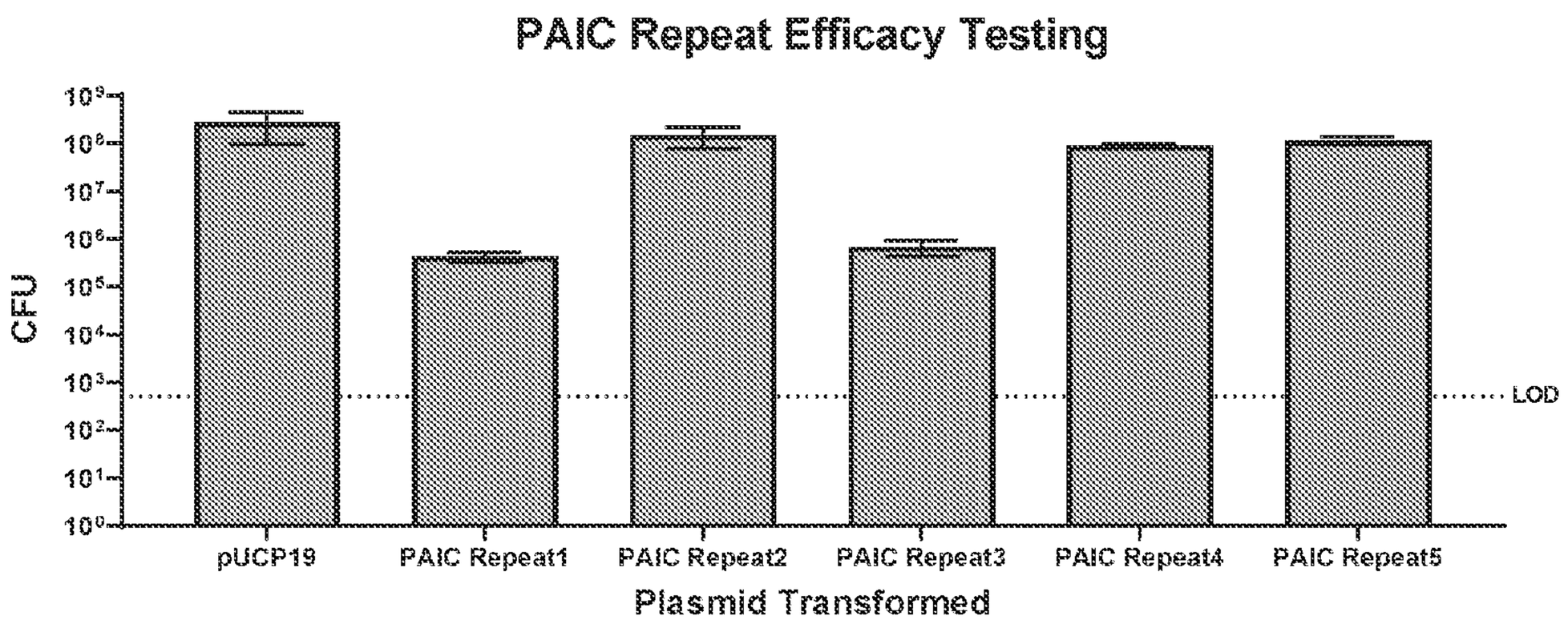

PAIC Repeat Efficacy Testing
CFU
LOD
pUCP19
PAIC Repeat1
PAIC Repeat2
PAIC Repeat3
PAIC Repeat4
PAIC Repeat5
Plasmid Transformed

Fig. 17

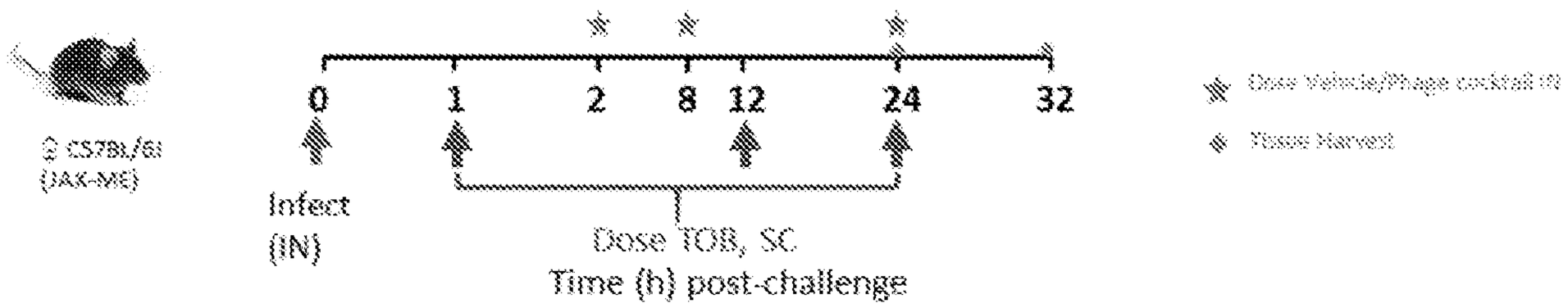
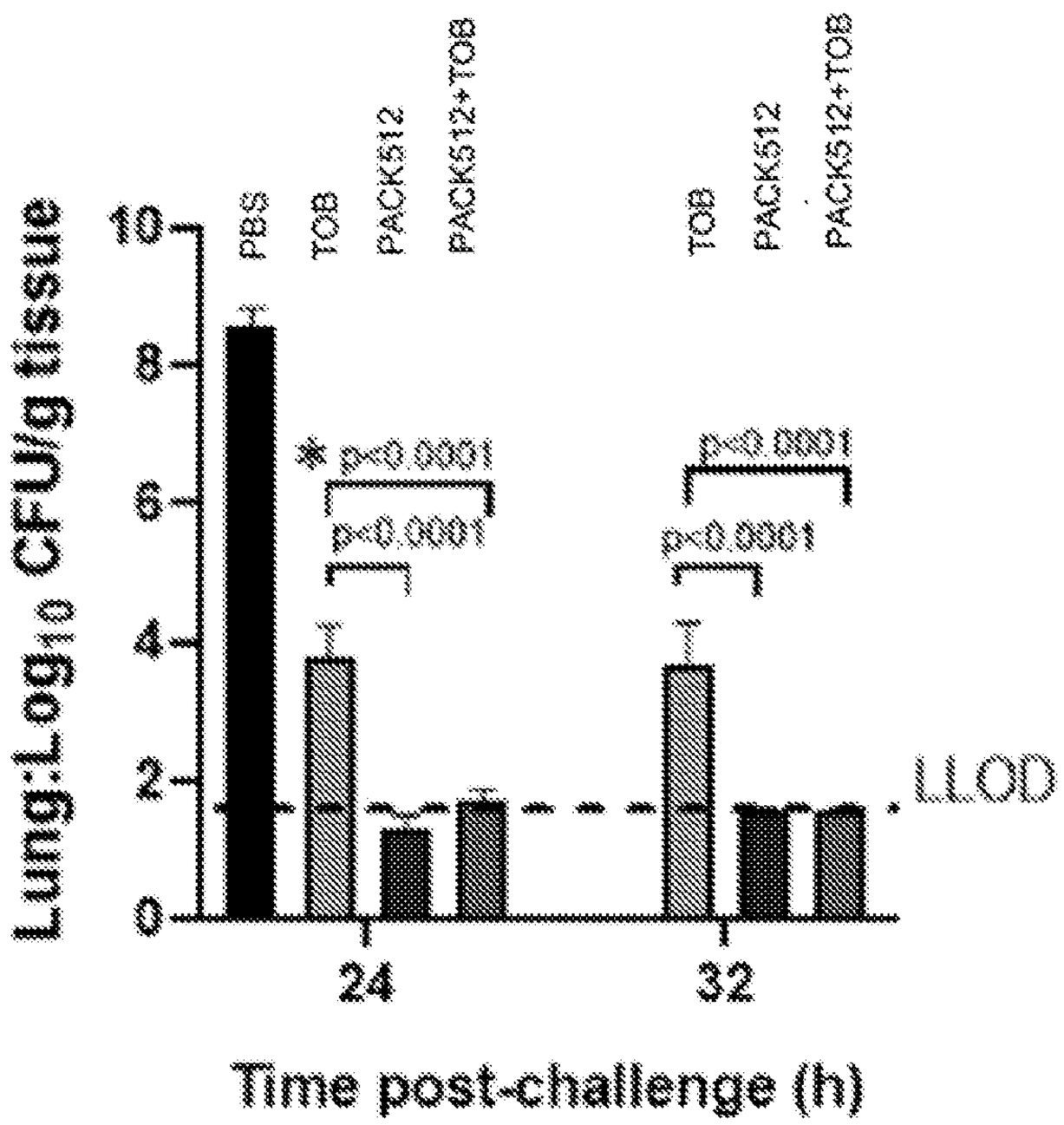
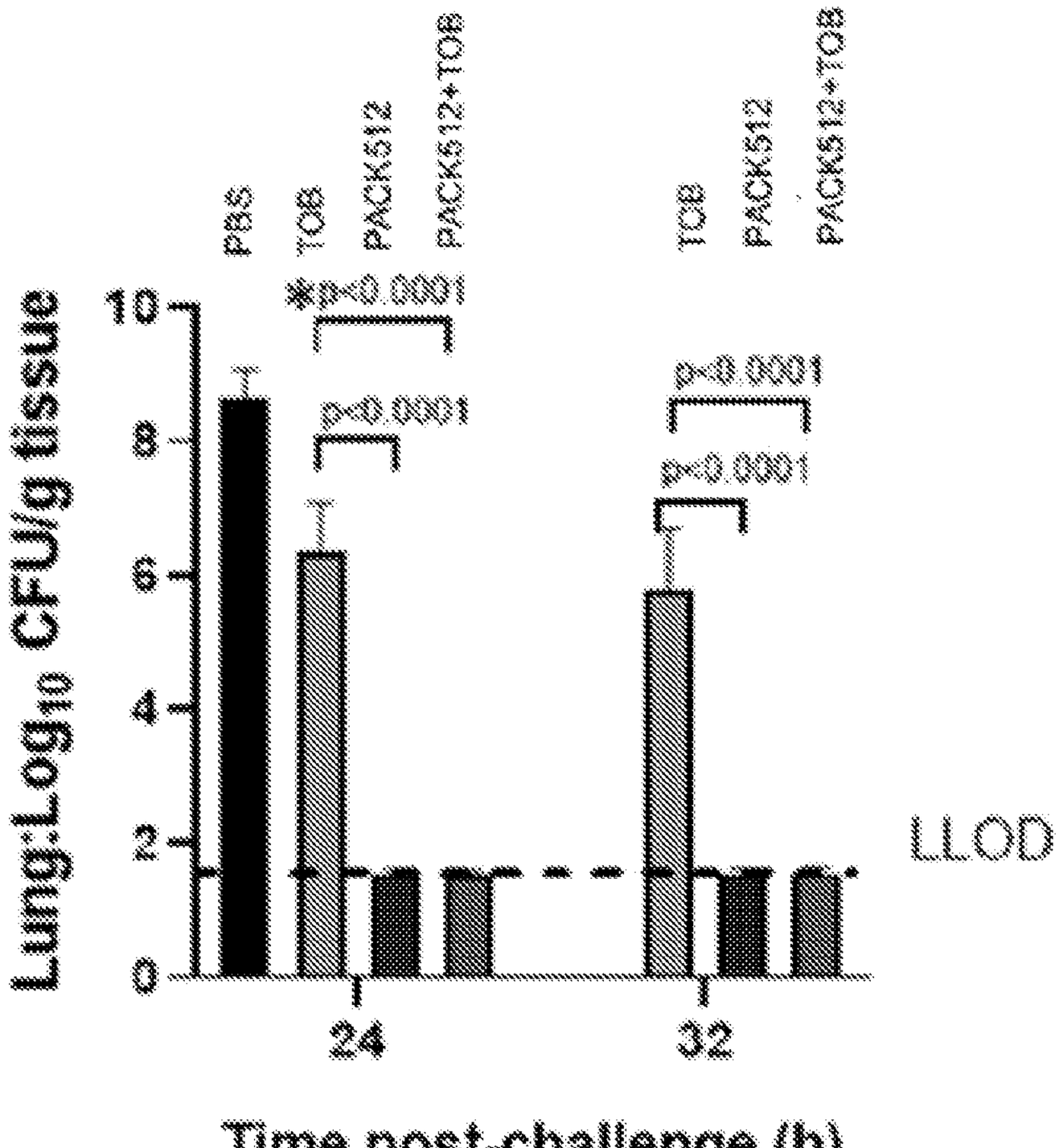


Fig. 18A



P. aeruginosa b2631
2018 CF isolate
TOB MIC 0.5 μg/mL

Fig. 18B



P. aeruginosa b1121
Respiratory isolate
TOB MIC 0.5 μg/mL

Fig. 18C

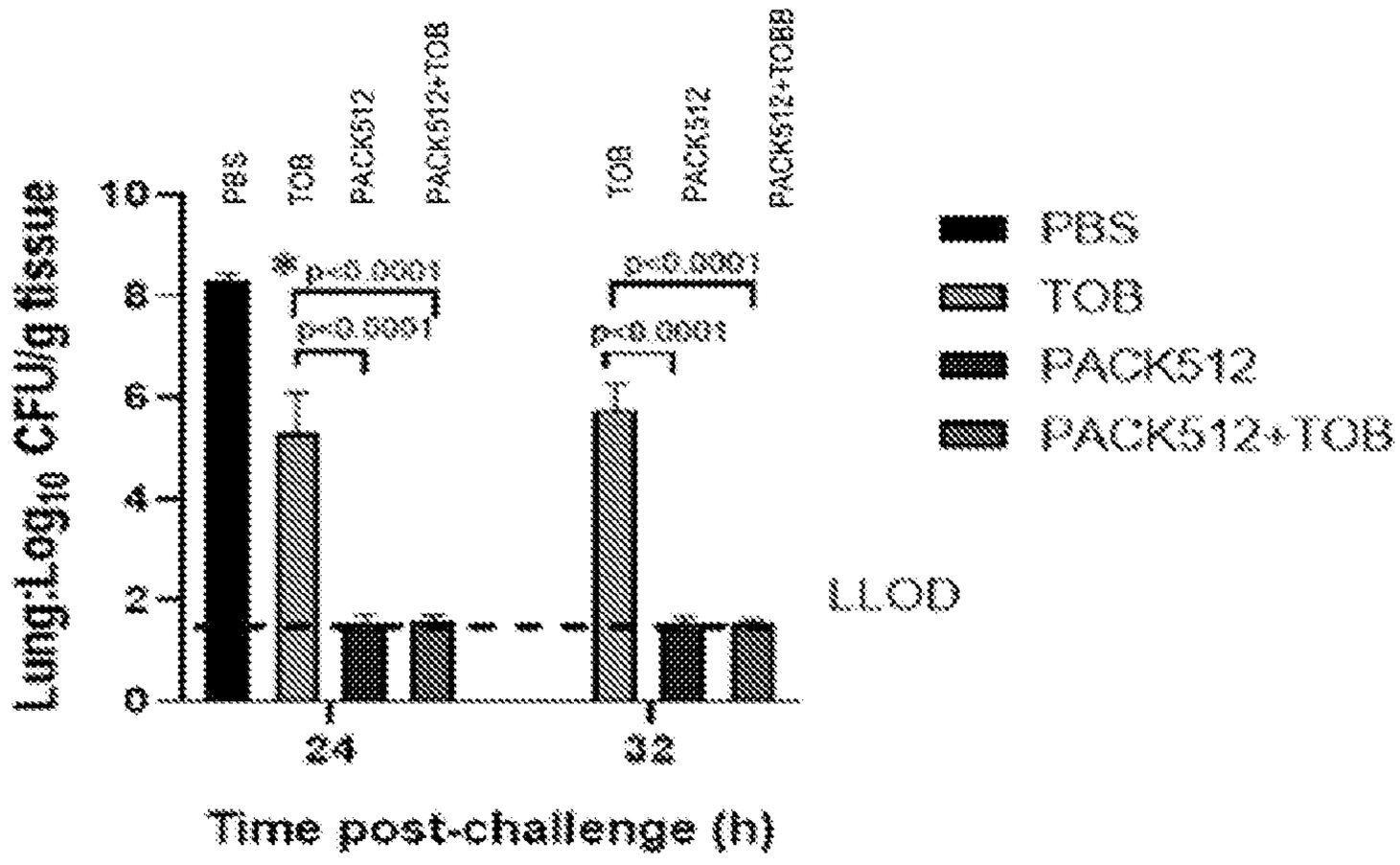


Fig. 18D

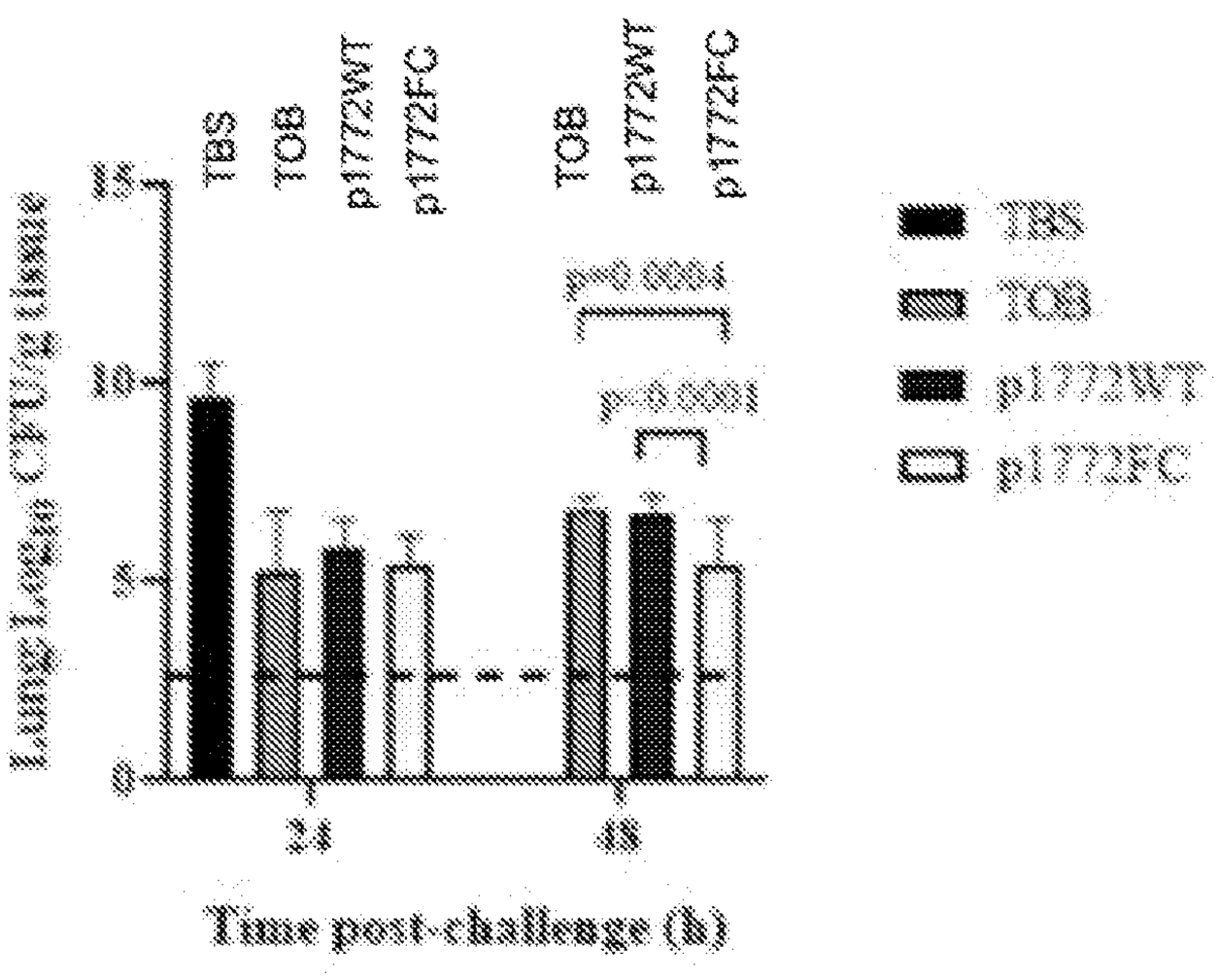


Fig. 18E

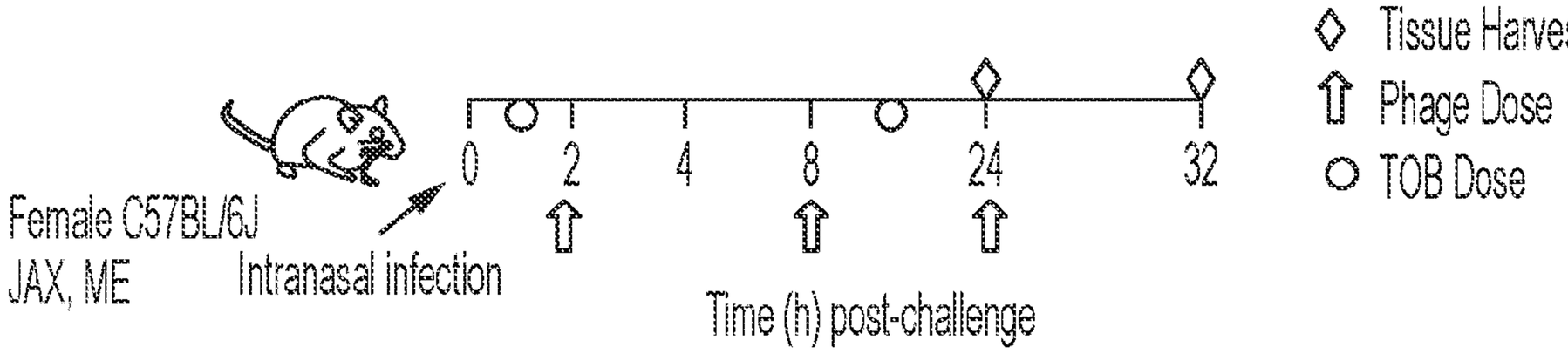


Fig. 18F

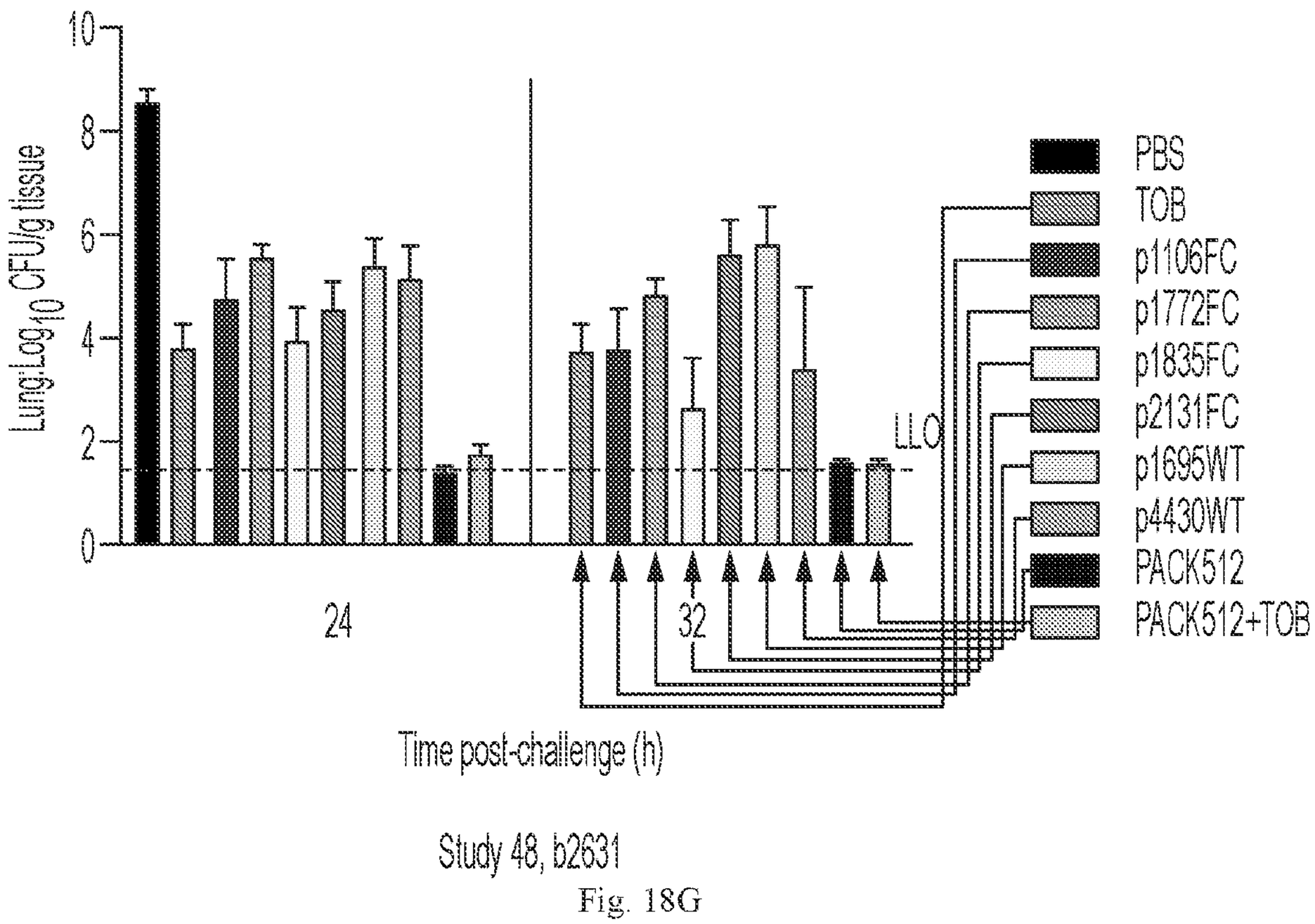
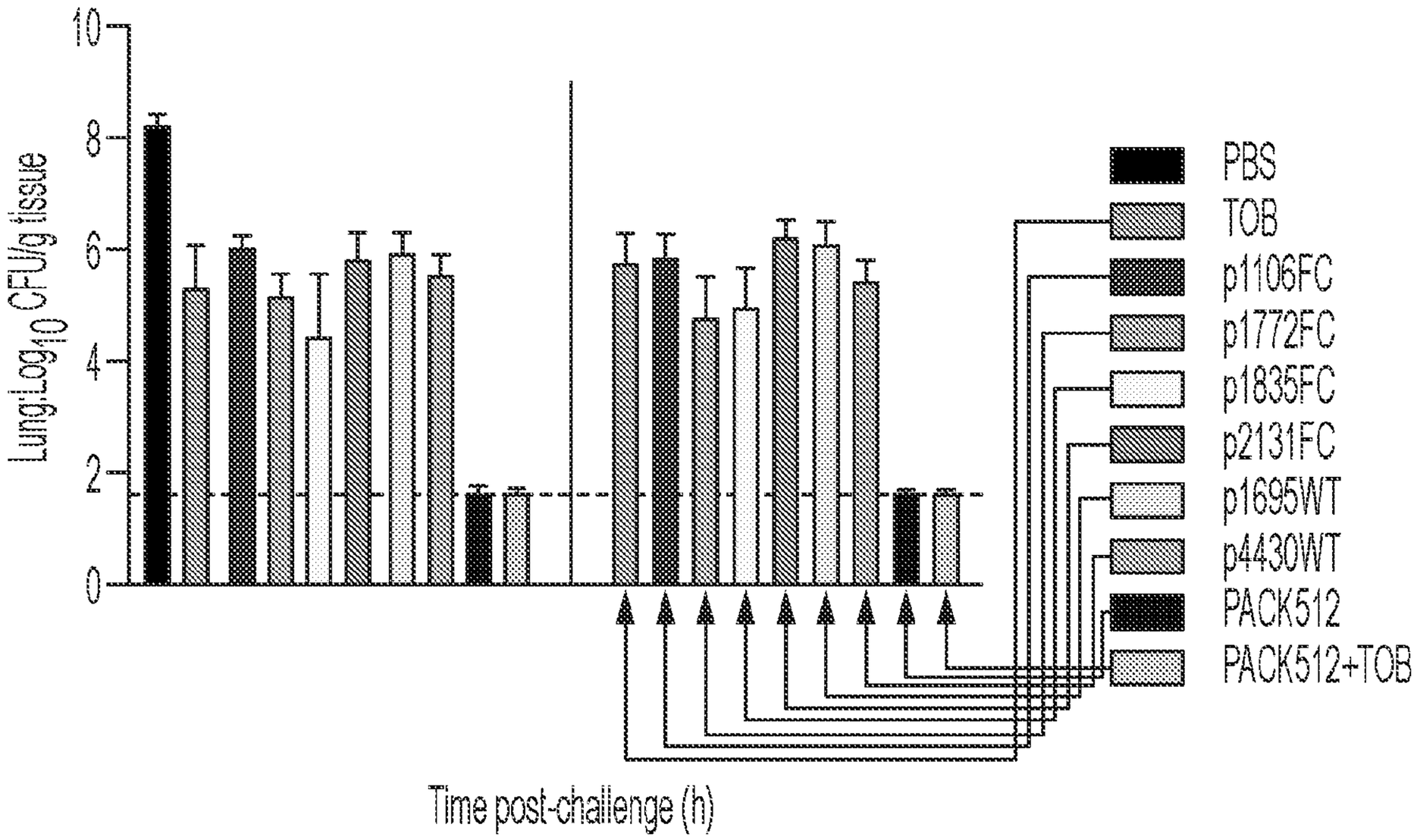
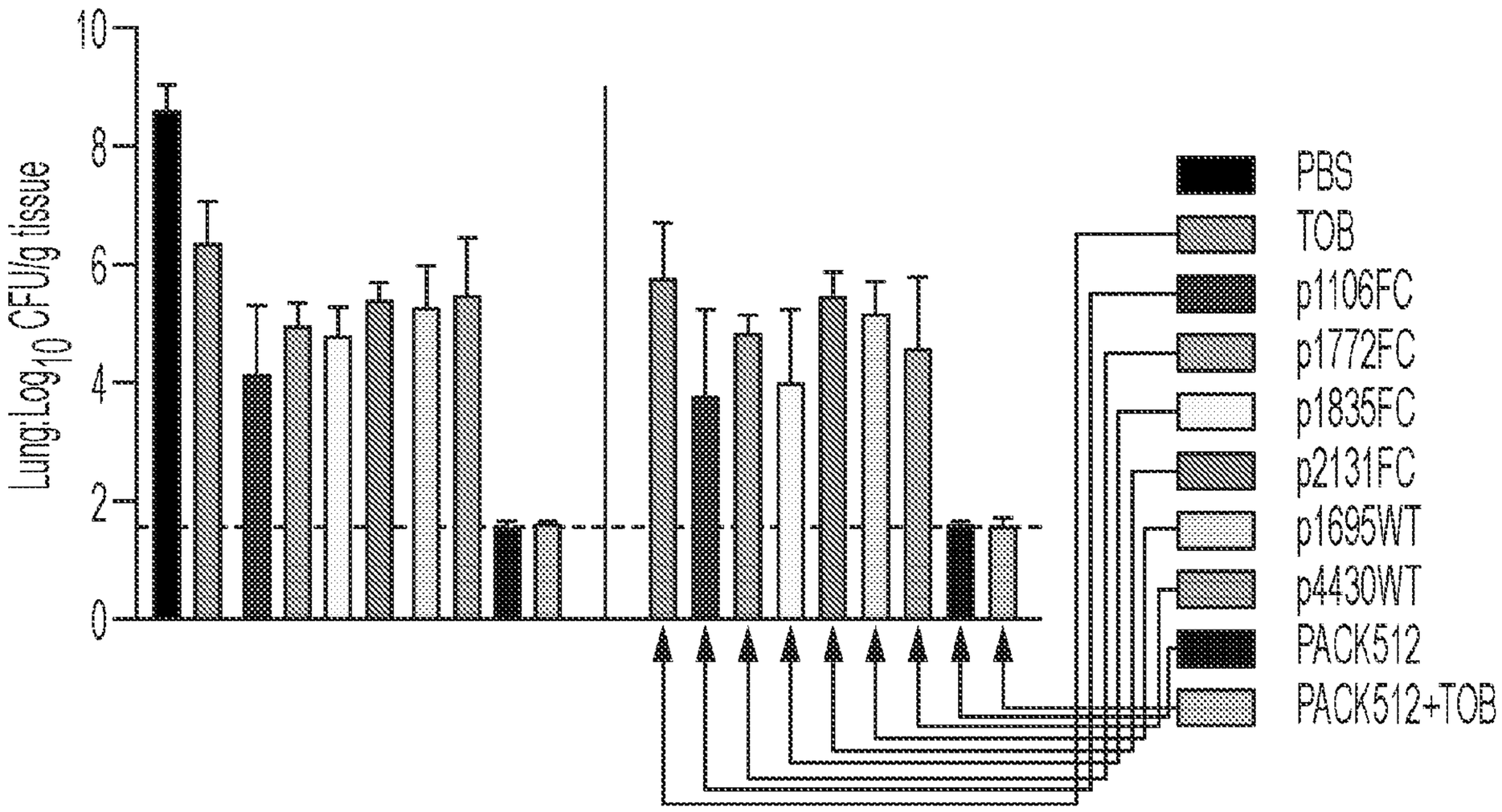


Fig. 18G



Study 49, b3144

Fig. 18H



Study 50, b1121

Fig. 18I

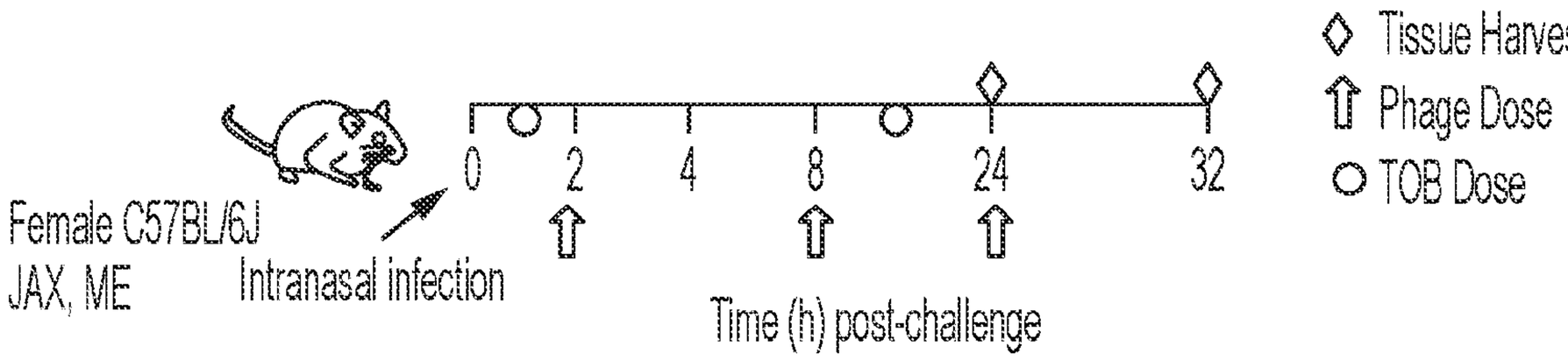
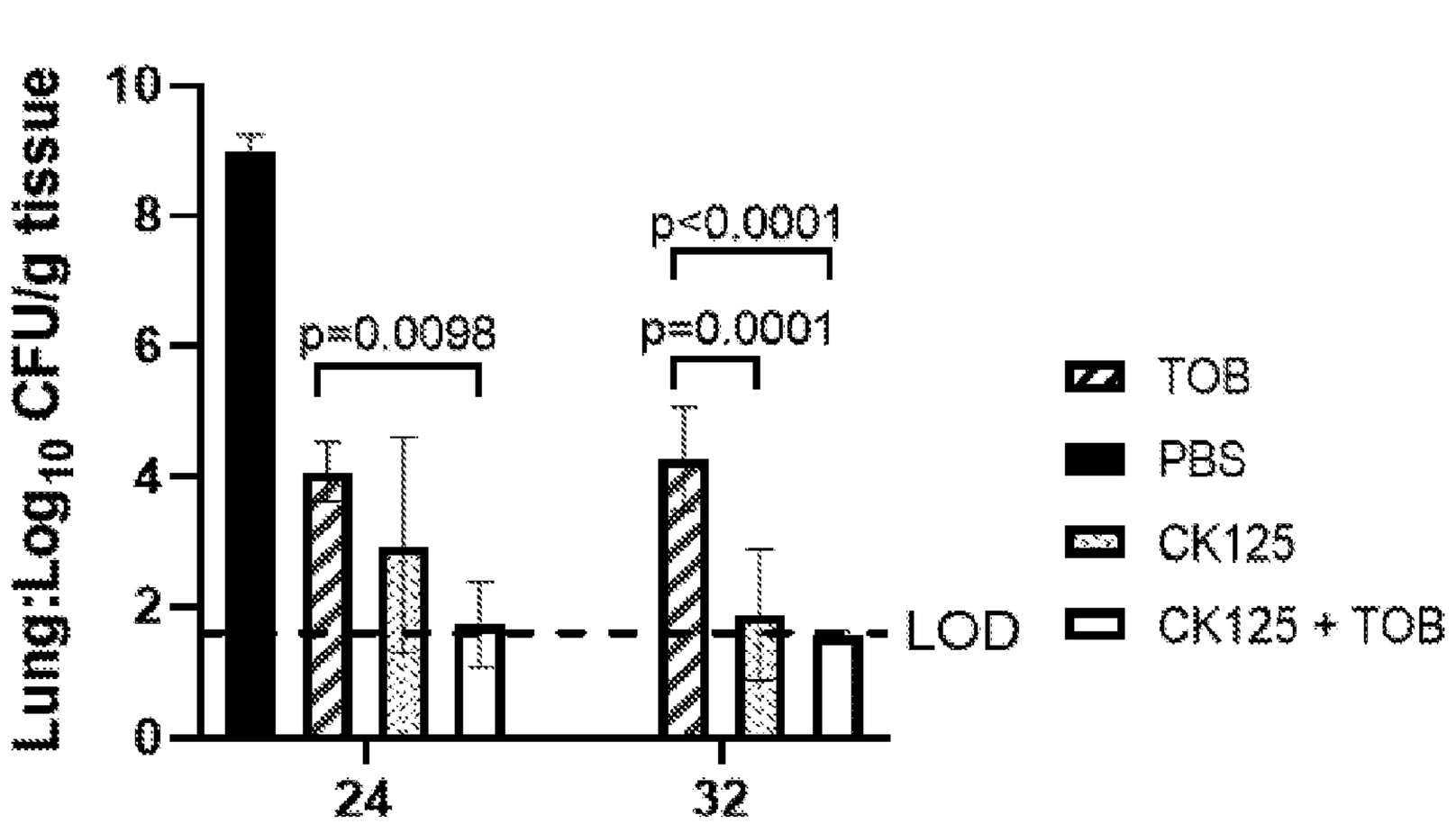
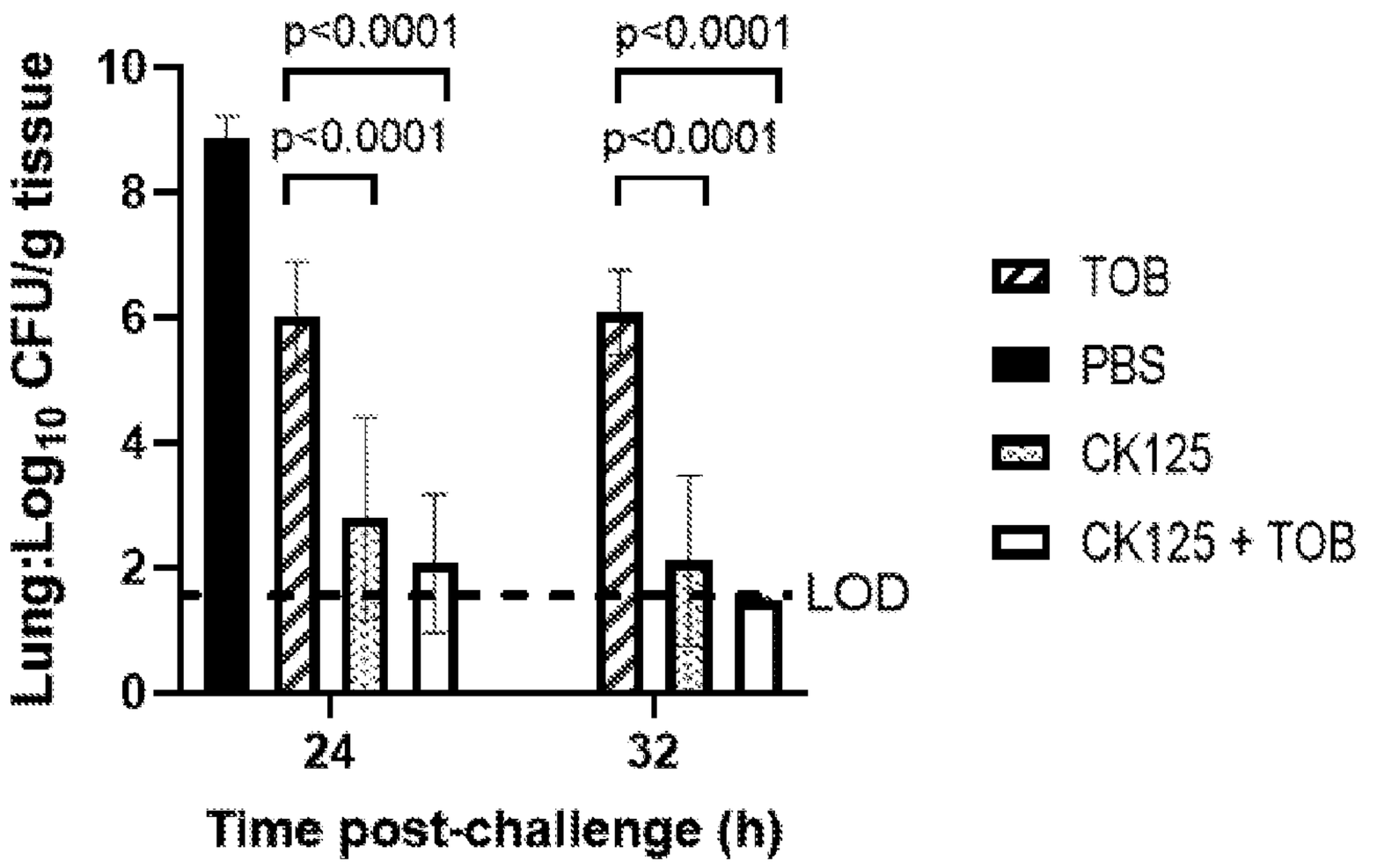


Fig. 19A



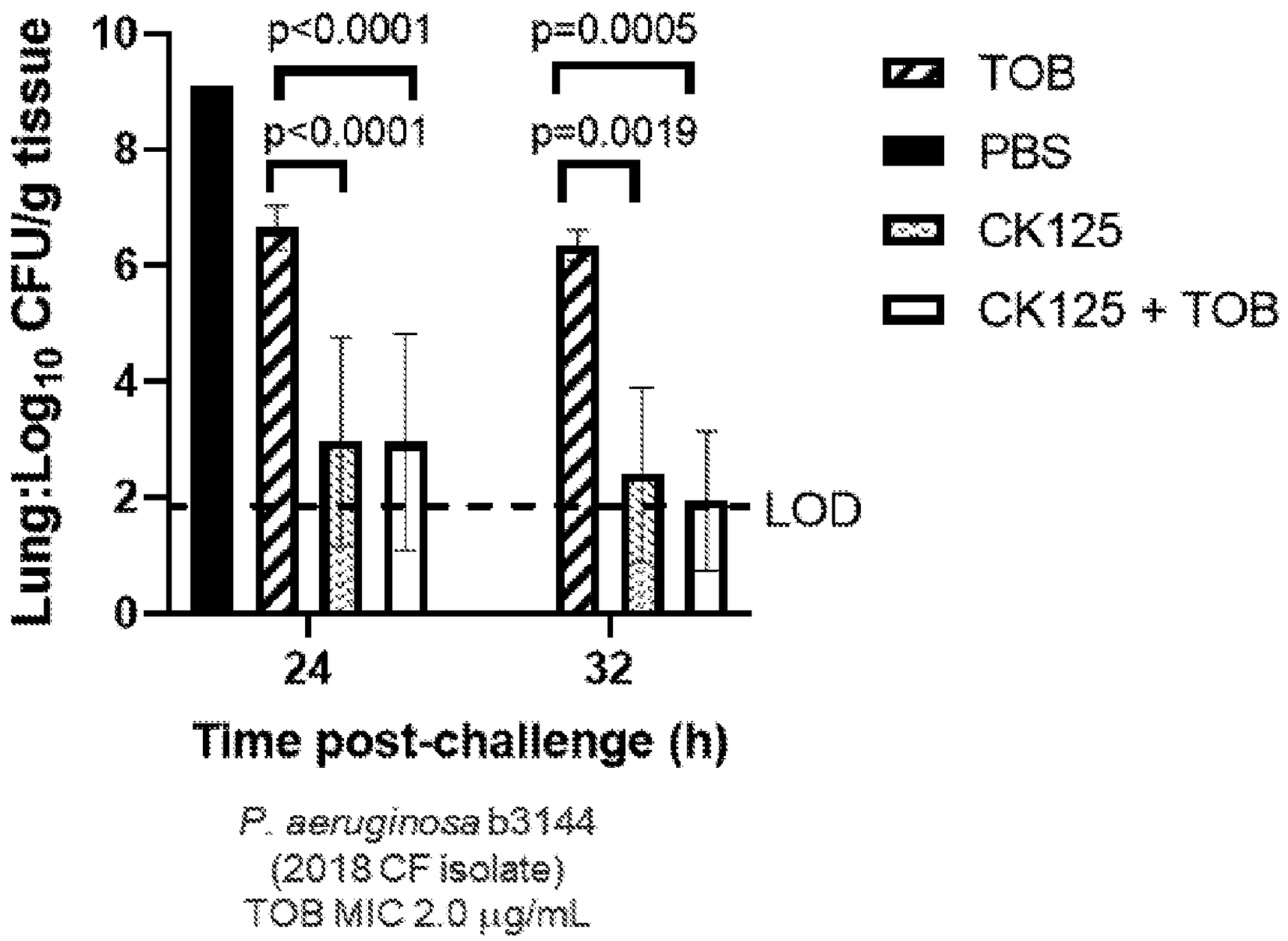
P. aeruginosa b2631
(2018 CF isolate)
TOB MIC 0.5 μg/mL

FIG. 19B



P. aeruginosa b1121
(Respiratory isolate)
TOB MIC 0.5 μg/mL

Fig. 19C



P. aeruginosa b3144
(2018 CF isolate)
TOB MIC 2.0 μg/mL

Fig. 19D

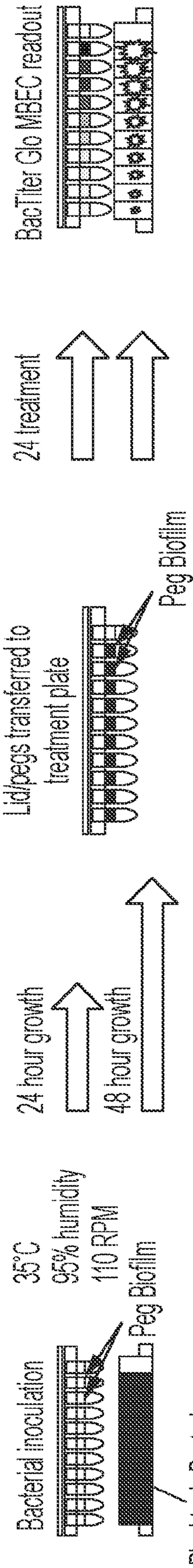


Fig. 20A

Test Article	Bacterial Strain	24hr MBEC IC50	48hr MBEC IC50
CK125 (MOI)	b1121	4.151e-08	2.355e-07
	b2631	3.907e-09	8.313e-09
Ciprofloxacin (mg/ml)	b1121	0.01196	0.01030
	b2631	0.00019	0.00287

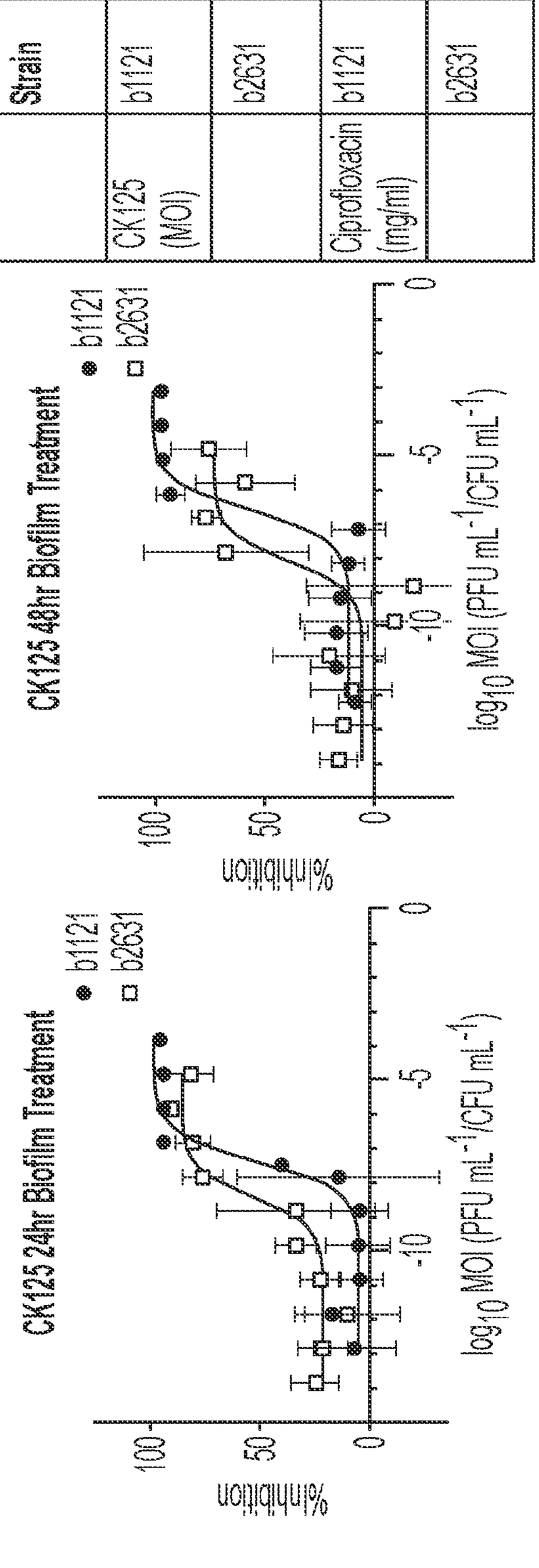


Fig. 20B

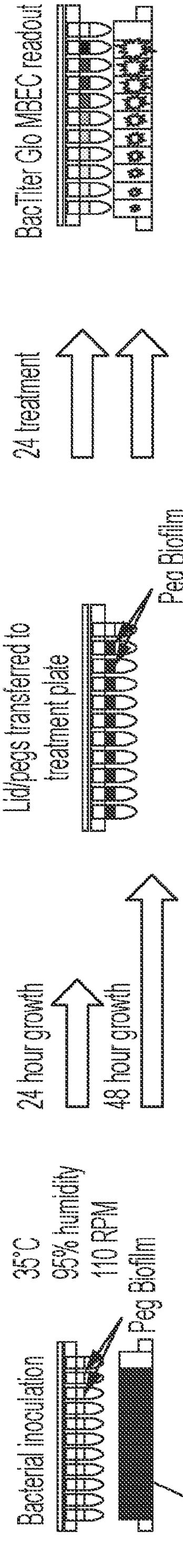

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24 treatment
Lid/pegs transferred to treatment plate
Peg Biofilm
24 hour growth
48 hour growth
35°C
95% humidity
110 RPM
Bacterial inoculation
Peg Biofilm
Planktonic Bacteria
PAK512 24h Wk1 MBEC Results
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b2631
b3144
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MOI PFU mL-1/CFU mL-1
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50
0
-5

Fig. 21

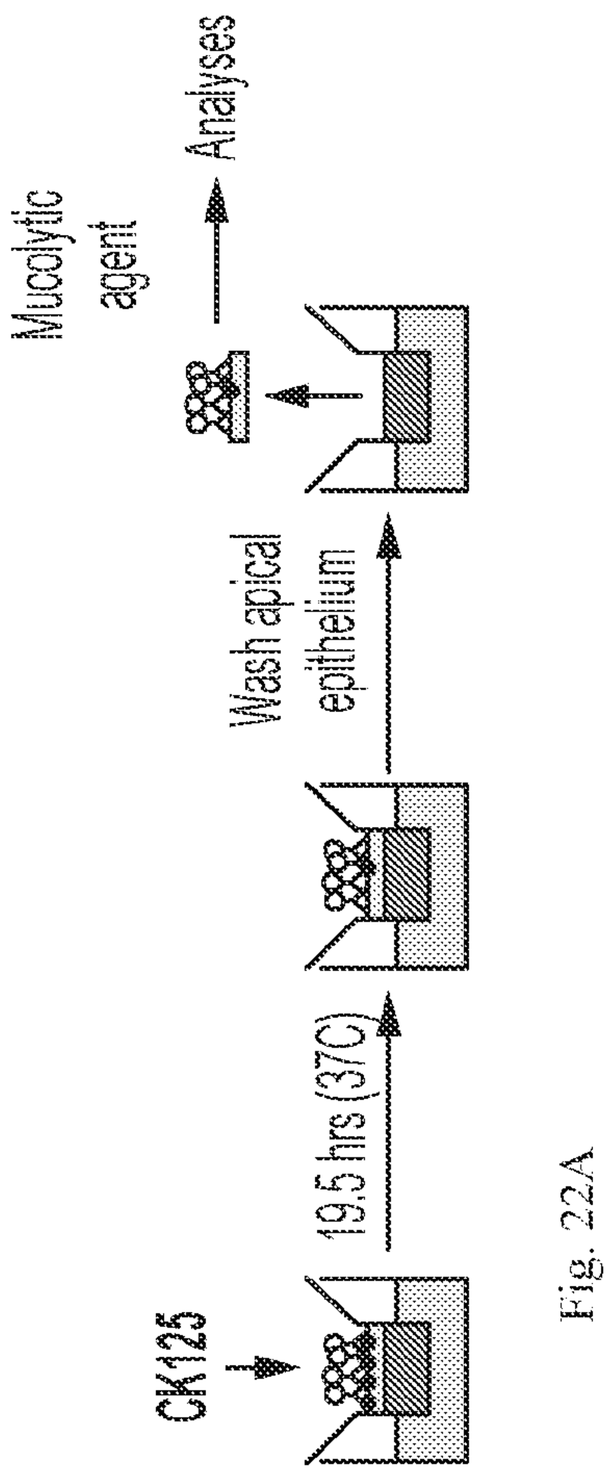


Fig. 22A

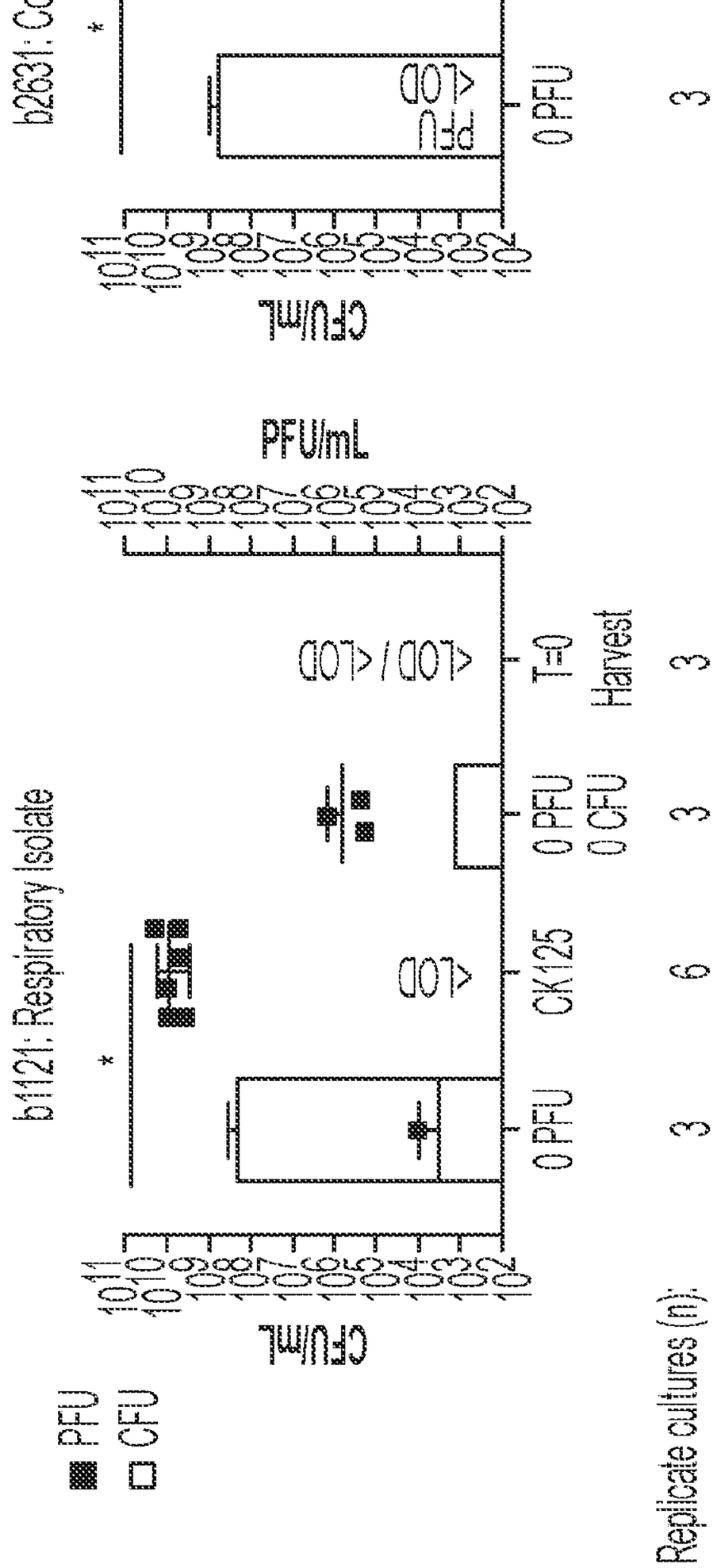


Fig. 22B

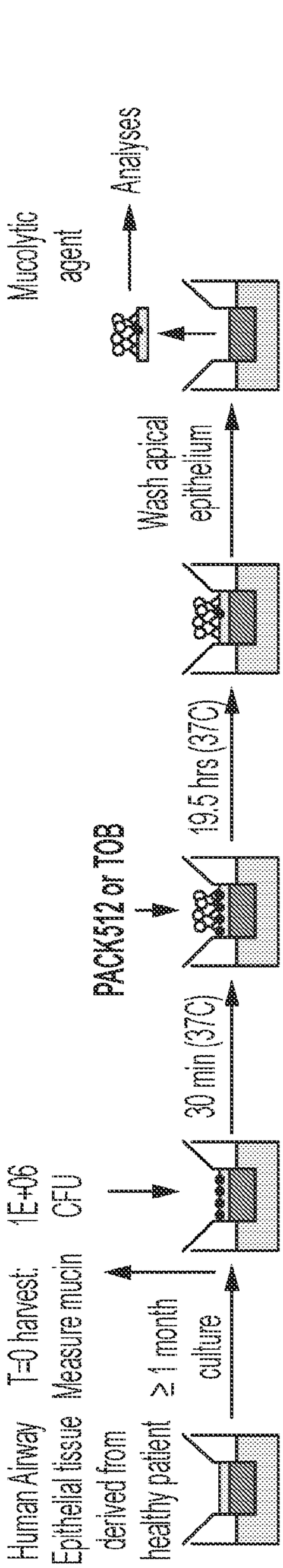


Fig. 23A

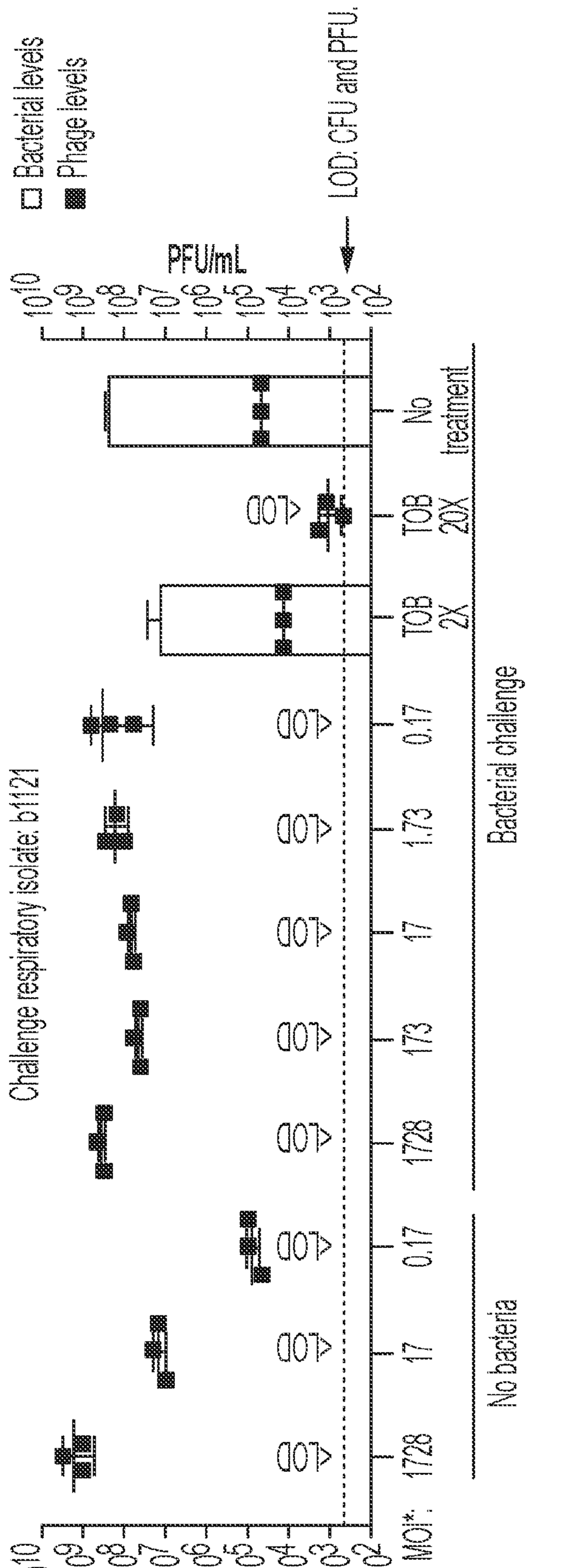


Fig. 23B

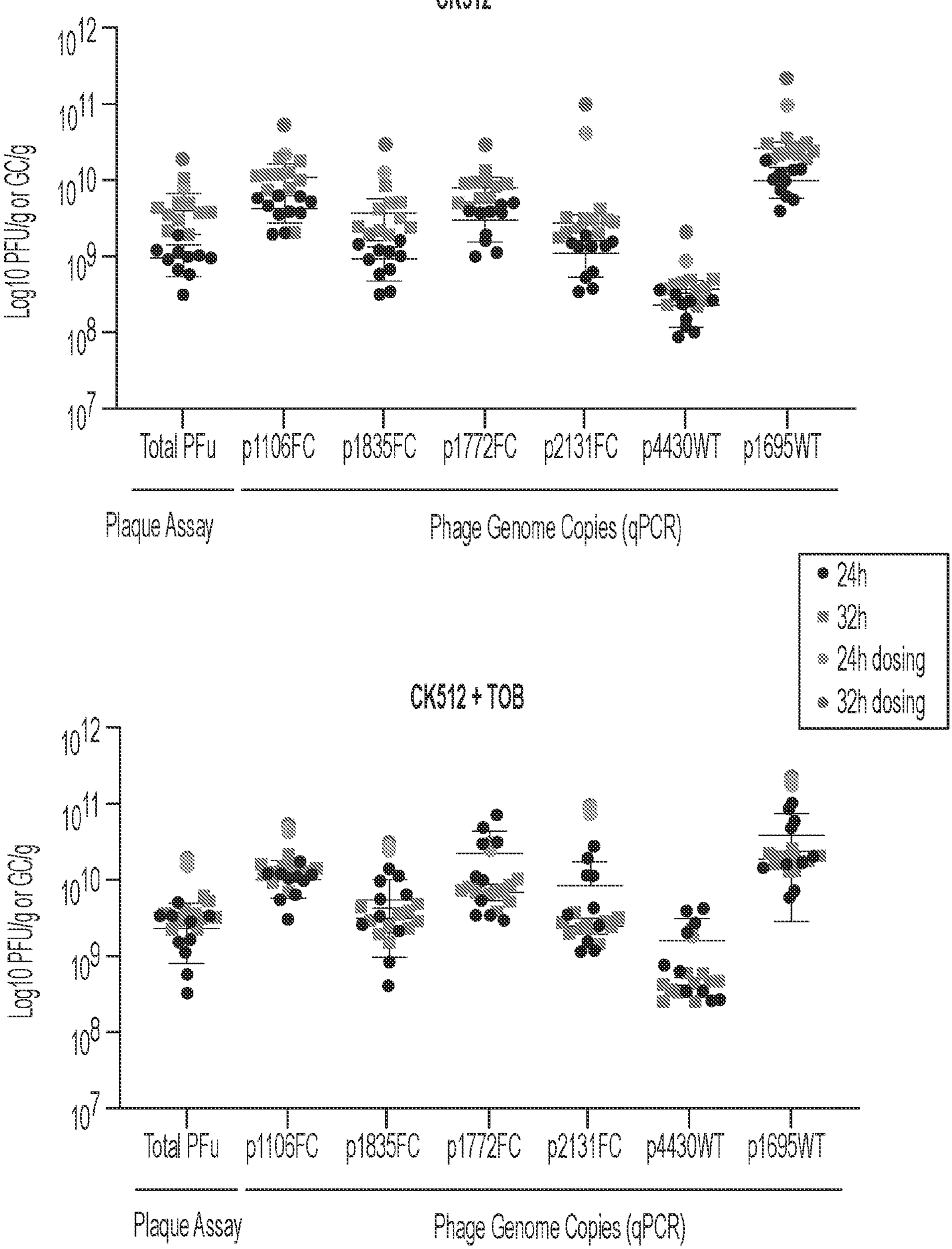

CK512
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10^{11}
10^{10}
10^{9}
10^{8}
10^{7}
Total PFu
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p1835FC
p1772FC
p2131FC
p4430WT
p1695WT
Plaque Assay
Phage Genome Copies (qPCR)
24h
32h
24h dosing
32h dosing
CK512 + TOB
Log10 PFU/g or GC/g
10^{12}
10^{11}
10^{10}
10^{9}
10^{8}
10^{7}
Total PFu
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p1772FC
p2131FC
p4430WT
p1695WT
Plaque Assay
Phage Genome Copies (qPCR)

Fig. 24

SEQUENCE LISTING

<110> LOCUS BIOSCIENCES, INC.
JANSSEN RESEARCH & DEVELOPMENT, LLC.

<120> PHAGE COMPOSITIONS FOR PSEUDOMONAS COMPRISING CRISPR-CAS SYSTEMS AND METHODS OF USE THEREOF

<130> 53240-743.601

<140>
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<150> 63/184,728
<151> 2021-05-05

<150> 63/110,288
<151> 2020-11-05

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<170> PatentIn version 3.5

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<213> Pseudomonas aeruginosa

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ctggaacgcc gtgacctacg tatgcac 207

<210> 11
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<220>
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<212> DNA
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<220>
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oligonucleotide

<400> 27
gtcgcgcccc gcacgggcgc gtggagtgaa ag 32

<210> 28
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oligonucleotide

<400> 28

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oligonucleotide

<400> 29
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oligonucleotide

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<210> 31
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oligonucleotide

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<210> 32
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oligonucleotide

<400> 32
gaaccaacgc atggcaggat caaaacctgc tgcc 34

<210> 33
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oligonucleotide

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<210> 34
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<223> Description of Artificial Sequence: Synthetic
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<210> 35
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<220>
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<210> 36
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 36
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<210> 37
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oligonucleotide

<400> 37
cgtgtggagt tggaaaatgg gcacgtcgtc accg 34

<210> 38
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oligonucleotide

<400> 38
agcggctgcc ccggagcgat cgcttgcgcg acgt 34

<210> 39
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oligonucleotide

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cctttgacac ccagtaccgt cacggtgacg tcgt 34

<210> 40
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oligonucleotide

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<210> 41
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oligonucleotide

<400> 41
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<210> 42
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oligonucleotide

<400> 42
aacatcatcg acacccccgg ccacgtcgac ttca 34

<210> 43
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oligonucleotide

<400> 43
tggtggaaca cgtcgccata ggtgaccttg ccga 34

<210> 44
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<212> DNA
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<210> 45
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<210> 46
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oligonucleotide

<400> 46
tccgcgatga gctgccgtcc caacaattca acac 34

<210> 47
<211> 34
<212> DNA
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oligonucleotide

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<210> 48
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oligonucleotide

<400> 48
agctcgatac catgaacagt gctacccacc ggga 34

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oligonucleotide

<400> 49
tcgcgctcgt ccggcatcga ccagcccatc cgcc 34

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<210> 51
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<400> 51
cagcgcttga tggtgcccgc gaagccctta ccct 34

<210> 52
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<400> 52
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<210> 53
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oligonucleotide

<400> 53
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<210> 54
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oligonucleotide

<400> 54
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<210> 55
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oligonucleotide

<400> 55
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<210> 56
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oligonucleotide

<400> 56
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<210> 57
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<210> 58
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<400> 58
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<210> 60
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<210> 61
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<210> 62
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<400> 62
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<210> 63
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oligonucleotide

<400> 63
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oligonucleotide

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oligonucleotide

<400> 65
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<210> 66
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 66
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<210> 67
<211> 34
<212> DNA

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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 67
cgggccggcc tgggtcagca gggtcaggtc ggat 34

<210> 68
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 68
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<210> 69
<211> 34
<212> DNA
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 69
agagcgcgaa cggcggactc gcggcccggg cccg 34

<210> 70
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 70
ttggctgcat cgatgttgcc ggtggcacct tcgc 34

<210> 71

<211> 34
<212> DNA
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 71
gaagctggcc cccggcggcg gcgtcagccg gccg 34

<210> 72
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 72
gaacccccga cacccttttg aggtgtactc cctt 34

<210> 73
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 73
cgcgatagct cagtcggtag agcaaatgac tgtt 34

<210> 74
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 74
cgggttgtgc tgggtggaca gcaccaccgc atcg 34

<210> 75
<211> 2235
<212> DNA
<213> Pseudomonas aeruginosa

<400> 75
atggacgcgg aggctagcga tactcacttt tttgctcact ccaccttaaa ggcagatcgc 60

agcgattggc agcctctggt cgagcatcta caggctgttg cccgtttggc aggagagaag 120

gctgccttct tcggcggcgg tgaattagct gctcttgctg gtctgttgca tgacttgggt 180

aaatacactg acgagtttca gcggcgtatt gcgggtgatg ccatccgtgt cgatcactct 240

actcgcgggg ccatactggc ggtagaacgc tatggcgcgc taggtcaatt gctagcctac 300

ggcatcgctg gccaccatgc cgggttggcc aatggccgcg aggctggtga gcgaactgcc 360

ttggtcgacc gcctgaaagg ggttgggctg ccacggttat tggaggggtg gtgcgtggaa 420

atcgtgctac ccgagcgcct tcaaccaccg ccactaaaag cgcgcctgga aagaggtttc 480

tttcagttgg cctttcttgg ccggatgctc ttttcctgct tggttgatgc ggattatcta 540

gataccgaag ccttctacca ccgcgtcgaa ggacggcgct cccttcgcga gcaagcgcgg 600

ccgaccttgg ccgagttacg cgcagccctt gatcggcatc tgactgagtt caagggagat 660

acgccggtca accgcgttcg cggggagata ttggccggcg tgcgcggcaa ggcgagcgaa 720

cttcccgggc tgttttctct cacagtgccc acaggaggcg gcaagaccct ggcctctctg 780

gctttcgccc tggatcacgc tctagctcat gggctgcgcc gggtgatcta cgtgattccc 840

ttcactagca tcgtcgagca gaacgctgcg gtattccgtc gtgcactcgg ggccttaggc 900

gaagaggcgg tgctggagca tcacagcgcc ttcgttgatg accgccggca gagcctggag 960

gccaagaaga aactgaacct agcgatggag aactgggacg cgcctatcgt ggtgaccact 1020

gcagtgcagt tcttcgaaag cctgtttgcc gaccgtccag cccagtgccg caagctacac 1080

aacatcgccg gcagcgtggt gattcttgac gaggcacaga ccctaccgct caagctgttg 1140

cggccctgcg ttgccgccct tgatgaactg gcgctcaact accgttgtag cccagttctc 1200

tgtactgcca cgcagccagc gcttcaatcg ccggatttca tcggtgggct gcaggacgta 1260

cgtgagctgg cgcccgagcc gcagcggctg ttccgggagt tggtgcgggt acgaatacgg 1320

acattgggcc cgctcgaaga tgcggccttg actgagcaga tcgccaggcg tgaacaagtg 1380

ctgtgcatcg tcaacaatcg acgccaggcc cgtgcgctct atgagtcgct tgccgagttg 1440

cccggtgccc gccatctcac caccctgatg tgcgccaagc accgtagcag cgtgctggcc 1500

gaggtgcgcc agatgctcaa aaaggggggag ccctgtcgcc tggtggccac ctcgctgatc 1560

gaggccggtg tggatgtgga ttttcccgtg gtactgcgtg ccgaggctgg attggattcc 1620

atcgcccagg ccgcgggacg ctgcaatcgc gaaggcaagc ggccgctggc cgaaagcgag 1680

gtgctggtgt tcgccgcggc caattctgac tgggcgccac ccgaggaact caagcagttc 1740

gcccaggccg cccgcgaagt gatgcgcctg cacccggatg attgcctgtc catggcggcc 1800

atcgagcggt attttcgcat actgtactgg cagaagggcg cggaggagtt ggatgcgggt 1860

aacctgctcg gcctgattga gagaggccgg ctcgatggcc tgccctacga gactttggcc 1920

accaagttcc gcatgatcga cagccttcaa ctgccggtga tcatcccatt tgatgacgag 1980

gccagagcag ccctgcgcga gctggagttc gccgacggct gcgccgccat cgcccgtcgc 2040

ctgcagccat atctggtgca gatgccacgc aagggttatc aggcattgcg ggaagccggt 2100

gcgatccagg cggcggcagg tacgcgttat ggtgagcagt ttatggcgtt ggtcaaccct 2160

gatctgtatc accaccaatt cgggttgcac tgggataatc cggcctttgt cagcagcgag 2220

cggctatgtt ggtag 2235

<210> 76
<211> 675
<212> DNA
<213> Pseudomonas aeruginosa

<400> 76
atggcctacg gaattcgctt aatggtctgg ggcgagcgtg cctgcttcac ccgcccggaa 60

atgaaggtgg aacgcgtctc ttacgatgcg atcacgccgt ccgccgcgcg cggcattctc 120

gaggctatcc actggaagcc ggcgattcgc tgggtggtgg atcgcattca agtgcttaag 180

ccgatccgct tcgaatccat ccggcgcaac gaggtcggcg gcaagctgtc cgctgtcagc 240

gtcggtaagg caatgaaggc cgggcgtact aatggtctgg tgaatctggt cgaggaggat 300

cgccagcagc gcgcgactac tctgctgcgc gatgtctcct atgtcatcga ggcgcatttc 360

gagatgactg acagggctgg cgccgacgat acggtgggca agcatctgga tatcttcaac 420

cgtcgcgcac ggaaggggca gtgcttccat acaccctgcc taggcgtgcg cgagtttccg 480

gccagttttc ggttgctgga agagggcagt gccgagcctg aagtcgatgc ctttctgcgc 540

ggcgagcgtg atctgggctg gatgctgcat gacattgact tcgccgatgg catgaccccg 600

cacttcttcc gtgccctgat gcgcgatggg ctgatcgagg tgccggcctt cagggcggca 660

gaggacaagg catga 675

<210> 77
<211> 1764
<212> DNA
<213> Pseudomonas aeruginosa

<400> 77
atgatccttt cggccctcaa tgactattat cagcgactgc tggagcgggg tgaagcgaat 60

atctcaccct tcggctacag ccaagaaaag atcagttacg ccctgctgct gtccgcacaa 120

ggagagttgc tggacgtgca ggacattcgc ttgctctctg gcaagaagcc tcaacccagg 180

cttatgagtg tgccgcagcc ggagaagcgc acctcgggca tcaagtccaa cgtactgtgg 240

gacaagacca gctatgtgct gggtgttagt gccaagggcg gagagcgtac tcagcaggag 300

cacgagtcct tcaagacgct gcaccggcag atcttggttg gggaaggcga ccccggtctg 360

caggccttgc tccagttcct cgactgttgg cagccggagc agttcaagcc cccgctgttc 420

agcgaagcaa tgctcgacag caacttagtg ttccgcctag acggccaaca acgctatctg 480

cacgagactc cggcggccct ggcgttgcgt acccggctgt tggccgacgg cgacagccgc 540

gaggggctgt gcctagtctg cggccaacgt cagccgttgg cgcgcctgca tccagcggtc 600

aagggcgtca atggtgccca gagttcgggg gcttccatcg tctccttcaa cctcgacgct 660

ttttcctcct acggcaagag ccaggggggaa aatgctccgg tctccgaaca ggccgccttt 720

gcctacacca cggtgctcaa ccatttgttg cgtcgcgacg agcacaaccg ccagcgcctg 780

cagattggcg acgcgagtgt ggtgttctgg gcgcaggcgg atactcctgc tcaggtggcc 840

gccgccgagt cgaccttctg gaacctgctg gagccacccg cagatgatgg tcaggaagcg 900

gaaaagctgc gcggcgtgct ggatgctgtg gccacggggc ggcccttgca tgagctcgac 960

tcgctaatgg aggaaggtac ccgcattttt gtgttagggc tggcgcccaa tacctcgcga 1020

ctgtccattc ggttctgggc agtcgatagc cttgcggtat tcacccagca tctggccgag 1080

catttccggg atatgcacct tgagcctctg ccctggaaga cggagccggc catctggcgc 1140

ttgctctatg ctaccgcgcc cagtcgtgac ggcagagcca agaccgaaga cgtactccca 1200

caactggccg gtgaaatgac ccgcgccatc ctgaccggca gccgctatcc gcgcagtttg 1260

ctagccaacc tgatcatgcg catgcgtgcc gacggcgacg tctctggcat acgcgtcgcg 1320

ctgtgcaagg ccgtgctcgc tcgcgaggca cgcctgagcg gcaaaattca ccaagaggag 1380

ctacctatga gtctcgacaa ggacgccagc aaccccggct atcgcttggg gaggctgttc 1440

gccgtgttgg aaggcgccca gcgcgcagcc ctgggcgaca gggtcaatgc cactatccgt 1500

gaccgctact acggtgccgc gtccagcacg ccagccacgg ttttcccgat actgctgcgc 1560

aacacacaaa accacttggc caagctgcgc aaggagaagc ccggactagc agtgaaccta 1620

gagcgcgata taggcgaaat cattgacggt atgcagagcc aattcccgcg ttgcctgcgc 1680

ctggaggacc agggacgctt tgctattggt tactaccaac aggcccaggc ccgtttcaac 1740

cgtggccccg attccgtcga gtaa 1764

<210> 78
<211> 870
<212> DNA
<213> Pseudomonas aeruginosa

<400> 78
atgaccgcca tctccaaccg ctacgagttc gtttacctct ttgatgtcag caatggcaat 60

cccaatggcg acccggatgc tggcaacatg ccgcgtctcg atccggaaac caaccagggg 120

ttggtcactg acgtttgcct caagcgcaag atccgcaact acgtcagcct ggagcaggaa 180

agtgcccccg gctatgccat ctatatgcag gaaaaatccg tgctgaataa ccagcacaaa 240

caggcctacg aggcgctcgg tatcgagtca gaggcaaaga aactgcccaa ggacgaagcc 300

aaggcgcgcg aactgacctc ttggatgtgc aagaacttct tcgatgtgcg tgctttcggg 360

gcggtgatga ccaccgagat taatgccggc caggtgcgtg gaccgatcca actggcattc 420

gccacgtcta tcgacccggt attgcctatg gaggtatcca tcacccgcat ggcggtgact 480

aacgaaaagg atttggagaa ggaacgcacc atgggacgca agcacatcgt gccttacggc 540

ttgtaccgcg cccatggttt catctctgcc aagttggccg agcgaaccgg cttttccgac 600

gacgacttgg aactgctatg gcgcgctttg gccaatatgt tcgaacacga ccgctcggcg 660

gcacgtggcg agatggcagc gcgcaagttg atcgtcttca agcatgagca tgccatgggc 720

aatgcacccg cccatgtgct gttcggcagc gttaaggtcg agcgagtcga gggggacgca 780

gttacaccag cacgcggttt ccaggattac cgtgtcagca tcgatgcgga agctctgcct 840

cagggcgtga gcgtgcgcga gtacctctag 870

<210> 79
<211> 744
<212> PRT
<213> Pseudomonas aeruginosa

<400> 79
Met Asp Ala Glu Ala Ser Asp Thr His Phe Phe Ala His Ser Thr Leu
1 5 10 15

Lys Ala Asp Arg Ser Asp Trp Gln Pro Leu Val Glu His Leu Gln Ala
20 25 30

Val Ala Arg Leu Ala Gly Glu Lys Ala Ala Phe Phe Gly Gly Gly Glu
35 40 45

Leu Ala Ala Leu Ala Gly Leu Leu His Asp Leu Gly Lys Tyr Thr Asp
50 55 60

Glu Phe Gln Arg Arg Ile Ala Gly Asp Ala Ile Arg Val Asp His Ser
65 70 75 80

Thr Arg Gly Ala Ile Leu Ala Val Glu Arg Tyr Gly Ala Leu Gly Gln
85 90 95

Leu Leu Ala Tyr Gly Ile Ala Gly His His Ala Gly Leu Ala Asn Gly

```
            100                 105                 110

Arg Glu Ala Gly Glu Arg Thr Ala Leu Val Asp Arg Leu Lys Gly Val
        115                 120                 125

Gly Leu Pro Arg Leu Leu Glu Gly Trp Cys Val Glu Ile Val Leu Pro
    130                 135                 140

Glu Arg Leu Gln Pro Pro Pro Leu Lys Ala Arg Leu Glu Arg Gly Phe
145                 150                 155                 160

Phe Gln Leu Ala Phe Leu Gly Arg Met Leu Phe Ser Cys Leu Val Asp
                165                 170                 175

Ala Asp Tyr Leu Asp Thr Glu Ala Phe Tyr His Arg Val Glu Gly Arg
            180                 185                 190

Arg Ser Leu Arg Glu Gln Ala Arg Pro Thr Leu Ala Glu Leu Arg Ala
        195                 200                 205

Ala Leu Asp Arg His Leu Thr Glu Phe Lys Gly Asp Thr Pro Val Asn
    210                 215                 220

Arg Val Arg Gly Glu Ile Leu Ala Gly Val Arg Gly Lys Ala Ser Glu
225                 230                 235                 240

Leu Pro Gly Leu Phe Ser Leu Thr Val Pro Thr Gly Gly Gly Lys Thr
                245                 250                 255

Leu Ala Ser Leu Ala Phe Ala Leu Asp His Ala Leu Ala His Gly Leu
            260                 265                 270

Arg Arg Val Ile Tyr Val Ile Pro Phe Thr Ser Ile Val Glu Gln Asn
        275                 280                 285

Ala Ala Val Phe Arg Arg Ala Leu Gly Ala Leu Gly Glu Glu Ala Val
    290                 295                 300
```

```
Leu Glu His His Ser Ala Phe Val Asp Asp Arg Arg Gln Ser Leu Glu
305                 310                 315                 320

Ala Lys Lys Lys Leu Asn Leu Ala Met Glu Asn Trp Asp Ala Pro Ile
                325                 330                 335

Val Val Thr Thr Ala Val Gln Phe Phe Glu Ser Leu Phe Ala Asp Arg
            340                 345                 350

Pro Ala Gln Cys Arg Lys Leu His Asn Ile Ala Gly Ser Val Val Ile
        355                 360                 365

Leu Asp Glu Ala Gln Thr Leu Pro Leu Lys Leu Leu Arg Pro Cys Val
    370                 375                 380

Ala Ala Leu Asp Glu Leu Ala Leu Asn Tyr Arg Cys Ser Pro Val Leu
385                 390                 395                 400

Cys Thr Ala Thr Gln Pro Ala Leu Gln Ser Pro Asp Phe Ile Gly Gly
                405                 410                 415

Leu Gln Asp Val Arg Glu Leu Ala Pro Glu Pro Gln Arg Leu Phe Arg
            420                 425                 430

Glu Leu Val Arg Val Arg Ile Arg Thr Leu Gly Pro Leu Glu Asp Ala
        435                 440                 445

Ala Leu Thr Glu Gln Ile Ala Arg Arg Glu Gln Val Leu Cys Ile Val
    450                 455                 460

Asn Asn Arg Arg Gln Ala Arg Ala Leu Tyr Glu Ser Leu Ala Glu Leu
465                 470                 475                 480

Pro Gly Ala Arg His Leu Thr Thr Leu Met Cys Ala Lys His Arg Ser
                485                 490                 495

Ser Val Leu Ala Glu Val Arg Gln Met Leu Lys Lys Gly Glu Pro Cys
```

```
            500                 505                 510

Arg Leu Val Ala Thr Ser Leu Ile Glu Ala Gly Val Asp Val Asp Phe
        515                 520                 525

Pro Val Val Leu Arg Ala Glu Ala Gly Leu Asp Ser Ile Ala Gln Ala
    530                 535                 540

Ala Gly Arg Cys Asn Arg Glu Gly Lys Arg Pro Leu Ala Glu Ser Glu
545                 550                 555                 560

Val Leu Val Phe Ala Ala Ala Asn Ser Asp Trp Ala Pro Pro Glu Glu
                565                 570                 575

Leu Lys Gln Phe Ala Gln Ala Ala Arg Glu Val Met Arg Leu His Pro
            580                 585                 590

Asp Asp Cys Leu Ser Met Ala Ala Ile Glu Arg Tyr Phe Arg Ile Leu
        595                 600                 605

Tyr Trp Gln Lys Gly Ala Glu Glu Leu Asp Ala Gly Asn Leu Leu Gly
    610                 615                 620

Leu Ile Glu Arg Gly Arg Leu Asp Gly Leu Pro Tyr Glu Thr Leu Ala
625                 630                 635                 640

Thr Lys Phe Arg Met Ile Asp Ser Leu Gln Leu Pro Val Ile Ile Pro
                645                 650                 655

Phe Asp Asp Glu Ala Arg Ala Ala Leu Arg Glu Leu Glu Phe Ala Asp
            660                 665                 670

Gly Cys Ala Ala Ile Ala Arg Arg Leu Gln Pro Tyr Leu Val Gln Met
        675                 680                 685

Pro Arg Lys Gly Tyr Gln Ala Leu Arg Glu Ala Gly Ala Ile Gln Ala
    690                 695                 700
```

```
Ala Ala Gly Thr Arg Tyr Gly Glu Gln Phe Met Ala Leu Val Asn Pro
705                 710                 715                 720


Asp Leu Tyr His His Gln Phe Gly Leu His Trp Asp Asn Pro Ala Phe
                725                 730                 735


Val Ser Ser Glu Arg Leu Cys Trp
            740
```

<210> 80
<211> 224
<212> PRT
<213> Pseudomonas aeruginosa

<400> 80

```
Met Ala Tyr Gly Ile Arg Leu Met Val Trp Gly Glu Arg Ala Cys Phe
1               5                   10                  15


Thr Arg Pro Glu Met Lys Val Glu Arg Val Ser Tyr Asp Ala Ile Thr
            20                  25                  30


Pro Ser Ala Ala Arg Gly Ile Leu Glu Ala Ile His Trp Lys Pro Ala
        35                  40                  45


Ile Arg Trp Val Val Asp Arg Ile Gln Val Leu Lys Pro Ile Arg Phe
    50                  55                  60


Glu Ser Ile Arg Arg Asn Glu Val Gly Gly Lys Leu Ser Ala Val Ser
65                  70                  75                  80


Val Gly Lys Ala Met Lys Ala Gly Arg Thr Asn Gly Leu Val Asn Leu
                85                  90                  95


Val Glu Glu Asp Arg Gln Gln Arg Ala Thr Thr Leu Leu Arg Asp Val
            100                 105                 110


Ser Tyr Val Ile Glu Ala His Phe Glu Met Thr Asp Arg Ala Gly Ala
        115                 120                 125
```

```
Asp Asp Thr Val Gly Lys His Leu Asp Ile Phe Asn Arg Arg Ala Arg
    130                 135                 140

Lys Gly Gln Cys Phe His Thr Pro Cys Leu Gly Val Arg Glu Phe Pro
145                 150                 155                 160

Ala Ser Phe Arg Leu Leu Glu Glu Gly Ser Ala Glu Pro Glu Val Asp
                165                 170                 175

Ala Phe Leu Arg Gly Glu Arg Asp Leu Gly Trp Met Leu His Asp Ile
            180                 185                 190

Asp Phe Ala Asp Gly Met Thr Pro His Phe Phe Arg Ala Leu Met Arg
        195                 200                 205

Asp Gly Leu Ile Glu Val Pro Ala Phe Arg Ala Ala Glu Asp Lys Ala
    210                 215                 220
```

<210> 81
<211> 587
<212> PRT
<213> Pseudomonas aeruginosa

<400> 81

```
Met Ile Leu Ser Ala Leu Asn Asp Tyr Tyr Gln Arg Leu Leu Glu Arg
1               5                   10                  15

Gly Glu Ala Asn Ile Ser Pro Phe Gly Tyr Ser Gln Glu Lys Ile Ser
            20                  25                  30

Tyr Ala Leu Leu Leu Ser Ala Gln Gly Glu Leu Leu Asp Val Gln Asp
        35                  40                  45

Ile Arg Leu Leu Ser Gly Lys Lys Pro Gln Pro Arg Leu Met Ser Val
    50                  55                  60

Pro Gln Pro Glu Lys Arg Thr Ser Gly Ile Lys Ser Asn Val Leu Trp
65                  70                  75                  80
```

```
Asp Lys Thr Ser Tyr Val Leu Gly Val Ser Ala Lys Gly Gly Glu Arg
                85                  90                  95

Thr Gln Gln Glu His Glu Ser Phe Lys Thr Leu His Arg Gln Ile Leu
            100                 105                 110

Val Gly Glu Gly Asp Pro Gly Leu Gln Ala Leu Leu Gln Phe Leu Asp
        115                 120                 125

Cys Trp Gln Pro Glu Gln Phe Lys Pro Pro Leu Phe Ser Glu Ala Met
    130                 135                 140

Leu Asp Ser Asn Leu Val Phe Arg Leu Asp Gly Gln Gln Arg Tyr Leu
145                 150                 155                 160

His Glu Thr Pro Ala Ala Leu Ala Leu Arg Thr Arg Leu Leu Ala Asp
                165                 170                 175

Gly Asp Ser Arg Glu Gly Leu Cys Leu Val Cys Gly Gln Arg Gln Pro
            180                 185                 190

Leu Ala Arg Leu His Pro Ala Val Lys Gly Val Asn Gly Ala Gln Ser
        195                 200                 205

Ser Gly Ala Ser Ile Val Ser Phe Asn Leu Asp Ala Phe Ser Ser Tyr
    210                 215                 220

Gly Lys Ser Gln Gly Glu Asn Ala Pro Val Ser Glu Gln Ala Ala Phe
225                 230                 235                 240

Ala Tyr Thr Thr Val Leu Asn His Leu Leu Arg Arg Asp Glu His Asn
                245                 250                 255

Arg Gln Arg Leu Gln Ile Gly Asp Ala Ser Val Val Phe Trp Ala Gln
            260                 265                 270

Ala Asp Thr Pro Ala Gln Val Ala Ala Ala Glu Ser Thr Phe Trp Asn
```

```
        275                 280                 285

Leu Leu Glu Pro Pro Ala Asp Asp Gly Gln Glu Ala Glu Lys Leu Arg
    290                 295                 300

Gly Val Leu Asp Ala Val Ala Thr Gly Arg Pro Leu His Glu Leu Asp
305                 310                 315                 320

Ser Leu Met Glu Glu Gly Thr Arg Ile Phe Val Leu Gly Leu Ala Pro
                325                 330                 335

Asn Thr Ser Arg Leu Ser Ile Arg Phe Trp Ala Val Asp Ser Leu Ala
            340                 345                 350

Val Phe Thr Gln His Leu Ala Glu His Phe Arg Asp Met His Leu Glu
        355                 360                 365

Pro Leu Pro Trp Lys Thr Glu Pro Ala Ile Trp Arg Leu Leu Tyr Ala
    370                 375                 380

Thr Ala Pro Ser Arg Asp Gly Arg Ala Lys Thr Glu Asp Val Leu Pro
385                 390                 395                 400

Gln Leu Ala Gly Glu Met Thr Arg Ala Ile Leu Thr Gly Ser Arg Tyr
                405                 410                 415

Pro Arg Ser Leu Leu Ala Asn Leu Ile Met Arg Met Arg Ala Asp Gly
            420                 425                 430

Asp Val Ser Gly Ile Arg Val Ala Leu Cys Lys Ala Val Leu Ala Arg
        435                 440                 445

Glu Ala Arg Leu Ser Gly Lys Ile His Gln Glu Glu Leu Pro Met Ser
    450                 455                 460

Leu Asp Lys Asp Ala Ser Asn Pro Gly Tyr Arg Leu Gly Arg Leu Phe
465                 470                 475                 480
```

```
Ala Val Leu Glu Gly Ala Gln Arg Ala Ala Leu Gly Asp Arg Val Asn
                485                 490                 495

Ala Thr Ile Arg Asp Arg Tyr Tyr Gly Ala Ala Ser Ser Thr Pro Ala
            500                 505                 510

Thr Val Phe Pro Ile Leu Leu Arg Asn Thr Gln Asn His Leu Ala Lys
        515                 520                 525

Leu Arg Lys Glu Lys Pro Gly Leu Ala Val Asn Leu Glu Arg Asp Ile
    530                 535                 540

Gly Glu Ile Ile Asp Gly Met Gln Ser Gln Phe Pro Arg Cys Leu Arg
545                 550                 555                 560

Leu Glu Asp Gln Gly Arg Phe Ala Ile Gly Tyr Tyr Gln Gln Ala Gln
                565                 570                 575

Ala Arg Phe Asn Arg Gly Pro Asp Ser Val Glu
            580                 585
```

<210> 82
<211> 289
<212> PRT
<213> Pseudomonas aeruginosa

<400> 82

```
Met Thr Ala Ile Ser Asn Arg Tyr Glu Phe Val Tyr Leu Phe Asp Val
1               5                   10                  15

Ser Asn Gly Asn Pro Asn Gly Asp Pro Asp Ala Gly Asn Met Pro Arg
            20                  25                  30

Leu Asp Pro Glu Thr Asn Gln Gly Leu Val Thr Asp Val Cys Leu Lys
        35                  40                  45

Arg Lys Ile Arg Asn Tyr Val Ser Leu Glu Gln Glu Ser Ala Pro Gly
    50                  55                  60
```

```
Tyr Ala Ile Tyr Met Gln Glu Lys Ser Val Leu Asn Asn Gln His Lys
65                  70                  75                  80

Gln Ala Tyr Glu Ala Leu Gly Ile Glu Ser Glu Ala Lys Lys Leu Pro
                85                  90                  95

Lys Asp Glu Ala Lys Ala Arg Glu Leu Thr Ser Trp Met Cys Lys Asn
            100                 105                 110

Phe Phe Asp Val Arg Ala Phe Gly Ala Val Met Thr Thr Glu Ile Asn
        115                 120                 125

Ala Gly Gln Val Arg Gly Pro Ile Gln Leu Ala Phe Ala Thr Ser Ile
    130                 135                 140

Asp Pro Val Leu Pro Met Glu Val Ser Ile Thr Arg Met Ala Val Thr
145                 150                 155                 160

Asn Glu Lys Asp Leu Glu Lys Glu Arg Thr Met Gly Arg Lys His Ile
                165                 170                 175

Val Pro Tyr Gly Leu Tyr Arg Ala His Gly Phe Ile Ser Ala Lys Leu
            180                 185                 190

Ala Glu Arg Thr Gly Phe Ser Asp Asp Asp Leu Glu Leu Leu Trp Arg
        195                 200                 205

Ala Leu Ala Asn Met Phe Glu His Asp Arg Ser Ala Ala Arg Gly Glu
    210                 215                 220

Met Ala Ala Arg Lys Leu Ile Val Phe Lys His Glu His Ala Met Gly
225                 230                 235                 240

Asn Ala Pro Ala His Val Leu Phe Gly Ser Val Lys Val Glu Arg Val
                245                 250                 255

Glu Gly Asp Ala Val Thr Pro Ala Arg Gly Phe Gln Asp Tyr Arg Val
```

260 265 270

Ser Ile Asp Ala Glu Ala Leu Pro Gln Gly Val Ser Val Arg Glu Tyr
275 280 285

Leu

<210> 83
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 83
acaagcggca cattgtgcct attgcgaatt aggcacaatg tgcctaatct aacgtcatgc 60

cagccacaac ggcgaggcgc caagaaggat agaagccgtc gcgccccgca cgggcgcgtg 120

gattgaaaca gaagggtcag ggccatgcgg tttttcctct gtggtcgcgc cccgcacggg 180

cgcgtggatt gaaacgagac cgaagagaac gtgccgacca ccgccgctgg tcgcgccccg 240

cacgggcgcg tggattgaaa ctgctgaaca gccatgattg attaactcct aaacggtcgc 300

gccccgcacg ggcgcgtgga ttgaaaccat gcaagcttgg cgtagcttcg tccctatcaa 360

agcttggag 369

<210> 84
<211> 373
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 84
acaagcggca cattgtgcct attgcgaatt aggcacaatg tgcctaatct aacgtcatgc 60

cagccacaac ggcgaggcgc caagaaggat agaagccgtc gcgccccgca cgggcgcgtg 120

gattgaaacg ctcgactggt cggtaaccac ttgtgtgtgg tgagtcgcgc cccgcacggg 180

cgcgtggatt gaaaccagtg catggcagcg aacgccgaga gccgacaccg tcgcgccccg 240

cacgggcgcg tggattgaaa ccgtaaacct aatgggcctg atctacagta atctagtcgc 300

gccccgcacg ggcgcgtgga ttgaaaccat gcaagcttgg cgtaggccgc ttcgtcccta 360

tcaaagcttg gag 373

<210> 85
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 85
acaagcggca cattgtgcct attgcgaatt aggcacaatg tgcctaatct aacgtcatgc 60

cagccacaac ggcgaggcgc caagaaggat agaagccgtc gcgccccgca cgggcgcgtg 120

gattgaaacg gtgctgaccg aggacgagaa ggaactgggc gtggtcgcgc cccgcacggg 180

cgcgtggatt gaaactccgc gatgagctgc cgtcccaaca attcaacacg tcgcgccccg 240

cacgggcgcg tggattgaaa caccaccgag acgcccacac cgtgcaagcc gccgggtcgc 300

gccccgcacg ggcgcgtgga ttgaaaccat gcaagcttgg cgtagcttcg tccctatcaa 360

agcttggag 369

<210> 86
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 86
acaagcggca cattgtgcct attgcgaatt aggcacaatg tgcctaatct aacgtcatgc 60

cagccacaac ggcgaggcgc caagaaggat agaagccgtc gcgccccgca cgggcgcgtg 120

gattgaaacg atgacaccaa cccggccaag gaagaccagg agtgtcgcgc cccgcacggg 180

cgcgtggatt gaaacaacgc gaagccctgt tgaaaccgct gcaactggtg tcgcgccccg 240

cacgggcgcg tggattgaaa cctatcgcga attcctgcag gctggcgcaa ccaaggtcgc 300

gccccgcacg ggcgcgtgga ttgaaaccat gcaagcttgg cgtagcttcg tccctatcaa 360

agcttggag 369

<210> 87
<211> 177
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 87
gaaaattatt ttaaatttcc tctagtcagg ccggaataac tccctataat gcgacaccag 60

tcgcgccccg cacgggcgcg tggattgaaa catttatcac aaaaggattg ttcgatgtcc 120

aacaagtcgc gccccgcacg ggcgcgtgga ttgaaacgca ctcccgttct ggataat 177

<210> 88
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
<221> modified_base
<222> (11)..(11)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (14)..(14)
<223> a, c, t, or g

<220>
<221> modified_base

<222> (32)..(32)
<223> a, c, t, or g

<400> 88
agaagggtca nggncatgcg gtttttcctc tntg 34

<210> 89
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
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oligonucleotide

<220>
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<222> (7)..(7)
<223> a, c, t, or g

<220>
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<222> (14)..(14)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (32)..(32)
<223> a, c, t, or g

<400> 89
agaaggntca gggncatgcg gtttttcctc tntg 34

<210> 90
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (7)..(7)
<223> a, c, t, or g

<220>
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<222> (11)..(11)
<223> a, c, t, or g

<220>
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<222> (32)..(32)
<223> a, c, t, or g

<400> 90
agaaggntca nggccatgcg gtttttcctc tntg 34

<210> 91
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (7)..(7)
<223> a, c, t, or g

<220>
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<222> (11)..(11)
<223> a, c, t, or g

<220>
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<222> (14)..(14)
<223> a, c, t, or g

<400> 91
agaaggntca nggncatgcg gtttttcctc tgtg 34

<210> 92
<211> 34
<212> DNA
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<223> a, c, t, or g

<220>
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<222> (11)..(11)
<223> a, c, t, or g

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<223> a, c, t, or g

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<223> a, c, t, or g

<400> 92
agaaggntca nggncatgcg gtttttcctc tntg 34

<210> 93
<211> 34
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<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (14)..(14)
<223> a, c, t, or g

<400> 93
agaagggtca gggncatgcg gtttttcctc tgtg 34

<210> 94
<211> 34
<212> DNA

<213> Artificial Sequence

<220>
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oligonucleotide

<400> 94
agaagggtca gggtcatgcg gtttttcctc tgtg 34

<210> 95
<211> 34
<212> DNA
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<220>
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oligonucleotide

<220>
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<222> (32)..(32)
<223> a, c, t, or g

<400> 95
agaagggtca gggccatgcg gtttttcctc tntg 34

<210> 96
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 96
agaagggtca gggccatgcg gtttttcctc tatg 34

<210> 97
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (7)..(7)
<223> a, c, t, or g

<400> 97
agaaggntca gggccatgcg gtttttcctc tgtg 34

<210> 98
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 98
agaaggatca gggccatgcg gtttttcctc tgtg 34

<210> 99
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (7)..(7)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (11)..(11)
<223> a, c, t, or g

<400> 99
agaaggntca nggccatgcg gtttttcctc tgtg 34

<210> 100
<211> 34

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 100
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<210> 101
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (32)..(32)
<223> a, c, t, or g

<400> 101
agaagggtca gggccatgcg gtttttcctc tntg 34

<210> 102
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 102
agaagggtca gggccatgcg gtttttcctc tatg 34

<210> 103
<211> 34
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<213> Artificial Sequence

<220>
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oligonucleotide

<220>
<221> modified_base
<222> (13)..(13)
<223> a, c, t, or g

<220>
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<223> a, c, t, or g

<220>
<221> modified_base
<222> (27)..(27)
<223> a, c, t, or g

<400> 103
gagaccgaag agnangtgcc gaccacngcc gctg 34

<210> 104
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
<221> modified_base
<222> (15)..(15)
<223> a, c, t, or g

<400> 104
gagaccgaag agaangtgcc gaccaccgcc gctg 34

<210> 105
<211> 34
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 105
gagaccgaag agaatgtgcc gaccaccgcc gctg 34

<210> 106
<211> 34
<212> DNA
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<220>
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oligonucleotide

<220>
<221> modified_base
<222> (27)..(27)
<223> a, c, t, or g

<400> 106
gagaccgaag agaacgtgcc gaccacngcc gctg 34

<210> 107
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 107
gagaccgaag agaacgtgcc gaccactgcc gctg 34

<210> 108
<211> 32
<212> DNA
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oligonucleotide

<220>
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<223> a, c, t, or g

<400> 108
gagaccgaag agnacgtgcc gaccaccgcc gc 32

<210> 109
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
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oligonucleotide

<400> 109
gagaccgaag aggacgtgcc gaccaccgcc gc 32

<210> 110
<211> 34
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<213> Artificial Sequence

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oligonucleotide

<220>
<221> modified_base
<222> (15)..(15)
<223> a, c, t, or g

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<222> (17)..(19)
<223> a, c, t, or g

<400> 110
tgctgaacag ccatnannna ttaactccta aacg 34

<210> 111
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
<221> modified_base
<222> (15)..(15)
<223> a, c, t, or g

<400> 111
tgctgaacag ccatnattga ttaactccta aacg 34

<210> 112
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 112
tgctgaacag ccataattga ttaactccta aacg 34

<210> 113
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
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oligonucleotide

<220>
<221> modified_base
<222> (15)..(15)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (19)..(19)
<223> a, c, t, or g

<400> 113
tgctgaacag ccatnattna ttaactccta aacg 34

<210> 114
<211> 34

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 114
tgctgaacag ccataattaa ttaactccta aacg 34

<210> 115
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (15)..(15)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (17)..(17)
<223> a, c, t, or g

<400> 115
tgctgaacag ccatnantga ttaactccta aacg 34

<210> 116
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 116
tgctgaacag ccataactga ttaactccta aacg 34

<210> 117
<211> 34

<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (15)..(15)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (18)..(19)
<223> a, c, t, or g

<400> 117
tgctgaacag ccatnatnna ttaactccta aacg 34

<210> 118
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 118
tgctgaacag ccataatcaa ttaactccta aacg 34

<210> 119
<211> 34
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<220>
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<222> (15)..(15)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (17)..(17)
<223> a, c, t, or g

<220>
<221> modified_base
<222> (19)..(19)
<223> a, c, t, or g

<400> 119
tgctgaacag ccatnantna ttaactccta aacg 34

<210> 120
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 120
tgctgaacag ccataactca ttaactccta aacg 34