



(51) International Patent Classification:

C12N 15/86 (2006.01) C12N 15/09 (2006.01)
C12N 15/90 (2006.01)

(21) International Application Number:

PCT/US2017/024369

(22) International Filing Date:

27 March 2017 (27.03.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/314,163 28 March 2016 (28.03.2016) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN,
KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,
NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS,
RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY,
TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

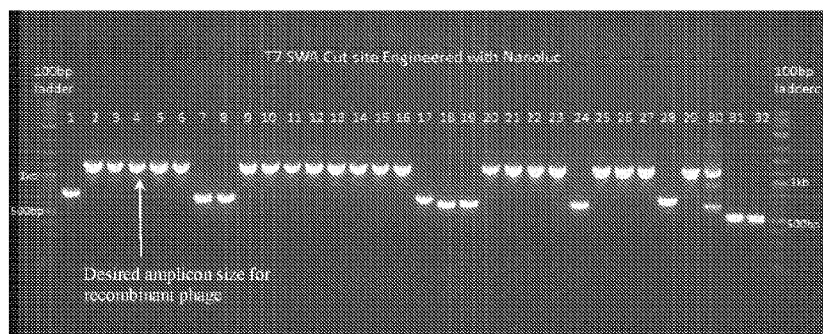
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report (Rule 48.2(g))

(54) Title: BACTERIOPHAGE ENGINEERING METHODS

Figure 2



(57) Abstract: The present disclosure provides methods and kits for generating recombinant bacteriophage genomes.

BACTERIOPHAGE ENGINEERING METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Application No. 62/314,163, filed March 28, 2016, the content of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present technology relates generally to methods and kits for generating recombinant bacteriophage genomes.

BACKGROUND

[0003] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0004] Model phages have been engineered using molecular biology techniques to deliver heterologous protein products to bacterial cells. *E.g.*, US 2009/0155215; M. J. Loessner *et al.*, *Applied and Environmental Microbiology*, Vol. 62, No. 4, pp. 1133-40 (1996)). The natural host range of model phage engineered to date is limited. Methods for creating variations in phage genomes and engineering new phage genomes may lead to the identification of phages with varied properties (*e.g.*, varied host ranges) that are useful for diagnostic and therapeutic purposes.

[0005] Engineering diverse phage is generally made more difficult by the properties of phage genomes. For example, phage genomes have relatively few restriction sites and are heavily modified, making use of traditional cloning techniques with phage challenging. Phages also have compact genomes with very little non-coding DNA, which can make it challenging to find sites within the genome that are compatible with traditional engineering. Many existing phage engineering technologies that rely on *in vitro* strategies are generally inefficient and challenging to scale up. Further, engineering phages within bacteria can be problematic due to toxicity of phages to bacteria as well as the difficulty in maintaining the stability of large engineered genomes.

SUMMARY OF THE PRESENT TECHNOLOGY

[0006] In one aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome with a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions

where the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; and (b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome (*a.k.a.*, “Break and Recombine 3.0” (BAR 3.0) method). The cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment. In some embodiments, the protospacer sequence is 5' GCTTACGCAGAAGATGCAGA 3' (SEQ ID NO: 5).

[0007] Additionally or alternatively, in some embodiments, the method further comprises propagating the recombinant bacteriophage genome in a bacterial host. The bacterial host may be a non-natural bacterial host cell or a natural bacterial host cell.

[0008] Additionally or alternatively, in some embodiments, the CRISPR enzyme is a Cas protein selected from the group consisting of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, and Csf4. In certain embodiments, the CRISPR enzyme is Cas9.

[0009] In certain embodiments of the method, the non-recombinant bacteriophage genome corresponds to K1-5 phage. The nucleic acid sequence of the recombinant bacteriophage genome may comprise SEQ ID NO: 3 or SEQ ID NO: 4.

[0010] In another aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome comprising a single first recognition site with a first restriction enzyme *in vitro* under conditions where the first restriction enzyme cleaves the first recognition site to produce a cleaved non-recombinant bacteriophage genome; and (b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome (*a.k.a.*, BAR 4.0 method). The cleaved non-recombinant

bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.

[0011] Additionally or alternatively, in some embodiments, the method further comprises propagating the recombinant bacteriophage genome in a bacterial host. The bacterial host may be a non-natural bacterial host cell or a natural bacterial host cell.

[0012] In some embodiments, the first restriction enzyme is *Swa*I. In other embodiments, the first restriction enzyme is *Nhe*I.

[0013] In certain embodiments of the method, the non-recombinant bacteriophage genome corresponds to *Escherichia coli* (*a.k.a.*, *E. coli*) T7. The nucleic acid sequence of the recombinant bacteriophage genome may comprise SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 6 or SEQ ID NO: 7.

[0014] Additionally or alternatively, in some embodiments of the BAR 3.0 and BAR 4.0 methods disclosed herein, the recombination system comprises a 5'-3' exonuclease, a DNA polymerase, and a DNA ligase.

[0015] In one aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome with (i) a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions where the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; or (ii) a restriction enzyme *in vitro* under conditions where the restriction enzyme cleaves a unique recognition site within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; (b) transforming the cleaved non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and (c) recombining *in vivo* the cleaved non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome (*a.k.a.*, BARner method). The cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous

nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.

[0016] The cleaved non-recombinant bacteriophage genome may be transformed into the bacterial host cell *via* electroporation. The bacterial host cell may be a non-natural bacterial host cell or a natural bacterial host cell. In some embodiments, the non-endogenous recombination system is induced in the bacterial host cell. In certain embodiments, the non-endogenous recombination system is induced by the addition of arabinose.

[0017] Additionally or alternatively, in some embodiments, the CRISPR enzyme is a Cas protein selected from the group consisting of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, and Csf4.

[0018] Additionally or alternatively, in some embodiments, the restriction enzyme is AclI, HindIII, SspI, MluCI Tsp509I, PciI, AgeI, BspMI, BfuAI, SexAI, MluI, BceAI, HpyCH4IV, HpyCH4III, BaeI, BsaXI, AflIII, SpeI, BsrI, BmrI, BglII, AfeI, AluI, StuI, ScaI, ClaI, BspDI, PI-SceI, NsiI, AseI, SwaI, CspCI, MfeI, BssSI, BssSαI, Nb.BssSI, BmgBI, PmlI, DraIII, AleI, EcoP15I, PvuII, AlwNI, BtsIMutI, TspRI, NdeI, NlaIII, CviAII, FatI, MslI, FspEI, XcmI, BstXI, PflMI, BccI, NcoI, BseYI, FauI, SmaI, XmaI, TspMI, Nt.CviPII, LpnPI, AciI, SacII, BsrBI, MspI, HpaII, ScrFI, BssKI, StyD4I, BsaJI, BslI, BtgI, NciI, AvrII, MnlI, BbvCI, Nb.BbvCI, Nt.BbvCI, SbfI, Bpu10I, Bsu36I, EcoNI, HpyAV, BstNI, PspGI, StyI, BcgI, PvuI, BstUI, EagI, RsrII, BsiEI, BsiWI, BsmBI, Hpy99I, MspAII, MspJI, SgrAI, BfaI, BspCNI, XhoI, PaeR7I, TliI, EarI, AcuI, PstI, BpmI, DdeI, SfcI, AflII, BpuEI, SmlI, Aval, BsoBI, MboII, BbsI, XmnI, BsmI, Nb.BsmI, EcoRI, HgaI, AatII, ZraI, Tth111I, PflFI, PshAI, AhdI, DrdI, Eco53kI, SacI, BseRI, PleI, Nt.BstNBI, MlyI, HinfI, EcoRV, MboI, Sau3AI, DpnII, BfuCI, DpnI, BsaBI, TfiI, BsrDI, Nb.BsrDI, BbvI, BtsI, BtsαI, Nb.BtsI, BstAPI, SfaNI, SphI, SrfI, NmeAIII, NaeI, NgoMIV, BglI, AsiSI, BtgZI, HinPII, HhaI, BssHII, NotI, Fnu4HI, Cac8I, MwoI, NheI, BmtI, SapI, BspQI, Nt.BspQI, BlpI, TseI, ApeKI, Bsp1286I, AlwI, Nt.AlwI, BamHI, FokI, BtsCI, HaeIII, PhoI, FseI, SfiI, NarI, KasI, SfoI, PluTI, AscI, EciI, BsmFI, ApaI, PspOMI, Sau96I, NlaIV, KpnI, Acc65I, BsaI, HphI, BstEII, AvaII, BanI, BaeGI, BsaHI, BanII, RsaI, CviQI, BstZ17I, BciVI, SalI, Nt.BsmAI, BsmAI, BcoDI, ApaLI, BsgI, AccI, Hpy166II, Tsp45I, HpaI, PmeI, HincII, BsiHKAI, ApoI, NspI, BsrFI, BsrFαI, BstYI, HaeII, CviKI-1, EcoO109I, PpuMI, I-CeuI, SnaBI, I-SceI, BspHI,

BspEI, MmeI, TaqaI, NruI, Hpy188I, Hpy188III, XbaI, BclI, HpyCH4V, FspI, PI-PspI, MscI, BsrGI, MseI, PacI, PsiI, BstBI, DraI, PspXI, BsaWI, BsaAI, and EaeI.

[0019] In another aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) transforming an intact non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and (b) recombining *in vivo* the intact non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome (*a.k.a.*, BREDner method). In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to a first region within the intact non-recombinant bacteriophage genome, and a 3' flanking region that is homologous to a second region within the intact non-recombinant bacteriophage genome, wherein the first region of the intact non-recombinant bacteriophage genome is located 5' to the second region of the intact non-recombinant bacteriophage genome. The intact non-recombinant bacteriophage genome may be transformed into the bacterial host cell *via* electroporation. The bacterial host cell may be a non-natural bacterial host cell or a natural bacterial host cell. In some embodiments, the non-endogenous recombination system is induced in the bacterial host cell. In certain embodiments, the non-endogenous recombination system is induced by the addition of arabinose.

[0020] Additionally or alternatively, in some embodiments of the BREDner and BARner methods disclosed herein, the recombination system comprises lambda Red proteins Gam, Exo, and Beta operably linked to an inducible promoter (*e.g.*, *araB* promoter).

[0021] In any of the above embodiments of the methods of the present technology, the heterologous nucleic acid is about 500-1050 base pairs or 1050 base pairs to 5 kb in length. The heterologous nucleic acid may comprise an open reading frame that encodes a bioluminescent protein, a fluorescent protein, a chemiluminescent protein, or any combination thereof. Examples of bioluminescent protein include Aequorin, firefly luciferase, *Renilla* luciferase, red luciferase, luxAB, or nanoluciferase. Examples of chemiluminescent protein include β -galactosidase, horseradish peroxidase (HRP), or alkaline phosphatase. Examples of fluorescent protein include TagBFP, Azurite, EBFP2, mKalamal, Sirius, Sapphire, T-Sapphire, ECFP, Cerulean, SCFP3A, mTurquoise, monomeric Midoriishi-Cyan, TagCFP, mTFP1, EGFP, Emerald, Superfolder GFP, Monomeric Azami Green, TagGFP2, mUKG, mWasabi, EYFP, Citrine, Venus, SYFP2, TagYFP, Monomeric

Kusabira-Orange, mKO_κ, mKO₂, mOrange, mOrange2, mRaspberry, mCherry, dsRed, mStrawberry, mTangerine, tdTomato, TagRFP, TagRFP-T, mApple, mRuby, mPlum, HcRed-Tandem, mKate2, mNeptune, NirFP, TagRFP657, IFP1.4, iRFP, mKeima Red, LSS-mKate1, LSS-mKate2, PA-GFP, PAmCherry1, PATagRFP, Kaede (green), Kaede (red), KikGR1 (green), KikGR1 (red), PS-CFP2, PS-CFP2, mEos2 (green), mEos2 (red), PSmOrange, or Dronpa.

[0022] Additionally or alternatively, in some embodiments of the methods disclosed herein, the open reading frame of the heterologous nucleic acid is operably linked to an expression control sequence that is capable of directing expression of the bioluminescent protein, the fluorescent protein, the chemiluminescent protein, or any combination thereof. The expression control sequence may be an inducible promoter or a constitutive promoter.

[0023] Also provided herein are recombinant bacteriophages comprising a genome having a nucleic acid sequence comprising any one of SEQ ID NOs: 1-4 or 6. Also disclosed herein are kits for integrating a heterologous nucleic acid sequence into a bacteriophage genome.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1 outlines the BAR 4.0 method of the present technology that was used to generate the DLPECO₂ phage strain, which contains a double insertion of the nanoluciferase (NanoLuc[®]) reporter gene.

[0025] Figure 2 shows the recovery of recombinant NanoLuc[®] T7 phages that contain a single insertion of the NanoLuc[®] reporter gene using the BAR 4.0 method disclosed herein. Isolated plaques were selected and screened for NanoLuc[®] insertion *via* PCR using primers that flanked the NanoLuc[®] insertion site. A 700 bp increase in amplicon size correlated with the successful insertion of the NanoLuc[®] reporter gene within the T7 genome at the *Swa*I restriction site.

[0026] Figure 3 shows the luminescence activity profile of the DLPECO₁ phage strain, which contains a single insertion of the NanoLuc[®] reporter gene.

[0027] Figure 4 shows a schematic of the NanoLuc[®] insertion into the T7 genome at the *Swa*I restriction site.

[0028] Figure 5 shows the recovery of recombinant NanoLuc[®] T7 phages that contain a second insertion of the NanoLuc[®] reporter gene using the BAR 4.0 method disclosed herein. Isolated plaques were selected and screened for NanoLuc[®] insertion within the T7 genome at

the NheI restriction site *via* PCR. A PCR product of approximately 1 kb correlated with the successful insertion of the NanoLuc[®] reporter gene within the T7 genome at the NheI restriction site.

[0029] Figure 6 shows the luminescence activity profile of the DLPECO2 phage strain, which contains a double insertion of the NanoLuc[®] reporter gene.

[0030] Figure 7 shows a schematic of the NanoLuc[®] insertion into the T7 genome at the NheI restriction site.

[0031] Figure 8 shows a comparison of the relative luminescence units (RLU) between the DLPECO1 (S) and the DLPECO2 (D) phage strains. Phage infection at different bacterial host cell concentrations was carried out for 60 minutes before measuring luminescence. The DLPECO2 phage strain exhibited increases in both luminescence levels and sensitivity relative to that observed with the DLPECO1 phage strain.

[0032] Figure 9 shows the specific host range of the recombinant NanoLuc[®] T7 phages that contain a double insertion of the NanoLuc[®] reporter gene.

[0033] Figure 10 shows the complete genome sequence of the recombinant NanoLuc[®] T7 phage strain DLPECO1, which contains a single insertion of the NanoLuc[®] reporter gene (SEQ ID NO: 1).

[0034] Figure 11 shows the complete genome sequence of the recombinant NanoLuc[®] T7 phage strain DLPECO2, which contains a double insertion of the NanoLuc[®] reporter gene (SEQ ID NO: 2).

[0035] Figure 12 shows the luminescence activity profile of 36 resulting plaques that were isolated after subjecting the non-recombinant bacteriophage K1-5 to the BAR 3.0 method disclosed herein.

[0036] Figure 13 shows that K5 *E. coli* infected with bacteriophage derived from isolate #30 exhibit a high degree of luminescence.

[0037] Figure 14 shows that a recombinant junction is present in a putative recombinant K1-5 phage, but not in wild-type K1-5 phage. A PCR product of approximately 916 bp correlated with the successful insertion of the NanoLuc[®] reporter gene.

[0038] Figure 15 shows the heterologous nucleic acid sequence that was inserted into K1-5 phage using the BAR 3.0 method disclosed herein (SEQ ID NO: 3).

[0039] Figure 16 shows the complete genome sequence of the recombinant NanoLuc[®] K1-5 phage. (SEQ ID NO: 4).

[0040] Figure 17 shows the heterologous nucleic acid sequence that was inserted near the NheI site in T7 phage using the BAR 4.0 method disclosed herein (SEQ ID NO: 6).

[0041] Figure 18 shows the heterologous nucleic acid sequence that was inserted near the SmaI site in T7 phage using the BAR 4.0 method disclosed herein (SEQ ID NO: 7).

DETAILED DESCRIPTION

[0042] It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

[0043] One of the most commonly used and well-established methods for engineering phage genomes is homologous recombination in their bacterial hosts, which can occur between two homologous DNA sequences as short as 23 bp (Alberts B *et al.*, MOLECULAR BIOLOGY OF THE CELL, 5th ed. Garland Science, New York, NY (2007); Snyder L *et al.*, MOLECULAR GENETICS OF BACTERIA, 4th ed. ASM Press, Washington, DC (2013)). Homologous recombination occurs between the plasmid and the phage genome, allowing the heterologous gene to be integrated into the phage genome and eventually packaged within the phage particle. However, homologous recombination only yields a small fraction of recombination progeny phage. Reported recombination rates range from 10^{-10} to 10^{-4} (Loessner M. *et al.*, *Appl Environ Microbiol* 62:1133–1140 (1996); Le S. *et al.*, *PLoS One* 8:e68562 (2013); Mahichi F. *et al.*, *FEMS Microbiol Lett* 295:211–217 (2009)). One of the major challenges of generating recombinant bacteriophages is that the recombinant processes used to create such bacteriophages are inefficient, and often result in a low yield of recombinant bacteriophage genomes. Transformation of large bacteriophage genomes (*e.g.*, about or greater than 40-48 kb) is prohibitive in many bacterial strains and species, making it difficult to isolate viable bacteriophage particles post-transformation. *See e.g.*, Chauthaiwale *et al.*, *Microbiological Reviews* 56 (4): 577-592 (1992); see also Vaughan *et al.*, *Nature Biotechnology* 14:309-314 (1996). Thus, finding the desired clone using conventional phage screening methods is labor-intensive and unpredictable.

[0044] The present disclosure provides methods for integrating a heterologous nucleic acid sequence into a bacteriophage genome, and isolating recombinant bacteriophages that express the heterologous nucleic acid sequence. The methods disclosed herein permit higher

recovery of recombinant bacteriophage genomes that express the phenotypic properties associated with the heterologous nucleic acid sequence relative to that observed with conventional phage engineering methods, such as bacteriophage recombineering of electroporated DNA (BRED) (Marinelli LJ *et al.*, *PLoS One* 3:e3957 (2008)). For example, the overall yield of recombinant bacteriophage genomes was about 44%-69% with the BAR 4.0 method of the present technology, and 2.78% with the BAR 3.0 method of the present technology. In contrast, no recombinant bacteriophages were generated using BRED (*i.e.*, 0% recovery of recombinant bacteriophage genomes).

[0045] In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, microbiology and recombinant DNA are used. *See, e.g.*, Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*.

Definitions

[0046] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise. For example, reference to “a cell” includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analytical chemistry and nucleic acid

chemistry and hybridization described below are those well-known and commonly employed in the art.

[0047] As used herein, the term “about” in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[0048] As used herein, “bacteriophage” or “phage” refers to a virus that infects bacteria. Bacteriophages are obligate intracellular parasites that multiply inside bacteria by co-opting some or all of the host biosynthetic machinery (*i.e.*, viruses that infect bacteria). Though different bacteriophages may contain different materials, they all contain nucleic acid and protein, and can under certain circumstances be encapsulated in a lipid membrane. Depending upon the phage, the nucleic acid can be either DNA or RNA (but not both).

[0049] As used herein, “expression” includes one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

[0050] As used herein, an “expression control sequence” refers to polynucleotide sequences which are necessary to affect the expression of coding sequences to which they are operably linked. Expression control sequences are sequences which control the transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.*, ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence. The term “control sequences” is intended to encompass, at a minimum, any component whose presence is essential for expression, and can also encompass an additional component whose presence is advantageous, for example, leader sequences.

[0051] As used herein, “heterologous nucleic acid sequence” is any sequence placed at a location in the genome where it does not normally occur. A heterologous nucleic acid sequence may comprise a sequence that does not naturally occur in a bacteriophage, or it may comprise only sequences naturally found in the bacteriophage, but placed at a non-normally occurring location in the genome. In some embodiments, the heterologous nucleic acid sequence is not a natural phage sequence. In certain embodiments, the heterologous nucleic acid sequence is a natural phage sequence that is derived from a different phage. In other embodiments, the heterologous nucleic acid sequence is a sequence that occurs naturally in the genome of a wild-type phage but is then relocated to another site where it does not naturally occur, rendering it a heterologous sequence at that new site.

[0052] “Homology” or “identity” or “similarity” refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same nucleobase or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99%) of “sequence identity” to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art. In some embodiments, default parameters are used for alignment. One alignment program is BLAST, using default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code=standard; filter=none; strand=both; cutoff=60; expect=10; Matrix=BLOSUM62; Descriptions=50 sequences; sort by =HIGH SCORE; Databases=non-redundant, GenBank+EMBL+DDBJ+PDB+GenBank CDS translations+SwissProtein+SPupdate+PIR. Details of these programs can be found at the National Center for Biotechnology Information. Biologically equivalent polynucleotides are those having the specified percent homology and encoding a polypeptide having the same or similar biological activity. Two sequences are deemed “unrelated” or “non-homologous” if they share less than 40% identity, or less than 25% identity, with each other.

[0053] As used herein, a “host cell” is a bacterial cell that can be infected by a phage to yield progeny phage particles. A host cell can form phage particles from a particular type of phage genomic DNA. In some embodiments, the phage genomic DNA is introduced into the host cell by infecting the host cell with a phage. In some embodiments, the phage genomic DNA is introduced into the host cell using transformation, electroporation, or any other suitable technique. In some embodiments, the phage genomic DNA is substantially pure when introduced into the host cell. In some embodiments, the phage genomic DNA is present in a vector when introduced into the host cell. The definition of host cell can vary from one phage to another. For example, *E. coli* may be the natural host cell for a particular type of phage, but *Klebsiella pneumoniae* is not.

[0054] As used herein, the term “isolated” refers to a substance or entity that has been separated from at least some of the components with which it was associated when initially produced (whether in nature or in an experimental setting). Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated substances and/or entities are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is “pure” if it is substantially free of other components.

[0055] As used herein, “operably linked” means that expression control sequences are positioned relative to the nucleic acid of interest to initiate, regulate or otherwise control transcription of the nucleic acid of interest.

[0056] As used herein, a “phage genome” includes naturally occurring phage genomes and derivatives thereof. Generally, the derivatives possess the ability to propagate in the same hosts as the naturally occurring phage. In some embodiments, the only difference between a naturally occurring phage genome and a derivative phage genome is at least one of a deletion and an addition of nucleotides from at least one end of the phage genome (if the genome is linear) or at least one point in the genome (if the genome is circular).

[0057] As used herein, the term “polynucleotide” or “nucleic acid” means any RNA or DNA, which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and

double-stranded regions, single- and double-stranded RNA, RNA that is mixture of single- and double-stranded regions, and hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, polynucleotide refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

[0058] As used herein, the term “recombinant” when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the material is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0059] As used herein, an endogenous nucleic acid sequence in the genome of an organism (or the encoded protein product of that sequence) is deemed “recombinant” herein if a heterologous sequence is placed adjacent to the endogenous nucleic acid sequence, such that the expression of this endogenous nucleic acid sequence is altered. In this context, a heterologous sequence is a sequence that is not naturally adjacent to the endogenous nucleic acid sequence, whether or not the heterologous sequence is itself endogenous to the organism (originating from the same organism or progeny thereof) or exogenous (originating from a different organism or progeny thereof). By way of example, a promoter sequence can be substituted (*e.g.*, by homologous recombination) for the native promoter of a gene in the genome of an organism, such that this gene has an altered expression pattern. This gene would be “recombinant” because it is separated from at least some of the sequences that naturally flank it. A nucleic acid is also considered “recombinant” if it contains any modifications that do not naturally occur in the corresponding nucleic acid in a genome. For instance, an endogenous coding sequence is considered “recombinant” if it contains an insertion, deletion or a point mutation introduced artificially, *e.g.*, by human intervention. A “recombinant nucleic acid” also includes a nucleic acid integrated into a host cell chromosome at a heterologous site and a nucleic acid construct present as an episome.

[0060] As used herein, a “recombinant bacteriophage genome” is a bacteriophage genome that has been genetically modified by the insertion of a heterologous nucleic acid

sequence into the bacteriophage genome. A “recombinant bacteriophage” means a bacteriophage that comprises a recombinant bacteriophage genome. In some embodiments, the bacteriophage genome is modified by recombinant DNA technology to introduce a heterologous nucleic acid sequence into the genome at a defined site. In some embodiments, the heterologous nucleic acid sequence is introduced with no corresponding loss of endogenous phage genomic nucleotides. In other words, if bases N1 and N2 are adjacent in the wild-type bacteriophage genome, the heterologous nucleic acid sequence is inserted between N1 and N2. Thus, in the resulting recombinant bacteriophage genome, the heterologous nucleic acid sequence is flanked by nucleotides N1 and N2. In some embodiments, endogenous phage nucleotides are removed or replaced during the insertion of the heterologous nucleic acid sequence. For example, in some embodiments, the heterologous nucleic acid sequence is inserted in place of some or all of the endogenous phage sequence which is removed. In some embodiments, endogenous phage sequences are removed from a position in the phage genome distant from the site(s) of insertion of the heterologous nucleic acid sequences.

[0061] As used herein, the terms “restriction endonucleases” and “restriction enzymes” refer to bacterial enzymes each of which cleave double-stranded DNA at or near a specific nucleotide sequence known as a “restriction site”, “recognition site”, or “double-stranded recognition site.”

[0062] As used herein, the term “sample” refers to clinical samples obtained from a subject or isolated microorganisms. In certain embodiments, a sample is obtained from a biological source (*i.e.*, a “biological sample”), such as tissue, bodily fluid, or microorganisms collected from a subject. Sample sources include, but are not limited to, mucus, sputum, bronchial alveolar lavage (BAL), bronchial wash (BW), whole blood, bodily fluids, cerebrospinal fluid (CSF), urine, plasma, serum, or tissue.

Bacteriophage

[0063] Bacteriophage are obligate intracellular parasites that multiply inside bacteria by co-opting some or all of the host biosynthetic machinery. Phages contain nucleic acid and protein, and may be enveloped by a lipid membrane. Depending upon the phage, the nucleic acid genome can be either DNA or RNA but not both, and can exist in either circular or linear forms. The size of the phage genome varies depending upon the phage. The simplest phages have genomes that are only a few thousand nucleotides in size, while the more complex phages may contain more than 100,000 nucleotides in their genome, and in rare instances

more than 1,000,000. The number and amount of individual types of protein in phage particles will vary depending upon the phage. The proteins function in infection and to protect the nucleic acid genome from environmental nucleases.

[0064] Phage genomes come in a variety of sizes and shapes (*e.g.*, linear or circular). Most phages range in size from 24-200 nm in diameter. The capsid is composed of many copies of one or more phage proteins, and acts as a protective envelope around the phage genome. Many phages have tails attached to the phage capsid. The tail is a hollow tube through which the phage nucleic acid passes during infection. The size of the tail can vary and some phages do not even have a tail structure. In the more complex phages, the tail is surrounded by a contractile sheath which contracts during infection of the bacterial host cell. At the end of the tail, phages have a base plate and one or more tail fibers attached to it. The base plate and tail fibers are involved in the binding of the phage to the host cell.

[0065] Lytic or virulent phages are phages which can only multiply in bacteria and lyse the bacterial host cell at the end of the life cycle of the phage. The lifecycle of a lytic phage begins with an eclipse period. During the eclipse phase, no infectious phage particles can be found either inside or outside the host cell. The phage nucleic acid takes over the host biosynthetic machinery and phage specific mRNAs and proteins are produced. Early phage mRNAs code for early proteins that are needed for phage DNA synthesis and for shutting off host DNA, RNA and protein biosynthesis. In some cases, the early proteins actually degrade the host chromosome. After phage DNA is made late mRNAs and late proteins are made. The late proteins are the structural proteins that comprise the phage as well as the proteins needed for lysis of the bacterial cell. In the next phase, the phage nucleic acid and structural proteins are assembled and infectious phage particles accumulate within the cell. The bacteria begin to lyse due to the accumulation of the phage lysis protein, leading to the release of intracellular phage particles. The number of particles released per infected cell can be as high as 1000 or more. Lytic phage may be enumerated by a plaque assay. The assay is performed at a low enough concentration of phage such that each plaque arises from a single infectious phage. The infectious particle that gives rise to a plaque is called a PFU (plaque forming unit).

[0066] Lysogenic phages are those that can either multiply *via* the lytic cycle or enter a quiescent state in the host cell. In the quiescent state, the phage genome exists as a prophage (*i.e.*, it has the potential to produce phage). In most cases, the phage DNA actually integrates into the host chromosome and is replicated along with the host chromosome and passed on to

the daughter cells. The host cell harboring a prophage is not adversely affected by the presence of the prophage and the lysogenic state may persist indefinitely. The lysogenic state can be terminated upon exposure to adverse conditions. Conditions which favor the termination of the lysogenic state include: desiccation, exposure to UV or ionizing radiation, exposure to mutagenic chemicals, *etc.* Adverse conditions lead to the production of proteases (rec A protein), the expression of the phage genes, reversal of the integration process, and lytic multiplication.

[0067] In some embodiments, a phage genome comprises at least 5 kilobases (kb), at least 10 kb, at least 15 kb, at least 20 kb, at least 25 kb, at least 30 kb, at least 35 kb, at least 40 kb, at least 45 kb, at least 50 kb, at least 55 kb, at least 60 kb, at least 65 kb, at least 70 kb, at least 75 kb, at least 80 kb, at least 85 kb, at least 90 kb, at least 95 kb, at least 100 kb, at least 105 kb, at least 110 kb, at least 115 kb, at least 120 kb, at least 125 kb, at least 130 kb, at least 135 kb, at least 140 kb, at least 145 kb, at least 150 kb, at least 175 kb, at least 200 kb, at least 225 kb, at least 250 kb, at least 275 kb, at least 300 kb, at least 325 kb, at least 350 kb, at least 375 kb, at least 400 kb, at least 425 kb, at least 450 kb, at least 475 kb, or at least 500 kb of nucleic acids.

Phage Engineering Methods of the Present Technology

BAR 3.0

[0068] In one aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome with a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions where the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; and (b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome. The cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment. In some embodiments, the protospacer sequence is 5' GCTTACGCAGAAGATGCAGA 3' (SEQ ID NO: 5).

[0069] In some embodiments of the BAR 3.0 method, the homologous 5' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0070] Additionally or alternatively, in some embodiments of the BAR 3.0 method, the homologous 3' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0071] Additionally or alternatively, in some embodiments, the BAR 3.0 method further comprises propagating the recombinant bacteriophage genome in a bacterial host. For example, the bacterial host may be transformed with the recombinant bacteriophage genome *via* electroporation. The bacterial host may be a non-natural bacterial host cell or a natural bacterial host cell.

[0072] Additionally or alternatively, in some embodiments of the BAR 3.0 method, the non-recombinant bacteriophage genome corresponds to T3, T7, M6, K11, F92, K1-5, and K1F. In certain embodiments of the BAR 3.0 method, the non-recombinant bacteriophage genome corresponds to K1-5 phage. In certain embodiments of the BAR 3.0 method, the non-recombinant bacteriophage genome corresponds to a phage group selected from the group consisting of *Myoviridae*, *Siphoviridae*, *Podoviridae*, *Lipothrixviridae*, *Rudiviridae*,

Ampullaviridae, Bucaudaviridae, Clavaviridae, Corticoviridae, Cystoviridae, Fuselloviridae, Globuloviridae, Guttaviridae, Inoviridae, Leviviridae, Mircoviridae, Plasmaviridae, and Tectiviridae. The nucleic acid sequence of the recombinant bacteriophage genome may comprise SEQ ID NO: 3 or SEQ ID NO: 4.

BAR 4.0

[0073] In another aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome comprising a single first recognition site with a first restriction enzyme *in vitro* under conditions where the first restriction enzyme cleaves the first recognition site to produce a cleaved non-recombinant bacteriophage genome; and (b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome. The cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.

[0074] In some embodiments of the BAR 4.0 method, the homologous 5' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0075] Additionally or alternatively, in some embodiments of the BAR 4.0 method, the homologous 3' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-

170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0076] Additionally or alternatively, in some embodiments, the BAR 4.0 method further comprises propagating the recombinant bacteriophage genome in a bacterial host. For example, the bacterial host may be transformed with the recombinant bacteriophage genome *via* electroporation. The bacterial host may be a non-natural bacterial host cell or a natural bacterial host cell.

[0077] Additionally or alternatively, in some embodiments of the BAR 4.0 method, the non-recombinant bacteriophage genome corresponds to T3, T7, M6, K11, F92, K1-5, and K1F. In certain embodiments of the BAR 4.0 method, the non-recombinant bacteriophage genome corresponds to *E. coli* T7. In certain embodiments of the BAR 4.0 method, the non-recombinant bacteriophage genome corresponds to a phage group selected from the group consisting of *Myoviridae*, *Siphoviridae*, *Podoviridae*, *Lipothrixviridae*, *Rudiviridae*, *Ampullaviridae*, *Bucaudaviridae*, *Clavaviridae*, *Corticoviridae*, *Cystoviridae*, *Fuselloviridae*, *Globuloviridae*, *Guttaviridae*, *Inoviridae*, *Leviviridae*, *Mircoviridae*, *Plasmaviridae*, and *Tectiviridae*. The nucleic acid sequence of the recombinant bacteriophage genome may comprise SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 6, or SEQ ID NO: 7.

BARner

[0078] In one aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) contacting a non-recombinant bacteriophage genome with (i) a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions where the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; or (ii) a restriction enzyme *in vitro* under conditions where the restriction enzyme cleaves a unique recognition site within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; (b) transforming the cleaved non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and (c) recombining *in vivo* the

cleaved non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome. The cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment. The cleaved non-recombinant bacteriophage genome may be transformed into the bacterial host cell *via* electroporation. The bacterial host cell may be a non-natural bacterial host cell or a natural bacterial host cell. In some embodiments, the non-endogenous recombination system is induced in the bacterial host cell. In certain embodiments, the non-endogenous recombination system is induced by the addition of arabinose.

[0079] In some embodiments of the BARner method, the homologous 5' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0080] Additionally or alternatively, in some embodiments of the BARner method, the homologous 3' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500

bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0081] Additionally or alternatively, in some embodiments of the BARner method, the non-recombinant bacteriophage genome corresponds to T3, T7, M6, K11, F92, K1-5, and K1F. In certain embodiments of the BARner method, the non-recombinant bacteriophage genome corresponds to a phage group selected from the group consisting of *Myoviridae*, *Siphoviridae*, *Podoviridae*, *Lipothrrixviridae*, *Rudiviridae*, *Ampullaviridae*, *Bucaudaviridae*, *Clavaviridae*, *Corticoviridae*, *Cystoviridae*, *Fuselloviridae*, *Globuloviridae*, *Guttaviridae*, *Inoviridae*, *Leviviridae*, *Mircoviridae*, *Plasmaviridae*, and *Tectiviridae*.

BREDner

[0082] In another aspect, the present disclosure provides a method for generating a recombinant bacteriophage genome comprising: (a) transforming an intact non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and (b) recombining *in vivo* the intact non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome. In some embodiments, the heterologous nucleic acid comprises a 5' flanking region that is homologous to a first region within the intact non-recombinant bacteriophage genome, and a 3' flanking region that is homologous to a second region within the intact non-recombinant bacteriophage genome, wherein the first region of the intact non-recombinant bacteriophage genome is located 5' to the second region of the intact non-recombinant bacteriophage genome. The intact non-recombinant bacteriophage genome may be transformed into the bacterial host cell *via* electroporation. The bacterial host cell may be a non-natural bacterial host cell or a natural bacterial host cell. In some embodiments, the non-endogenous recombination system is induced in the bacterial host cell. In certain embodiments, the non-endogenous recombination system is induced by the addition of arabinose.

[0083] In some embodiments of the BREDner method, the homologous 5' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-

320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0084] Additionally or alternatively, in some embodiments of the BREDner method, the homologous 3' flanking region of the heterologous nucleic acid has a length of about 20-30 base pairs (bps), 30-40 bps, 40-50 bps, 50-60 bps, 60-70 bps, 70-80 bps, 80-90 bps, 90-100 bps, 100-110 bps, 110-120 bps, 120-130 bps, 130-140 bps, 140-150 bps, 150-160 bps, 160-170 bps, 170-180 bps, 180-190 bps, 190-200 bps, 200-210 bps, 210-220 bps, 220-230 bps, 230-240 bps, 240-250 bps, 250-260 bps, 260-270 bps, 270-280 bps, 280-290 bps, 290-300 bps, 300-310 bps, 310-320 bps, 320-330 bps, 330-340 bps, 340-350 bps, 350-360 bps, 360-370 bps, 370-380 bps, 380-390 bps, 390-400 bps, 400-410 bps, 410-420 bps, 420-430 bps, 430-440 bps, 440-450 bps, 450-460 bps, 460-470 bps, 470-480 bps, 480-490 bps, 490-500 bps, 500-510 bps, 510-520 bps, 520-530 bps, 530-540 bps, 540-550 bps, 550-560 bps, 560-570 bps, 570-580 bps, 580-590 bps, or 590-600 bps.

[0085] Additionally or alternatively, in some embodiments of the BREDner method, the intact non-recombinant bacteriophage genome corresponds to T3, T7, M6, K11, F92, K1-5, and K1F. In certain embodiments of the BREDner method, the non-recombinant bacteriophage genome corresponds to a phage group selected from the group consisting of *Myoviridae*, *Siphoviridae*, *Podoviridae*, *Lipothrixviridae*, *Rudoviridae*, *Ampullaviridae*, *Bucaudaviridae*, *Clavaviridae*, *Corticoviridae*, *Cystoviridae*, *Fuselloviridae*, *Globuloviridae*, *Guttaviridae*, *Inoviridae*, *Leviviridae*, *Mircoviridae*, *Plasmaviridae*, and *Tectiviridae*.

[0086] Additionally or alternatively, in any of the above embodiments of the methods disclosed herein (BAR 3.0, BAR 4.0, BARner and BREDner), the recombination system comprises a 5'-3' exonuclease, a DNA polymerase, and a DNA ligase. In one embodiment, the 5'-3' exonuclease is T5 exonuclease, the DNA polymerase is Phusion[®] DNA polymerase, and the DNA ligase is *Taq* ligase. In other embodiments of the methods disclosed herein, the recombination system comprises lambda Red proteins Gam, Exo, and Beta operably linked to an inducible promoter (*e.g.*, *araB* promoter). In certain embodiments of the methods disclosed herein, the recombination system comprises RecET (RecE, RecT) operons. In other embodiments of the methods disclosed herein, the recombination system comprises RecA recombinase, or a RecA gain-of-function variant.

[0087] Accurate identification of bacterial species within a biological sample informs the selection of suitable therapies for treating bacterial infections. Recombinant bacteriophage generated using the methods disclosed herein, may be used to identify bacteria present within a biological sample (*e.g.*, whole blood, plasma, serum). Such methods entail contacting the biological sample with a recombinant bacteriophage generated using the methods disclosed herein, and detecting the presence of bacterial host cells infected by the recombinant phage, wherein the recombinant phage comprises a heterologous nucleic acid that encodes a detectable gene product, thereby leading to the identification of bacteria present within the biological sample.

[0088] Additionally or alternatively, recombinant bacteriophage generated using the methods disclosed herein, may be used in methods for profiling antibiotic susceptibility of bacteria present within a biological sample (*e.g.*, whole blood, plasma, serum). These methods include (a) contacting the biological sample with an antibiotic and a recombinant bacteriophage generated using the methods disclosed herein, (b) detecting the presence of bacterial host cells infected by the recombinant phage, wherein the recombinant phage comprises a heterologous nucleic acid that encodes a detectable gene product, and (c) determining that the antibiotic is effective in inhibiting the bacteria present in the biological sample when the number of recombinant phage infected bacterial host cells is reduced relative to that observed in an untreated control sample.

CRISPR Enzymes

[0089] A variety of CRISPR enzymes are available for use in conjunction with the disclosed BAR 3.0 and BARner methods of the present disclosure. In some embodiments, the CRISPR enzyme is a Type II CRISPR enzyme. In some embodiments, the CRISPR enzyme catalyzes DNA cleavage. In some embodiments, the CRISPR enzyme catalyzes RNA cleavage. In some embodiments, the CRISPR enzyme is any Cas9 protein, for instance any naturally-occurring bacterial Cas9 as well as any variants, homologs or orthologs thereof. Non-limiting examples of Cas proteins include Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9 (also known as Csn1 and Csx12), Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, homologues thereof, or variants thereof. In some embodiments, the CRISPR enzyme cleaves both strands of the target nucleic acid at the Protospacer Adjacent

Motif (PAM) site. In certain embodiments of the BAR 3.0 method, the CRISPR enzyme is Cas9.

Restriction Enzymes

[0090] A variety of restriction enzymes are available for use in conjunction with the disclosed BAR 4.0 and BARner methods of the present disclosure. Non-limiting examples of restriction enzymes include AclI, HindIII, SspI, MluCI Tsp509I, PciI, AgeI, BspMI, BfuAI, SexAI, MluI, BceAI, HpyCH4IV, HpyCH4III, BaeI, BsaXI, AflIII, SpeI, BsrI, BmrI, BglII, AfeI, AluI, StuI, ScaI, ClaI, BspDI, PI-SceI, NsiI, AseI, SwaI, CspCI, MfeI, BssSI, BssSαI, Nb.BssSI, BmgBI, PmlI, DraIII, AleI, EcoP15I, PvuII, AlwNI, BtsIMutI, TspRI, NdeI, NlaIII, CviAII, FatI, MslI, FspEI, XcmI, BstXI, PflMI, BccI, NcoI, BseYI, FauI, SmaI, XmaI, TspMI, Nt.CviPII, LpnPI, AciI, SacII, BsrBI, MspI, HpaII, ScrFI, BssKI, StyD4I, BsaJI, BslI, BtgI, NciI, AvrII, MnlI, BbvCI, Nb.BbvCI, Nt.BbvCI, SbfI, Bpu10I, Bsu36I, EcoNI, HpyAV, BstNI, PspGI, StyI, BcgI, PvuI, BstUI, EagI, RsrII, BsiEI, BsiWI, BsmBI, Hpy99I, MspAII, MspJI, SgrAI, BfaI, BspCNI, XhoI, PaeR7I, TliI, EarI, AclI, PstI, BpmI, DdeI, SfcI, AflII, BpuEI, SmlI, AvaI, BsoBI, MboII, BbsI, XmnI, BsmI, Nb.BsmI, EcoRI, HgaI, AatII, ZraI, Tth111I, PflFI, PshAI, AhdI, DrdI, Eco53kI, SacI, BseRI, PleI, Nt.BstNBI, MlyI, HinfI, EcoRV, MboI, Sau3AI, DpnII, BfuCI, DpnI, BsaBI, TfiI, BsrDI, Nb.BsrDI, BbvI, BtsI, BtsαI, Nb.BtsI, BstAPI, SfaNI, SphI, SrfI, NmeAIII, NaeI, NgoMIV, BglI, AsiSI, BtgZI, HinPII, HhaI, BssHII, NotI, Fnu4HI, Cac8I, MwoI, NheI, BmtI, SapI, BspQI, Nt.BspQI, BlnI, TseI, ApeKI, Bsp1286I, AlwI, Nt.AlwI, BamHI, FokI, BtsCI, HaeIII, PhoI, FseI, SfiI, NarI, KasI, SfoI, PluTI, AscI, EciI, BsmFI, ApaI, PspOMI, Sau96I, NlaIV, KpnI, Acc65I, BsaI, HphI, BstEII, AvaII, BanI, BaeGI, BsaHI, BanII, RsaI, CviQI, BstZ17I, BciVI, SalI, Nt.BsmAI, BsmAI, BcoDI, ApaLI, BsgI, AccI, Hpy166II, Tsp45I, HpaI, PmeI, HincII, BsiHKAII, ApoI, NspI, BsrFI, BsrFαI, BstYI, HaeII, CviKI-1, EcoO109I, PpuMI, I-CeuI, SnaBI, I-SceI, BspHI, BspEI, MmeI, TaqαI, NruI, Hpy188I, Hpy188III, XbaI, BclI, HpyCH4V, FspI, PI-PspI, MscI, BsrGI, MseI, PacI, PsiI, BstBI, DraI, PspXI, BsaWI, BsaAI, and EaeI. In some embodiments of the BAR 4.0 method, the first restriction enzyme is SwaI. In other embodiments of the BAR 4.0 method, the first restriction enzyme is NheI.

Heterologous Nucleic Acids

[0091] In some embodiments of the methods disclosed herein, the heterologous nucleic acid comprises an open reading frame that encodes a bioluminescent protein, a fluorescent protein, a chemiluminescent protein, or any combination thereof. In some embodiments, the encoded gene product(s) produces a detectable signal upon exposure to the appropriate

stimuli, and the resulting signal permits detection of bacterial host cells infected by the recombinant phage. In certain embodiments, the open reading frame encodes a protein that serves as a marker that can be identified by screening bacterial host cells infected by a recombinant phage comprising a heterologous nucleic acid sequence comprising the open reading frame. Examples of such markers include by way of example and without limitation: a fluorescent label, a luminescent label, a chemiluminescence label, or an enzymatic label. In some embodiments, the heterologous nucleic acid sequence further comprises sequences naturally found in the bacteriophage, but placed at a non-normally occurring location in the genome.

[0092] In some embodiments, the length of the heterologous nucleic acid sequence is at least 100 bases, at least 200 based, at least 300 bases, at least 400 bases, at least 500 bases, at least 600 bases, at least 700 bases, at least 800 bases, at least 900 bases, at least 1 kilobase (kb), at least 1.1 kb, at least 1.2 kb, at least 1.3 kb, at least 1.4 kb, at least 1.5 kb, at least 1.6 kb, at least 1.7 kb, at least 1.8 kb, at least 1.9 kb, at least 2.0 kb, at least 2.1 kb, at least 2.2 kb, at least 2.3 kb, at least 2.4 kb, at least 2.5 kb, at least 2.6 kb, at least 2.7 kb, at least 2.8 kb, at least 2.9 kb, at least 3.0 kb, at least 3.1 kb, at least 3.2 kb, at least 3.3 kb, at least 3.4 kb, at least 3.5 kb, at least 3.6 kb, at least 3.7 kb, at least 3.8 kb, at least 3.9 kb, at least 4.0 kb, at least 4.5 kb, at least 5.0 kb, at least 5.5 kb, at least 6.0 kb, at least 6.5 kb, at least 7.0 kb, at least 7.5 kb, at least 8.0 kb, at least 8.5 kb, at least 9.0 kb, at least 9.5 kb, at least 10 kb, or more. In certain embodiments, the heterologous nucleic acid sequence comprises a length that is less than or equal to a length selected from the group consisting of 1 kb, 2 kb, 3 kb, 4 kb, 5 kb, 6 kb, 7 kb, 8 kb, 9 kb, and 10 kb. In some embodiments, the heterologous nucleic acid sequence comprises a length that is less than or equal to the maximum length of heterologous nucleic acid sequence that can be packaged into a phage particle comprising the phage genome.

[0093] In some embodiments, the length of the heterologous nucleic acid sequence is from 100 to 500 bases, from 200 to 1,000 bases, from 500 to 1,000 bases, from 500 to 1,500 bases, from 1 kb to 2 kb, from 1.5 kb to 2.5 kb, from 2.0 kb to 3.0 kb, from 2.5 kb to 3.5 kb, from 3.0 kb to 4.0 kb, from 3.5 kb to 4.5 kb, from 4.0 kb to 5.0 kb, from 4.5 kb to 5.5 kb, from 5.0 kb to 6.0 kb, from 5.5 kb to 6.5 kb, from 6.0 kb to 7.0 kb, from 6.5 kb to 7.5 kb, from 7.0 kb to 8.0 kb, from 7.5 kb to 8.5 kb, from 8.0 kb to 9.0 kb, from 8.5 kb to 9.5 kb, or from 9.0 kb to 10.0 kb.

[0094] In some embodiments, the heterologous nucleic acid sequence is inserted into the phage genome with no loss of endogenous phage genomic sequence. In some embodiments, the heterologous nucleic acid sequence replaces an endogenous phage genomic sequence. In some embodiments, the heterologous nucleic acid sequence includes an endogenous phage genomic sequence that was previously excised from the phage genome.

[0095] In certain embodiments, the heterologous nucleic acid sequence replaces an endogenous phage genomic sequence that is less than the length of the heterologous nucleic acid sequence. Accordingly, in some embodiments, the length of the recombinant phage genome is longer than the length of the wild-type phage genome. In some embodiments, the heterologous nucleic acid sequence replaces an endogenous phage genomic sequence that is greater than the length of the heterologous nucleic acid sequence. Thus, in some embodiments, the length of the recombinant phage genome is shorter than the length of the wild-type phage genome. In certain embodiments, the heterologous nucleic acid sequence replaces an endogenous phage genomic sequence that is equal to the length of the heterologous nucleic acid sequence.

[0096] In certain embodiments, the open reading frame of the heterologous nucleic acid encodes a protein that confers a phenotype of interest on a host cell infected by a recombinant phage expressing the heterologous nucleic acid. In some embodiments, the phenotype of interest is the expression of the gene product encoded by the open reading frame of the heterologous nucleic acid.

[0097] In certain embodiments, the open reading frame of the heterologous nucleic acid is operably linked to an expression control sequence that is capable of directing expression of the open reading frame, wherein the open reading frame encodes a bioluminescent protein, a fluorescent protein, a chemiluminescent protein, or any combination thereof. In some embodiments, the expression control sequence is located within the heterologous nucleic acid sequence. In other embodiments, the expression control sequence is located in the endogenous phage genome sequence. For example, the open reading frame may be inserted into the phage genome downstream of or in the place of an endogenous phage open reading frame sequence. In some embodiments, the expression control sequence is an inducible promoter or a constitutive promoter. *See e.g., Djordjevic & Klaenhammer, Methods in Cell Science* 20(1):119-126 (1998). The inducible promoter or constitutive promoter may be an endogenous phage promoter sequence, a non-endogenous phage promoter sequence, or a

bacterial host promoter sequence. Additionally or alternatively, in some embodiments, the inducible promoter is a pH-sensitive promoter, or a temperature sensitive promoter.

[0098] In some embodiments, the heterologous nucleic acid sequence comprises a first open reading frame and at least one supplemental open reading frame. In certain embodiments, the first and the at least one supplemental open reading frames are operably linked to the same expression control sequences. In some embodiments, the first and the at least one supplemental open reading frames are operably linked to different expression control sequences.

[0099] Fluorescent proteins include but are not limited to blue/UV fluorescent proteins (for example, TagBFP, Azurite, EBFP2, mKalamal, Sirius, Sapphire, and T-Sapphire), cyan fluorescent proteins (for example, ECFP, Cerulean, SCFP3A, mTurquoise, monomeric Midoriishi-Cyan, TagCFP, and mTFP1), green fluorescent proteins (for example, EGFP, Emerald, Superfolder GFP, Monomeric Azami Green, TagGFP2, mUKG, and mWasabi), yellow fluorescent proteins (for example, EYFP, Citrine, Venus, SYFP2, and TagYFP), orange fluorescent proteins (for example, Monomeric Kusabira-Orange, mKOκ, mKO2, mOrange, and mOrange2), red fluorescent proteins (for example, mRaspberry, mCherry, dsRed, mStrawberry, mTangerine, tdTomato, TagRFP, TagRFP-T, mApple, and mRuby), far-red fluorescent proteins (for example, mPlum, HcRed-Tandem, mKate2, mNeptune, and NirFP), near-IR fluorescent proteins (for example, TagRFP657, IFP1.4, and iRFP), long stokes-shift proteins (for example, mKeima Red, LSS-mKate1, and LSS-mKate2), photoactivatable fluorescent proteins (for example, PA-GFP, PAmCherry1, and PAmTagRFP), photoconvertible fluorescent proteins (for example, Kaede (green), Kaede (red), KikGR1 (green), KikGR1 (red), PS-CFP2, PS-CFP2, mEos2 (green), mEos2 (red), PSmOrange, and PSmOrange), fluorescein, rhodamine, and photoswitchable fluorescent proteins (for example, Dronpa).

[00100] Examples of bioluminescent proteins are aequorin (derived from the jellyfish *Aequorea victoria*) and luciferases (including luciferases derived from firefly and *Renilla*, nanoluciferase, red luciferase, luxAB, and the like). These proteins have also been genetically separated into two distinct functional domains that will generate light only when the protein domains are closely co-localized. A variety of emission spectrum-shifted mutant derivatives of both of these proteins have been generated over the past decade and have been used for multi-color imaging and co-localization within a living cell.

[00101] Examples of chemiluminescent protein include β -galactosidase, horseradish peroxidase (HRP), and alkaline phosphatase. Peroxidases generate peroxide that oxidizes luminol in a reaction that generates light, whereas alkaline phosphatases remove a phosphate from a substrate molecule, destabilizing it and initiating a cascade that results in the emission of light.

[00102] In some embodiments, the open reading frame of the heterologous nucleic acid comprises an epitope that can be detected with an antibody or other binding molecule. For example, an antibody that recognizes the epitope may be directly linked to a signal generating moiety (such as by covalent attachment of a chemiluminescent or fluorescent protein), or can be detected using at least one additional binding reagent such as a secondary antibody, directly linked to a signal generating moiety. In some embodiments, the epitope is absent in wild-type bacteriophage and the bacterial host cell. Accordingly, detection of the epitope in a sample demonstrates the presence of a bacterial host cell infected by a recombinant phage comprising a heterologous nucleic acid, wherein the open reading frame of the heterologous nucleic acid comprises the epitope.

[00103] In other embodiments, the open reading frame of the heterologous nucleic acid comprises a polypeptide tag sequence, such that the expression product of the open reading frame comprises the tag fused to a polypeptide or protein encoded by the open reading frame (*e.g.*, poly-histidine, FLAG, Glutathione S-transferase (GST) *etc.*).

Kits

[00104] The present technology provides kits for integrating a heterologous nucleic acid sequence into a bacteriophage genome. Also provided herein are recombinant bacteriophages comprising a genome having a nucleic acid sequence comprising any one of SEQ ID NOs: 1-4 or 6.

[00105] In one aspect, the kits of the present technology comprise (a) one or more coded/labeled vials that contain a plurality of bacteriophage genomes, (b) a recombination system, and (c) at least one CRISPR enzyme, or restriction enzyme.

[00106] In some embodiments, each coded/labeled vial containing a plurality of bacteriophage genomes corresponds to a different bacteriophage type. In other embodiments, each coded/labeled vial containing a plurality of bacteriophage genomes corresponds to the same bacteriophage type. In some embodiments, each phage vial is assigned a unique code that identifies the bacteriophage in the phage vial, or the types of bacteria that the

bacteriophage strain infects. The unique code can be encoded by a machine discernible pattern, such as a bar code, a QR code, an alphanumeric string, or any other pattern that can be discerned by a reader. Each unique code may be shown as, for example, a bar code sticker on a vial or container storing a corresponding phage sample. In some embodiments, the kit is stored under conditions that permit the preservation of the bacteriophage genomes for extended periods, such as under bacteriophage-specific, controlled temperature, moisture, and pH conditions.

[00107] In some embodiments, the kits comprise a recombination system that includes a 5'-3' exonuclease, a DNA polymerase, and a DNA ligase. For example, in one embodiment, the 5'-3' exonuclease is T5 exonuclease, the DNA polymerase is Phusion® DNA polymerase, and the DNA ligase is Taq ligase. In other embodiments of the kits, the recombination system comprises lambda Red proteins Gam, Exo, and Beta operably linked to an inducible promoter (*e.g.*, *araB* promoter). In certain embodiments of the kits, the recombination system comprises RecET (RecE, RecT) operons. In other embodiments, the recombination system comprises RecA recombinase or variants thereof.

[00108] Additionally or alternatively, in some embodiments, the kits comprise one or more CRISPR enzymes selected from the group consisting of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, and Csf4. The one or more CRISPR enzymes may be coupled to a sgRNA. In certain embodiments, the sgRNA targets the protospacer sequence 5' GCTTACGCAGAAGATGCAGA 3' (SEQ ID NO: 5).

[00109] Additionally or alternatively, in some embodiments, the kits comprise one or more restriction enzymes selected from the group consisting of AclI, HindIII, SspI, MluCI, Tsp509I, PciI, AgeI, BspMI, BfuAI, SexAI, MluI, BceAI, HpyCH4IV, HpyCH4III, BaeI, BsaXI, AflIII, SpeI, BsrI, BmrI, BglII, AfeI, AluI, StuI, ScaI, ClaI, BspDI, PI-SceI, NsiI, AseI, SwaI, CspCI, MfeI, BssSI, BssSαI, Nb.BssSI, BmgBI, PmlI, DraIII, AleI, EcoP15I, PvuII, AlwNI, BtsIMutI, TspRI, NdeI, NlaIII, CviAII, FatI, MslI, FspEI, XcmI, BstXI, PflMI, BccI, NcoI, BseYI, FauI, SmaI, XmaI, TspMI, Nt.CviPII, LpnPI, AciI, SacII, BsrBI, MspI, HpaII, ScrFI, BssKI, StyD4I, BsaJI, BslI, BtgI, NciI, AvrII, MnlI, BbvCI, Nb.BbvCI, Nt.BbvCI, SbfI, Bpu10I, Bsu36I, EcoNI, HpyAV, BstNI, PspGI, StyI, BcgI, PvuI, BstUI, EagI, RsrII, BsiEI, BsiWI, BsmBI, Hpy99I, MspAII, MspJI, SgrAI, BfaI, BspCNI, XhoI,

PaeR7I, TliI, EarI, AcuI, PstI, BpmI, DdeI, SfcI, AflII, BpuEI, SmlI, AvaI, BsoBI, MboII, BbsI, XmnI, BsmI, Nb.BsmI, EcoRI, HgaI, AatII, ZraI, Tth111I, PflFI, PshAI, AhdI, DrdI, Eco53kI, SacI, BseRI, PleI, Nt.BstNBI, MlyI, HinfI, EcoRV, MboI, Sau3AI, DpnII, BfuCI, DpnI, BsaBI, TfiI, BsrDI, Nb.BsrDI, BbvI, BtsI, BtsOI, Nb.BtsI, BstAPI, SfaNI, SphI, SrfI, NmeAIII, NaeI, NgoMIV, BglI, AsiSI, BtgZI, HinPII, HhaI, BssHII, NotI, Fnu4HI, Cac8I, MwoI, NheI, BmtI, SapI, BspQI, Nt.BspQI, BlpI, TseI, ApeKI, Bsp1286I, AlwI, Nt.AlwI, BamHI, FokI, BtsCI, HaeIII, PhoI, FseI, SfiI, NarI, KasI, SfoI, PluTI, AscI, EciI, BsmFI, ApaI, PspOMI, Sau96I, NlaIV, KpnI, Acc65I, BsaI, HphI, BstEII, AvaII, BanI, BaeGI, BsaHI, BanII, RsaI, CviQI, BstZ17I, BciVI, SalI, Nt.BsmAI, BsmAI, BcoDI, ApaLI, BsgI, AccI, Hpy166II, Tsp45I, HpaI, PmeI, HincII, BsiHKAII, ApoI, NspI, BsrFI, BsrFαI, BstYI, HaeII, CviKI-1, EcoO109I, PpuMI, I-CeuI, SnaBI, I-SceI, BspHI, BspEI, MmeI, TaqαI, NruI, Hpy188I, Hpy188III, XbaI, BclI, HpyCH4V, FspI, PI-PspI, MscI, BsrGI, MseI, PacI, PsiI, BstBI, DraI, PspXI, BsaWI, BsaAI, and EaeI.

[00110] Additionally or alternatively, in some embodiments, the kits further comprise vials containing natural or non-natural bacterial host cells. In some embodiments, the bacterial host cells are *E. coli*. In certain embodiments, the bacterial host cells are *E. coli* strain DH10B.

[00111] In some embodiments, the kits further comprise positive control heterologous nucleic acid sequences to correct for any variability in the recombination systems between experimental runs. The kits may also comprise instructions for use, software for automated analysis, containers, packages such as packaging intended for commercial sale and the like.

[00112] The kit may further comprise one or more of: wash buffers and/or reagents, hybridization buffers and/or reagents, labeling buffers and/or reagents, and detection means. The buffers and/or reagents are usually optimized for the particular detection technique for which the kit is intended. Protocols for using these buffers and reagents for performing different steps of the procedure may also be included in the kit. Further optional components of the kits may include expression media for gene products encoded by the heterologous nucleic acids disclosed herein, such as a medium containing nutrients and cofactors for bioluminescence, devices such as a lamp configured to illuminate at specific wavelengths of light to detect biofluorescence, and devices for measuring the extent of heterologous nucleic acid expression, such as a photometer or photodetector.

[00113] Additionally or alternatively, the kits disclosed herein may also include coded and labeled vials that contain a plurality of antibiotics.

EXAMPLES

Example 1: BAR 4.0 Phage Engineering Methods of the Present Technology in T7 Phage

[00114] This Example demonstrates that the BAR 4.0 methods of the present technology are useful for integrating a heterologous nucleic acid into a bacteriophage genome (*e.g.*, T7 phage genome) and for isolating recombinant bacteriophages that express the heterologous nucleic acid sequence.

[00115] Transformation of large DNA inserts into bacteria has traditionally been prohibitive in many bacterial strains and species. Piers D. *et al.*, *Microbiol Mol Biol Rev.* 80(3):523-43 (2016). Previous attempts to generate recombinant NanoLuc[®] T3 bacteriophage and recombinant NanoLuc[®] T7 bacteriophage in RecA⁺ or RecA⁻ K12 *E. coli* strains via conventional methods such as BRED were unsuccessful. Indeed, no recombinant phages were obtained using BRED.

[00116] BAR 4.0 is an *in vitro* recombination method and permits the transformation of large DNA inserts into bacterial cells. Figure 1 outlines the BAR 4.0 method of the present technology that was used to generate the recombinant T7 phage strains DLPECO1 and DLPECO2, which contain a single and a double insertion of the NanoLuc[®] reporter gene, respectively. The complete genome sequences of the DLPECO1 and DLPECO2 phage strains are shown in Figure 10 and Figure 11, respectively. Figure 17 shows the heterologous nucleic acid sequence that was inserted near the NheI site in T7 phage using the BAR 4.0 method disclosed herein (SEQ ID NO: 6). Figure 18 shows the heterologous nucleic acid sequence that was inserted near the SmaI site in T7 phage using the BAR 4.0 method disclosed herein (SEQ ID NO: 7).

[00117] T7 bacteriophage DNA was extracted from a clarified phage lysate using the Zymo ZR Viral DNA Kit (Cat no. D3015) (Zymo Research, Irvine, CA). About 100 ng of T7 phage DNA was digested with the restriction enzyme SmaI (NEB R0604) (New England Biolabs, Ipswich, MA) according to the manufacturer's specifications. A gBlock (synthesized by Integrated DNA Technologies, Coralville, IA) containing the NanoLuc[®] gene surrounded by 60 bp of homology to the viral genome was inserted into the SmaI cut site by Gibson Assembly[®] (New England Biolabs, Ipswich, MA).

[00118] 2 µl of the resulting T7/NanoLuc[®] fusion product was electroporated into NEB10β cells (NEB C3030K) (New England Biolabs, Ipswich, MA). Cells were plated on LB agar with a 0.65% soft agar overlay. After incubation at 37 °C overnight, isolated plaques were selected and screened for NanoLuc[®] insertion *via* PCR using primers that flanked the NanoLuc[®] insertion site (Figure 2). A 700 bp increase in amplicon size correlated with the successful insertion of the NanoLuc[®] reporter gene within the T7 genome at the *Swa*I restriction site. See Figure 2. NanoLuc[®] production was evaluated by infecting bacterial host cells with recombinant phage strain DLPECO1 and measuring luminescence between 10-60 minutes at different bacterial host cell concentrations. Figure 3 demonstrates that the intensity of the NanoLuc[®] signal produced by a recombinant T7 phage strain containing a single NanoLuc[®] insertion was dependent on bacterial cell concentration and time.

[00119] After a recombinant T7 phage with a single NanoLuc[®] insertion at the *Swa*I site (see Figure 4) was isolated, a second NanoLuc[®] insertion was made at the *Nhe*I restriction site (NEB R0131) (New England Biolabs, Ipswich, MA) using the cloning protocol outlined above. After incubation at 37 °C overnight, isolated plaques were selected and screened for the second NanoLuc[®] insertion *via* PCR using primers that flanked the second NanoLuc[®] insertion site (*i.e.*, spanned the junction between NanoLuc[®] and phage genomic DNA). A PCR product of approximately 1 kb correlated with the successful insertion of the NanoLuc[®] reporter gene within the T7 genome at the *Nhe*I restriction site. See Figure 5 and Figure 7. Thus, the overall yield of recombinant T7 phage genomes obtained using the BAR 4.0 technique was about 44% to about 69%.

[00120] NanoLuc[®] production was evaluated by infecting bacterial host cells with recombinant phage strain DLPECO2 and measuring luminescence between 10-60 minutes at different bacterial host cell concentrations. Figure 6 demonstrates that the intensity of the NanoLuc[®] signal produced by a recombinant T7 phage strain containing a double NanoLuc[®] insertion was dependent on bacterial cell concentration and time. Figure 8 demonstrates that the recombinant T7 phage strain containing a double NanoLuc[®] insertion exhibited significantly higher luminescence, along with significantly increased sensitivity relative to that observed with the recombinant T7 phage strain containing a single NanoLuc[®] insertion.

[00121] To ensure that NanoLuc[®] production was specific to a bacterial host cell that could be infected by T7 phage, DH10B cells (which are the normal T7 host) were infected in parallel with the uropathogenic *E. coli* strain UPEC, which cannot be infected by T7. Figure

9 shows that luminescence was detected in the infected DH10B cells, whereas no luminescence was detected in UPEC.

Table 1

Strain Name	Phage Type	Phage Family	Heterologous reporter	Host Range	Modifications to Phage Genomes
DLPECO1	T7	<i>Podoviridae</i>	Nanoluciferase	K12 <i>E. coli</i>	SwaI insertion contains lacZ alpha fragment with ribosomal binding site
DLPECO2	T7	<i>Podoviridae</i>	Nanoluciferase	K12 <i>E. coli</i>	NheI insertion into DLPECO1

[00122] These results demonstrate that the methods of the present technology generate recombinant bacteriophage genomes that (a) contain a heterologous nucleic acid sequence of interest, and (b) express the phenotypic properties associated with the heterologous nucleic acid sequence of interest. Accordingly, the methods disclosed herein are useful for generating recombinant bacteriophage genomes.

Example 2: BAR 3.0 Phage Engineering Methods of the Present Technology in K1-5 Phage

[00123] This Example demonstrates that the BAR 3.0 methods of the present technology are useful for integrating a heterologous nucleic acid into a bacteriophage genome (e.g., K1-5 phage genome) and for isolating recombinant bacteriophages that express the heterologous nucleic acid sequence.

[00124] K1-5 phage is a 44,385 bp, terminally redundant, lytic bacteriophage that infects numerous strain of *E. coli* with either the K1 or K5 capsule type. The NanoLuc[®] luciferase gene (with an upstream ribosome binding site (RBS)) was inserted towards the 3' end of the K1-5 genome using the BAR 3.0 methods disclosed herein. The intended genomic insertion site for the NanoLuc[®] reporter was between nucleotide positions 43,913 and 43,914. A sgRNA-Cas9 conjugate that targets the protospacer sequence 5' GCTTACGCAGAAGATGCAGA 3' (SEQ ID NO: 5) was designed so as to induce cleavage between nucleotide positions 43,898 and 43,899 of the K1-5 genome. The RBS/NanoLuc[®] cassette also contained the nucleic acid sequence present at the 3' end of K1-5 genome that

would be excised by the sgRNA-Cas9 conjugate. Thus, the heterologous nucleic acid insert comprised: 5' (nucleotide positions 43,872 to 43,913 of K1-5 genome) + (RBS) + (NanoLuc[®]) + (nucleotide positions 43,914 to 44,385 of K1-5 genome) 3'. Figure 15 shows the heterologous nucleic acid sequence that was inserted into K1-5 phage using the BAR 3.0 method disclosed herein (SEQ ID NO: 3). Figure 16 shows the complete genome sequence of the recombinant NanoLuc[®] K1-5 phage. (SEQ ID NO: 4).

[00125] To generate the sgRNA, a target specific DNA oligonucleotide was synthesized and used as a template for the EnGen[®] sgRNA Synthesis Kit, *S. pyogenes* (New England Biolabs, Ipswich, MA). The target specific DNA oligonucleotide contains the T7 promoter sequence, the target protospacer sequence, and a 14 nucleotide overlap sequence complementary to the *S. pyogenes* Cas9 Scaffold Oligo supplied in the EnGen[®] sgRNA reaction mix. The target specific DNA oligonucleotide was mixed with the EnGen 2X sgRNA Reaction Mix (NTPs, dNTPs, *S. pyogenes* Cas9 Scaffold Oligo) and the EnGen sgRNA Enzyme Mix (DNA and RNA polymerases) at room temperature. The DNA synthesis and transcription reactions occurred at 37 °C during a 30 minute incubation period. The resulting sgRNA contained the target-specific/crRNA sequence as well as the tracrRNA. DNA contaminants were subsequently removed with DNase I treatment and the sgRNA was purified with an RNA cleanup kit.

[00126] *S. pyogenes* Cas9 nuclease (New England Biolabs, Ipswich, MA) was co-incubated with the purified sgRNA according to the supplier's protocol, and was subsequently used to cleave approximately 2.4 µg of purified K1-5 genomic DNA. Cleaved K1-5 genomic DNA was purified using phenol: chloroform: isoamyl alcohol extraction, followed by ethanol precipitation.

[00127] Approximately 2 µg of cleaved K1-5 genomic DNA and 200 ng of the insert DNA were combined in a Gibson assembly reaction using NEBuilder[®] HiFi DNA Assembly Cloning Kit (New England Biolabs, Ipswich, MA). The reaction occurred at 50 °C for 1 hour, and was subsequently purified using phenol: chloroform: isoamyl alcohol extraction, followed by ethanol precipitation.

[00128] Approximately 440 ng of total DNA from this purified reaction was transformed into NEB[®] 10-beta Electrocompetent *E. coli* (New England Biolabs, Ipswich, MA), a non-natural bacterial host, *via* electroporation (2.4kV, 600Ω, 25 µF) and was recovered in 950 µl of SOC medium (2% tryptone, 0.5% yeast extract, 10 mM NaCl, 2.5 mM KCl, 10 mM

MgCl₂, 10 mM MgSO₄, and 20 mM glucose) for approximately 2 hours at 37 °C. The transformation reaction was centrifuged such that the supernatant (containing phage particles) could be used to infect a native host. About 100 µl of the supernatant was used to infect 100 µl of K5 *E. coli*. The infection was plated in 3 mL of 0.65% LB top agar and incubated at 37 °C overnight to allow plaque development.

[00129] *Phenotypic Analysis.* Hundreds of plaques were observed after overnight incubation. A total of 36 plaques were picked into 20 µL 10mM Tris-HCl + 10mM MgSO₄. These isolates were used to infect 100 µL of log-phase K5 *E. coli* for approximately 1 hour in the presence of MgSO₄. Figure 12 shows that the RLU generated by isolate #30 was several times higher than any other isolate. Isolate #30 was further analyzed by infecting larger K5 *E. coli* cultures with isolate #30 for a longer duration to determine if the high RLU value was actually indicative of a recombinant phage or merely a technical error. The remainder of the isolate #30 infection was used to re-infect 5 mL cultures of log-phase K5 *E. coli*. Figure 13 shows that only the sample containing both bacterial cells and phage (derived from isolate #30) produced higher RLUs relative to samples that only contained phage or bacterial cells after 1.25 hours. The overall yield of recombinant K1-5 phage genomes obtained using the BAR 3.0 technique was about 2.78%. Thus, Figure 13 demonstrates that the BAR 3.0 methods disclosed herein yielded recombinant NanoLuc[®] K1-5 phage genomes.

[00130] *Genotypic Analysis.* The isolate #30 plaque was used as a template for PCR to screen for the presence of a recombinant junction spanning from inside the NanoLuc[®] reporter insert to the phage genome. Figure 14 shows that a recombinant junction was detected in the recombinant K1-5 phage derived from isolate #30, but not in wild-type K1-5 phage. A PCR product of approximately 916 bp correlated with the successful insertion of the NanoLuc[®] reporter gene. Thus, Figure 14 demonstrates that the BAR 3.0 methods disclosed herein yielded recombinant NanoLuc[®] K1-5 phage genomes.

[00131] These results demonstrate that the methods of the present technology generate recombinant bacteriophage genomes that (a) contain a heterologous nucleic acid sequence of interest, and (b) express the phenotypic properties associated with the heterologous nucleic acid sequence of interest. Accordingly, the methods disclosed herein are useful for generating recombinant bacteriophage genomes.

Example 3: BREDner Phage Engineering Methods of the Present Technology

[00132] This Example demonstrates that the BREDner methods of the present technology are useful for generating recombinant bacteriophage genomes.

[00133] The BREDner protocol takes advantage of the increased homologous recombination rate conferred by the λ Red recombinase system of the pKD46 plasmid (GenBank Acc. No.: AY048746.1). The expression of λ Red recombinase genes (gam-bet-exo) are operably linked to the *araB* promoter. Bacterial host cells are transformed with the pKD46 plasmid and a second plasmid that comprises a nanoluciferase sequence (e.g., NanoLuc[®]) that is flanked on both sides by 100-500 bp of homologous phage sequence. The homologous recombination system is induced in the transformed bacterial host cells that contain the pKD46 plasmid and the second plasmid by adding 10 mM arabinose.

[00134] After growing the bacterial host cells containing both pKD46 and the second plasmid to mid-log phase in the presence of arabinose, cells are washed and concentrated 100 $\times$ in 1M sorbitol for use in electroporation. Approximately 100 ng of phage DNA is electroporated into the bacterial host cells containing both pKD46 and the second plasmid. The electroporated cells are then allowed to recover for 1 hour before plating in 0.65% top agar containing the corresponding phage host strain. Plates are incubated overnight and the resulting plaques are screened by PCR, or for NanoLuc[®] production to select for recombinant luminescent phages.

[00135] These results will demonstrate that the methods of the present technology generate recombinant bacteriophage genomes that (a) contain a heterologous nucleic acid sequence of interest, and (b) express the phenotypic properties associated with the heterologous nucleic acid sequence of interest. Accordingly, the methods disclosed herein are useful for generating recombinant bacteriophage genomes.

Example 4: BARner Phage Engineering Methods of the Present Technology

[00136] This Example demonstrates that the BARner methods of the present technology are useful for generating recombinant bacteriophage genomes.

[00137] The BARner protocol is a modification of the BREDner protocol which uses a restriction enzyme to introduce a double strand break in the phage DNA surrounding the desired insertion site for a heterologous nucleic acid sequence of interest.

[00138] The BARner protocol takes advantage of the increased homologous recombination rate conferred by the λ Red recombinase system of the pKD46 plasmid (GenBank Acc. No.: AY048746.1). The expression of the λ Red recombinase genes (gam-bet-exo) is operably linked to the *araB* promoter. Bacterial host cells are transformed with the pKD46 plasmid and a second plasmid that comprises a nanoluciferase sequence (*e.g.*, NanoLuc[®]) that is flanked on both sides by 100-500 bp of homologous phage sequence. The homologous recombination system is induced in the transformed bacterial host cells that contain the pKD46 plasmid and the second plasmid by adding 10 mM arabinose. After growing the bacterial host cells containing both pKD46 and the second plasmid to mid-log phase in the presence of arabinose, the cells are washed and concentrated 100× in 1M sorbitol. Approximately 100 ng of phage DNA is cleaved with the appropriate restriction enzyme and purified using phenol/chloroform before being electroporated into the cells. Electroporated cells are recovered for one hour and plated on 0.65% top agar containing the appropriate host strain. Plates are incubated overnight and the resulting plaques are screened by PCR, or for NanoLuc[®] production to select for recombinant luminescent phages.

[00139] These results will demonstrate that the methods of the present technology generate recombinant bacteriophage genomes that (a) contain a heterologous nucleic acid sequence of interest, and (b) express the phenotypic properties associated with the heterologous nucleic acid sequence of interest. Accordingly, the methods disclosed herein are useful for generating recombinant bacteriophage genomes.

EQUIVALENTS

[00140] The present technology is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[00141] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[00142] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[00143] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

CLAIMS

1. A method for generating a recombinant bacteriophage genome comprising:

(a) contacting a non-recombinant bacteriophage genome with a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions where

the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; and

(b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome.
2. The method of claim 1, wherein the cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment.
3. The method of claim 2, wherein the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.
4. The method of any one of claims 1-3, further comprising propagating the recombinant bacteriophage genome in a bacterial host.
5. The method of claim 4, wherein the bacterial host is a non-natural bacterial host cell.
6. The method of any one of claims 1-5, wherein the CRISPR enzyme is a Cas protein selected from the group consisting of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, and Csf4.
7. The method of any one of claims 1-6, wherein the protospacer sequence is 5' GCTTACGCAGAAGATGCAGA 3' (SEQ ID NO: 5).

8. The method of any one of claims 1-7, wherein the non-recombinant bacteriophage genome corresponds to K1-5 phage.
9. The method of any one of claims 1-8, wherein the nucleic acid sequence of the recombinant bacteriophage genome comprises SEQ ID NO: 3.
10. The method of any one of claims 1-9, wherein the nucleic acid sequence of the recombinant bacteriophage genome comprises SEQ ID NO: 4.
11. A method for generating a recombinant bacteriophage genome comprising:
 - (a) contacting a non-recombinant bacteriophage genome comprising a single first recognition site with a first restriction enzyme *in vitro* under conditions where the first restriction enzyme cleaves the first recognition site to produce a cleaved non-recombinant bacteriophage genome; and
 - (b) recombining *in vitro* the cleaved non-recombinant bacteriophage genome with a heterologous nucleic acid in the presence of a recombination system under conditions to produce a recombinant bacteriophage genome.
12. The method of claim 11, wherein the cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment.
13. The method of claim 12, wherein the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.
14. The method of any one of claims 11-13, wherein the non-recombinant bacteriophage genome corresponds to *E. coli* T7.
15. The method of any one of claims 11-14, further comprising propagating the recombinant bacteriophage genome in a bacterial host cell.
16. The method of claim 15, wherein the bacterial host cell is a natural bacterial host cell.
17. The method of any one of claims 11-16, wherein the first restriction enzyme is *Swa*I.

18. The method of any one of claims 11-16, wherein the first restriction enzyme is NheI.
19. The method of any one of claims 1-18, wherein the heterologous nucleic acid is about 500-1050 base pairs in length.
20. The method of any one of claims 1-19, wherein the recombination system comprises a 5'-3' exonuclease, a DNA polymerase, and a DNA ligase.
21. A method for generating a recombinant bacteriophage genome comprising:
 - (a) contacting a non-recombinant bacteriophage genome with
 - (i) a sgRNA-CRISPR enzyme conjugate *in vitro* under conditions where the sgRNA-CRISPR enzyme conjugate cleaves a protospacer sequence within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome; or
 - (ii) a restriction enzyme *in vitro* under conditions where the restriction enzyme cleaves a unique recognition site within the non-recombinant bacteriophage genome to produce a cleaved non-recombinant bacteriophage genome;
 - (b) transforming the cleaved non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and
 - (c) recombining *in vivo* the cleaved non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome.
22. The method of claim 21, wherein the cleaved non-recombinant bacteriophage genome comprises a first cleaved bacteriophage genomic fragment and a second cleaved bacteriophage genomic fragment.
23. The method of claim 22, wherein the heterologous nucleic acid comprises a 5' flanking region that is homologous to the 3' end of the first cleaved bacteriophage genomic fragment, and a 3' flanking region that is homologous to the 5' end of the second cleaved bacteriophage genomic fragment.

24. The method of any one of claims 21-23, wherein the CRISPR enzyme is a Cas protein selected from the group consisting of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, and Csf4.

25. The method of any one of claims 21-23, wherein the restriction enzyme is AclI, HindIII, SspI, MluCI Tsp509I, PciI, AgeI, BspMI, BfuAI, SexAI, MluI, BceAI, HpyCH4IV, HpyCH4III, BaeI, BsaXI, AflIII, SpeI, BsrI, BmrI, BglII, AfeI, AluI, StuI, ScaI, ClaI, BspDI, PI-SceI, NsiI, AseI, SwaI, CspCI, MfeI, BssSI, BssS α I, Nb.BssSI, BmgBI, PmlI, DraIII, AleI, EcoP15I, PvuII, AlwNI, BtsIMutI, TspRI, NdeI, NlaIII, CviAII, FatI, MslI, FspEI, XcmI, BstXI, PflMI, BccI, NcoI, BseYI, FauI, SmaI, XmaI, TspMI, Nt.CviPII, LpnPI, AciI, SacII, BsrBI, MspI, HpaII, ScrFI, BssKI, StyD4I, BsaJI, BslI, BtgI, NciI, AvrII, MnlI, BbvCI, Nb.BbvCI, Nt.BbvCI, SbfI, Bpu10I, Bsu36I, EcoNI, HpyAV, BstNI, PspGI, StyI, BcgI, PvuI, BstUI, EagI, RsrII, BsiEI, BsiWI, BsmBI, Hpy99I, MspAII, MspJI, SgrAI, BfaI, BspCNI, XhoI, PaeR7I, TliI, EarI, AcuI, PstI, BpmI, DdeI, SfcI, AflII, BpuEI, SmlI, AvaI, BsoBI, MboII, BbsI, XmnI, BsmI, Nb.BsmI, EcoRI, HgaI, AatII, ZraI, Tth111I, PflFI, PshAI, AhdI, DrdI, Eco53kI, SacI, BseRI, PleI, Nt.BstNBI, MlyI, HinfI, EcoRV, MboI, Sau3AI, DpnII, BfuCI, DpnI, BsaBI, TfiI, BsrDI, Nb.BsrDI, BbvI, BtsI, Bts α I, Nb.BtsI, BstAPI, SfaNI, SphI, SrfI, NmeAIII, NaeI, NgoMIV, BglI, AsiSI, BtgZI, HinPII, HhaI, BssHII, NotI, Fnu4HI, Cac8I, MwoI, NheI, BmtI, SapI, BspQI, Nt.BspQI, BlpI, TseI, ApeKI, Bsp1286I, AlwI, Nt.AlwI, BamHI, FokI, BtsCI, HaeIII, PhoI, FseI, SfiI, NarI, KasI, SfoI, PluTI, AscI, EciI, BsmFI, ApaI, PspOMI, Sau96I, NlaIV, KpnI, Acc65I, BsaI, HphI, BstEII, AvaII, BanI, BaeGI, BsaHI, BanII, RsaI, CviQI, BstZ17I, BciVI, SalI, Nt.BsmAI, BsmAI, BcoDI, ApaLI, BsgI, AccI, Hpy166II, Tsp45I, HpaI, PmeI, HincII, BsiHKAII, ApoI, NspI, BsrFI, BsrFaI, BstYI, HaeII, CviKI-1, EcoO109I, PpuMI, I-CeuI, SnaBI, I-SceI, BspHI, BspEI, MmeI, Taq α I, NruI, Hpy188I, Hpy188III, XbaI, BclI, HpyCH4V, FspI, PI-PspI, MscI, BsrGI, MseI, PacI, PsiI, BstBI, DraI, PspXI, BsaWI, BsaAI, and EaeI.

26. A method for generating a recombinant bacteriophage genome comprising:

(a) transforming an intact non-recombinant bacteriophage genome into a bacterial host cell, wherein the bacterial host cell comprises a vector that expresses a heterologous nucleic acid; and

(b) recombining *in vivo* the intact non-recombinant bacteriophage genome with the heterologous nucleic acid in the presence of a non-endogenous recombination system under conditions to produce a recombinant bacteriophage genome.

27. The method of claim 26, wherein the heterologous nucleic acid comprises

(a) a 5' flanking region that is homologous to a first region within the intact non-recombinant bacteriophage genome; and

(b) a 3' flanking region that is homologous to a second region within the intact non-recombinant bacteriophage genome, wherein the first region of the intact non-recombinant bacteriophage genome is located 5' to the second region of the intact non-recombinant bacteriophage genome.

28. The method of any one of claims 21-27, wherein the bacterial host cell is a non-natural bacterial host cell or a natural bacterial host cell.

29. The method of any one of claims 21-28, wherein the non-endogenous recombination system is induced in the bacterial host cell.

30. The method of claim 29, wherein the non-endogenous recombination system is induced by the addition of arabinose.

31. The method of any one of claims 21-30, wherein the non-endogenous recombination system comprises lambda Red proteins Gam, Exo, and Beta operably linked to an inducible promoter.

32. The method of claim 31, wherein the inducible promoter is *araB*.

33. The method of any one of claims 1-8 or 11-32, wherein the heterologous nucleic acid comprises an open reading frame that encodes a bioluminescent protein, a fluorescent protein, a chemiluminescent protein, or any combination thereof.

34. The method of claim 33, wherein the open reading frame of the heterologous nucleic acid is operably linked to an expression control sequence that is capable of directing expression of the bioluminescent protein, the fluorescent protein, the chemiluminescent protein, or any combination thereof.

35. The method of claim 33 or 34, wherein the bioluminescent protein is Aequorin, firefly luciferase, *Renilla* luciferase, red luciferase, luxAB, or nanoluciferase.
36. The method of claim 33 or 34, wherein the chemiluminescent protein is β -galactosidase, horseradish peroxidase (HRP), or alkaline phosphatase.
37. The method of claim 33 or 34, wherein the fluorescent protein is TagBFP, Azurite, EBFP2, mKalama1, Sirius, Sapphire, T-Sapphire, ECFP, Cerulean, SCFP3A, mTurquoise, monomeric Midoriishi-Cyan, TagCFP, mTFP1, EGFP, Emerald, Superfolder GFP, Monomeric Azami Green, TagGFP2, mUKG, mWasabi, EYFP, Citrine, Venus, SYFP2, TagYFP, Monomeric Kusabira-Orange, mKO_κ, mKO₂, mOrange, mOrange2, mRaspberry, mCherry, dsRed, mStrawberry, mTangerine, tdTomato, TagRFP, TagRFP-T, mApple, mRuby, mPlum, HcRed-Tandem, mKate2, mNeptune, NirFP, TagRFP657, IFP1.4, iRFP, mKeima Red, LSS-mKate1, LSS-mKate2, PA-GFP, PAmCherry1, PATagRFP, Kaede (green), Kaede (red), KikGR1 (green), KikGR1 (red), PS-CFP2, PS-CFP2, mEos2 (green), mEos2 (red), PSmOrange, or Dronpa.
38. The method of any one of claims 34-37, wherein the expression control sequence is an inducible promoter or a constitutive promoter.
39. The method of claim 6, wherein the CRISPR enzyme is Cas9.
40. The method of any one of claims 11-26, wherein the nucleic acid sequence of the recombinant bacteriophage genome comprises SEQ ID NO: 2.
41. The method of any one of claims 11-26, wherein the nucleic acid sequence of the recombinant bacteriophage genome comprises SEQ ID NO: 1.
42. The method of any one of claims 11-26, wherein the nucleic acid sequence of the recombinant bacteriophage genome comprises one or more of SEQ ID NO: 6 or SEQ ID NO: 7.

Figure 1

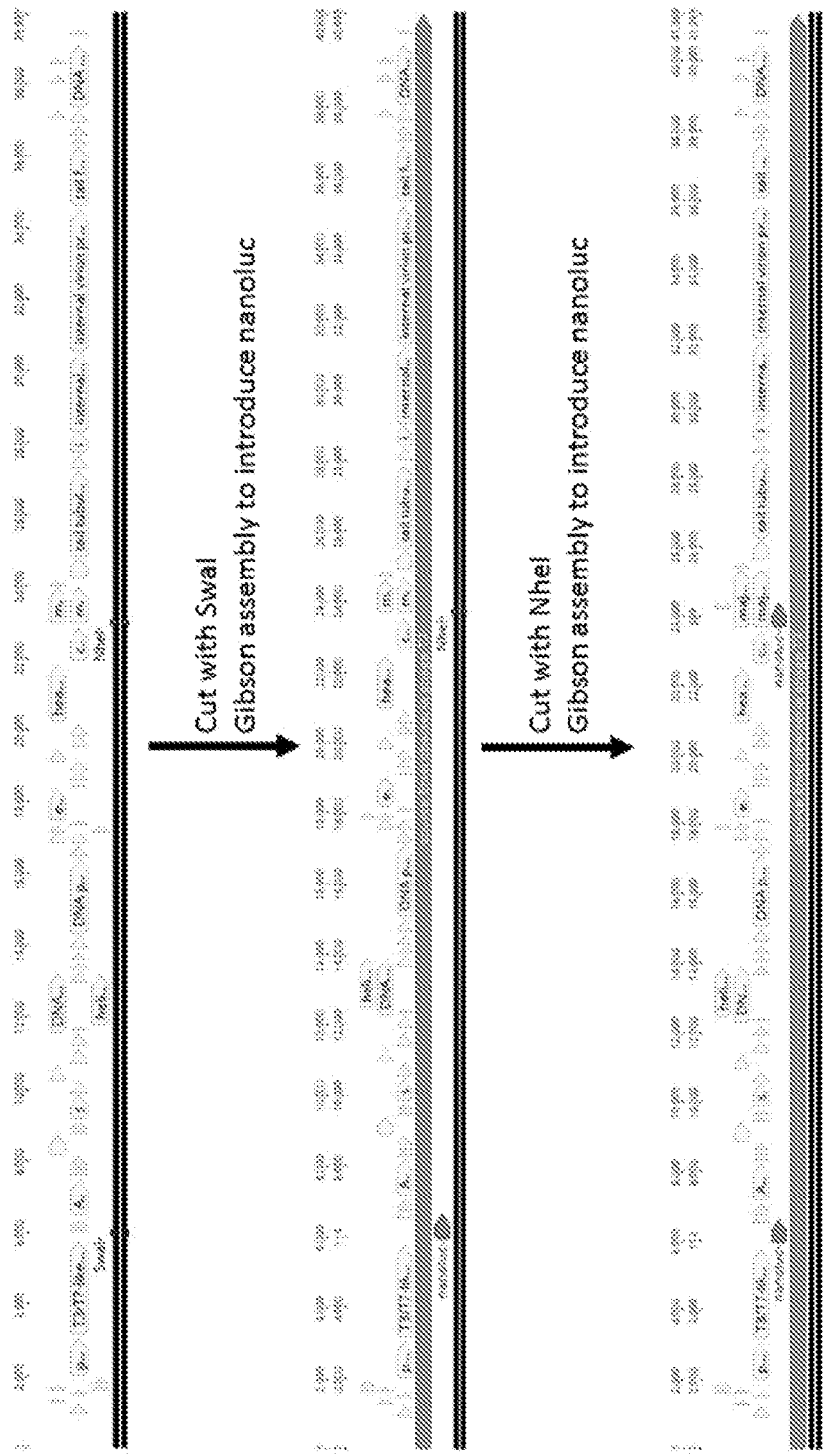


Figure 2

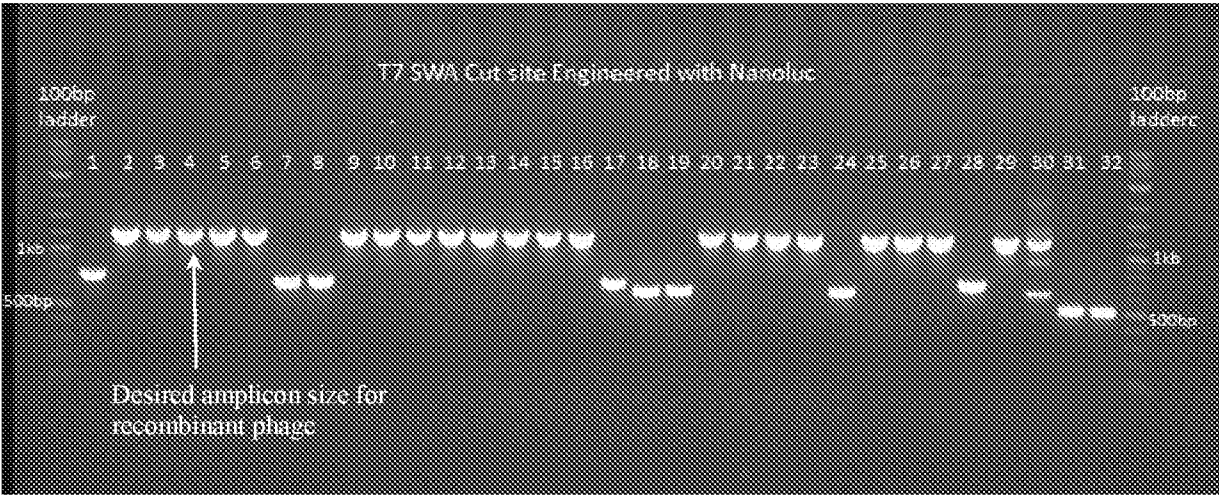


Figure 3

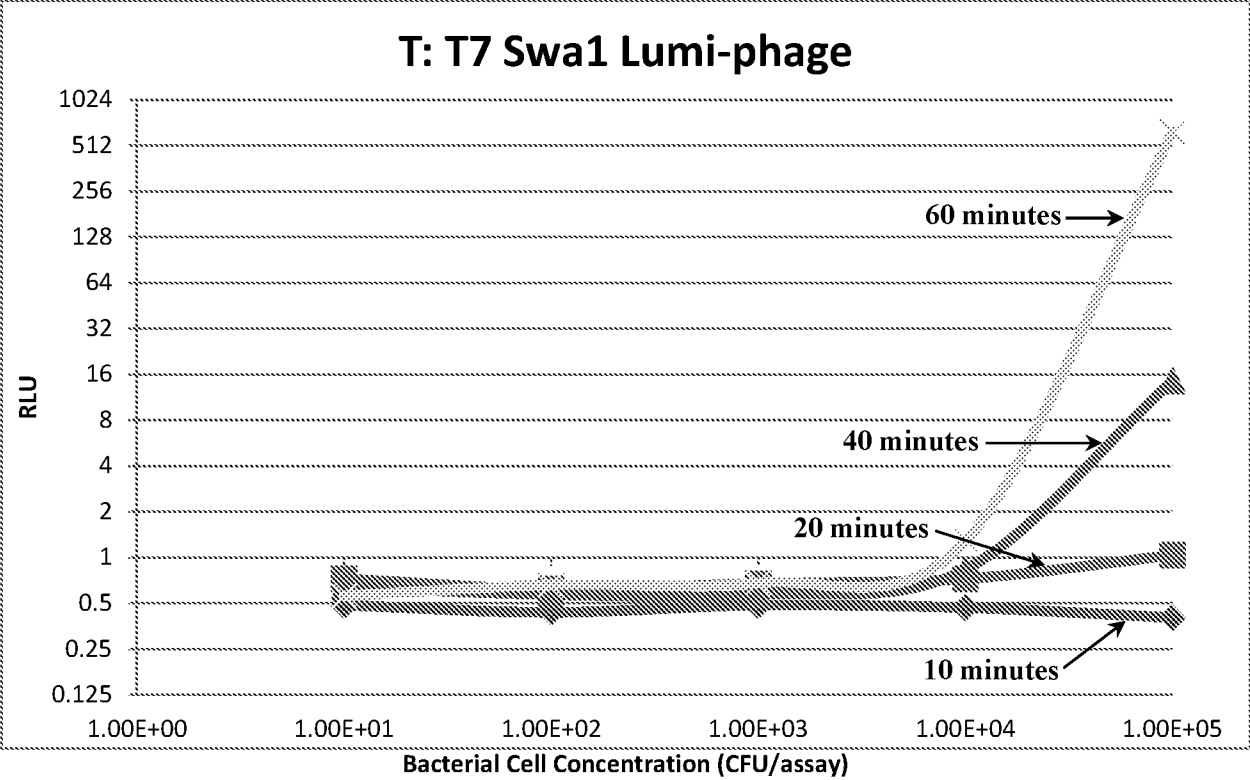


Figure 4

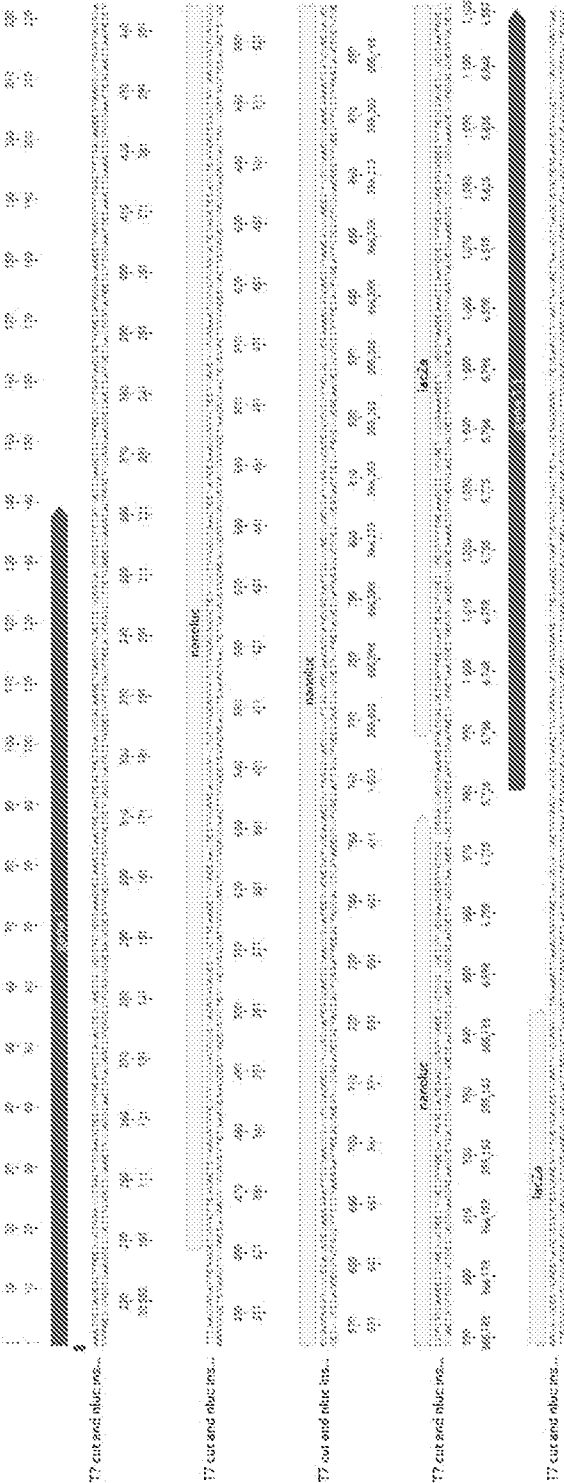


Figure 5

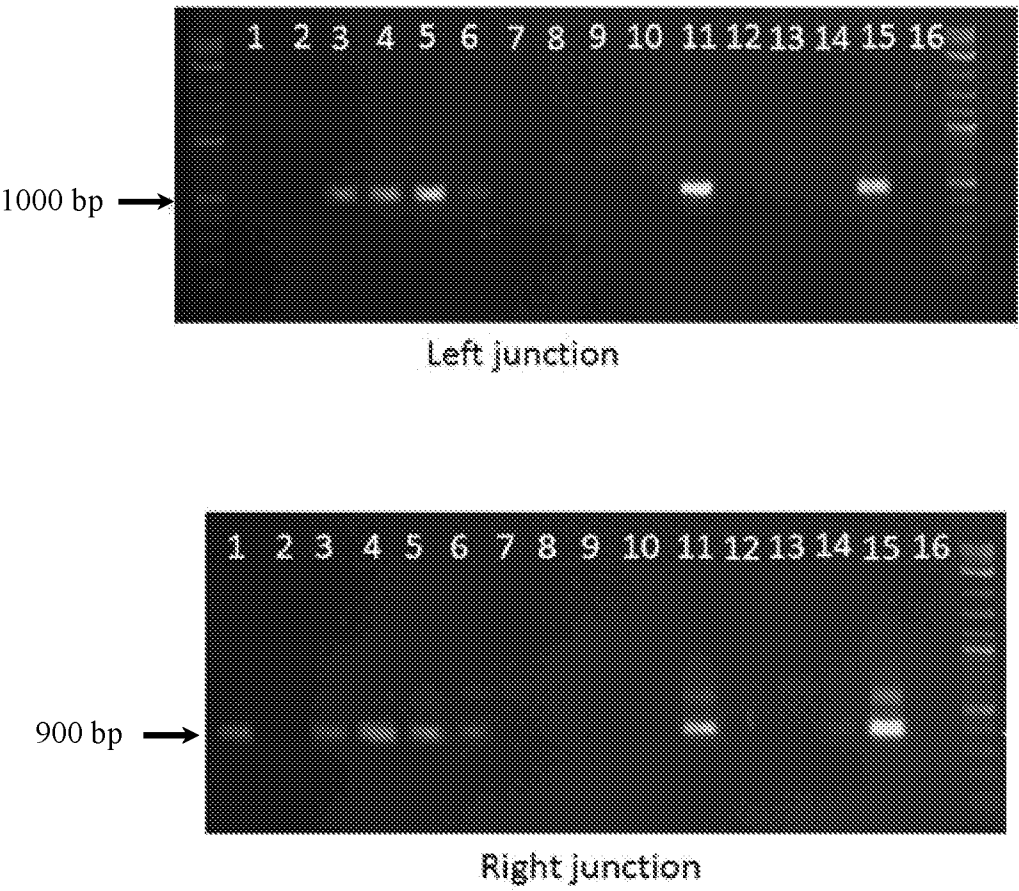


Figure 6

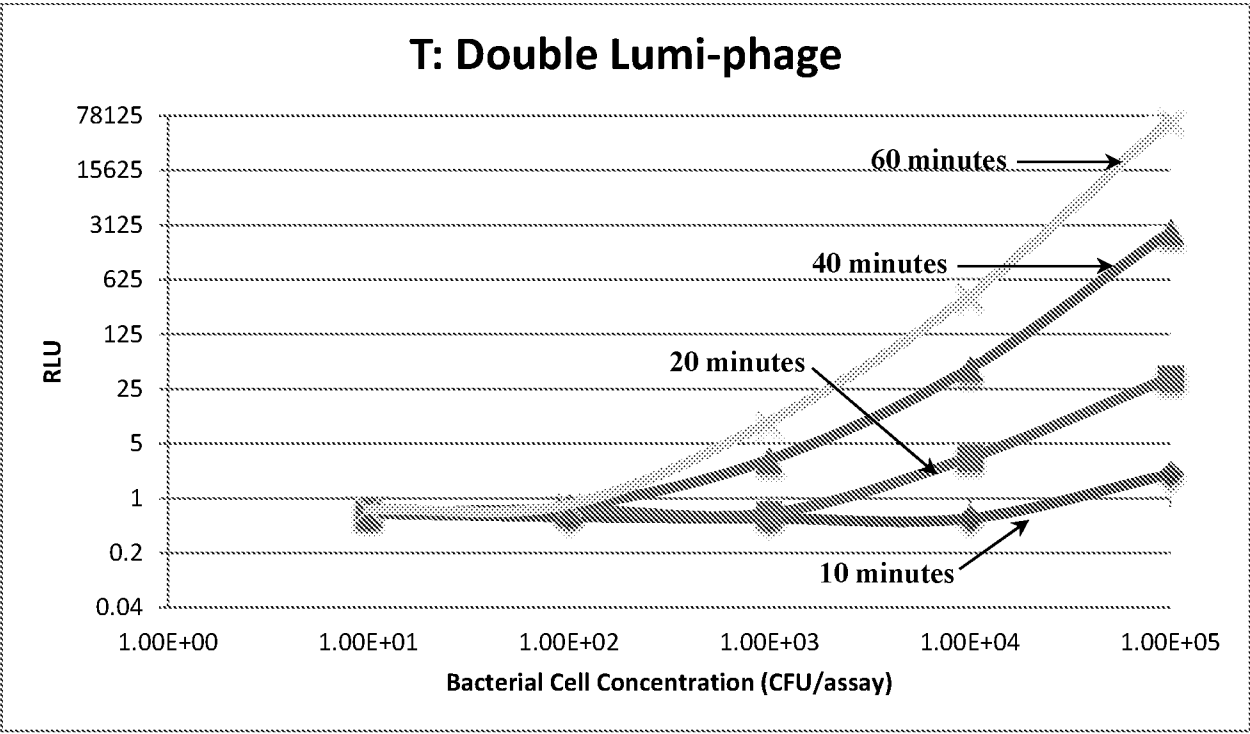


Figure 7

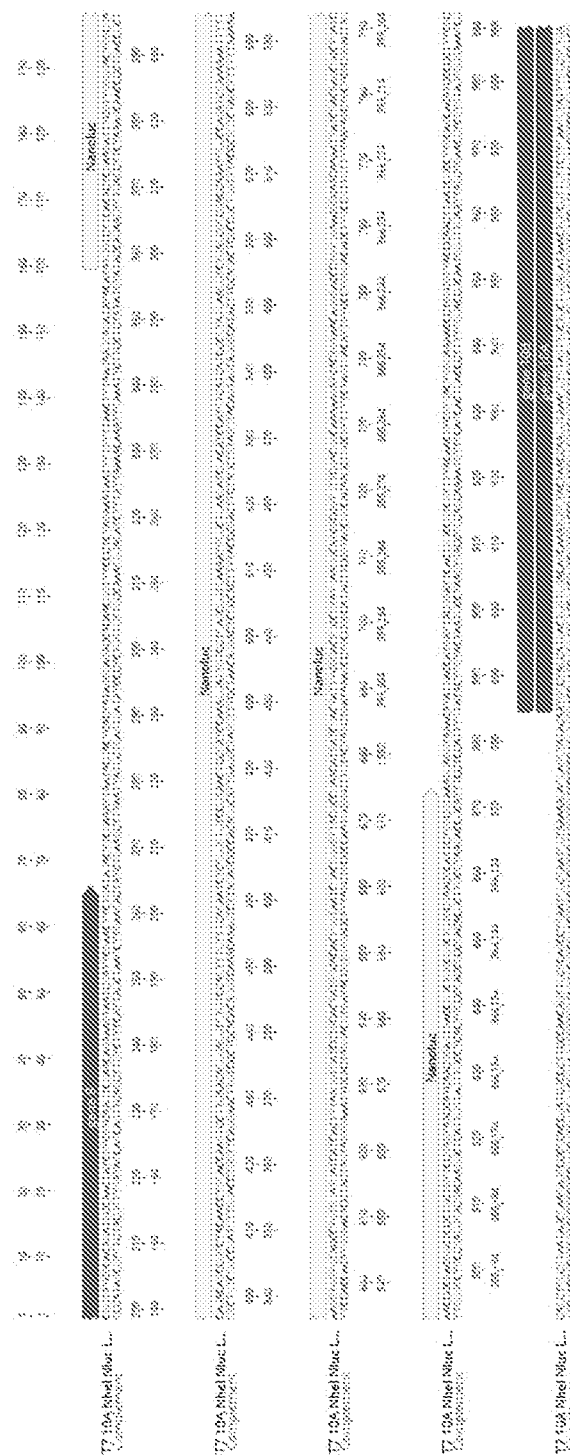


Figure 8

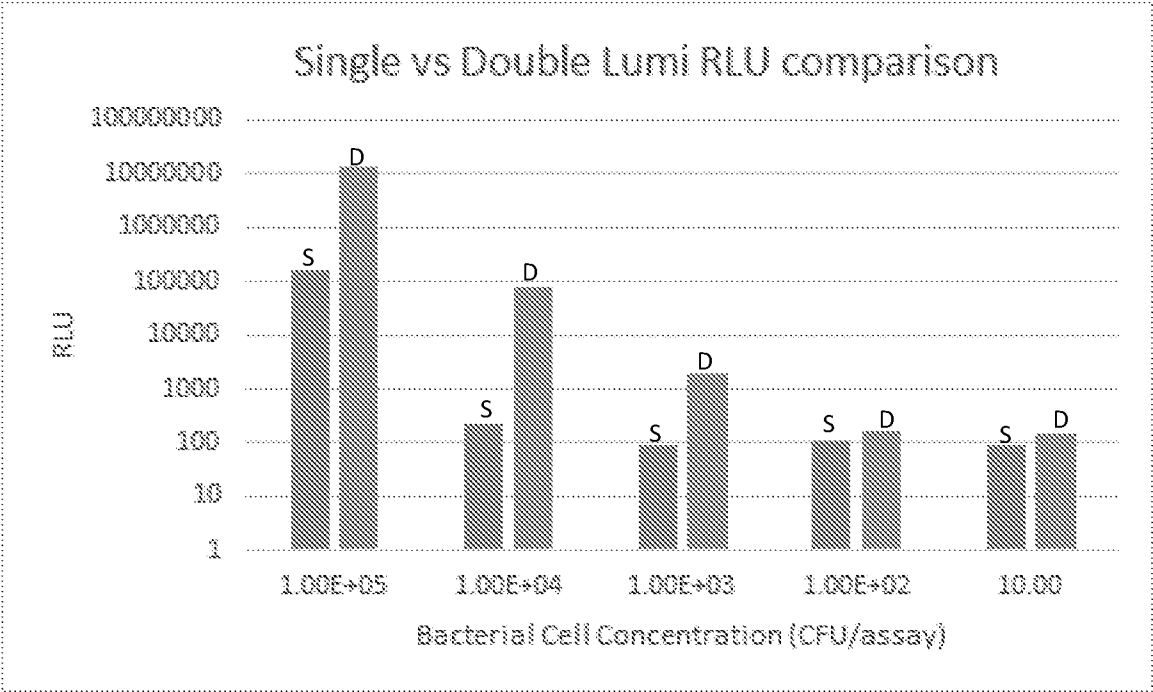


Figure 9

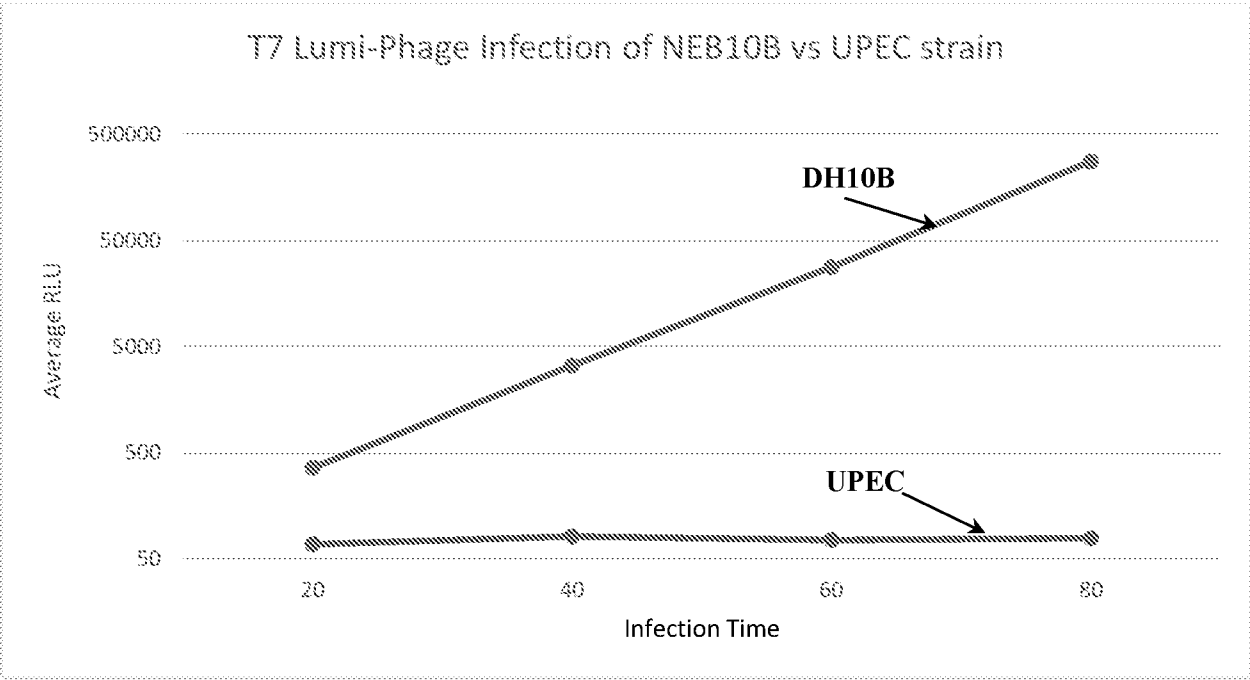


Figure 10

>DLPECO1_T7_cut_and_nluc_insert Enterobacteria phage T7, complete genome
(SEQ ID NO: 1)

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Figure 10 (CONTD.)

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Figure 10 (CONTD.)

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Figure 10 (CONTD.)

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ACGGAATGGAGTGGTGGAACTTCAACGAAGAGATGATGGACTATAACGTTTCAGGACGTTGTGGTAACATAAGCT

Figure 10 (CONTD.)

CTCCTTGAGAAGCTACTCTCTGACAAACATTACTTCCCTCCTGAGATTGACTTTACGGACGTAGGATACACTAC
GTTCTGGTCAGAATCCCTTGAGGCCGTTGACATTGAACATCGTGCTGCATGGCTGCTCGCTAAACAAGAGCGCA
ACGGGTTCCCGTTTGACACAAAAGCAATCGAAGAGTTGTACGTAGAGTTAGCTGCTCGCCGCTCTGAGTTGCTC
CGTAAATTGACCGAAACGTTTCGGCTCGTGGTATCAGCCTAAAGGTGGCACTGAGATGTTCTGCCATCCGCGAAC
AGGTAAGCCACTACCTAAATACCCTCGCATTAAGACACCTAAAGTTGGTGGTATCTTTAAGAAGCCTAAGAACA
AGGCACAGCGAGAAGGCCGTGAGCCTTGCGAACTTGATACCCGCGAGTACGTTGCTGGTGCTCCTTACACCCCA
GTTGAACATGTTGTGTTTAACCCTTCGTCTCGTGACCACATTGAGAAGAACTCCAAGAGGCTGGGTGGGTCCC
GACCAAGTACACCGATAAGGGTGCTCCTGTGGTGGACGATGAGGTACTCGAAGGAGTACGTGTAGATGACCCTG
AGAAGCAAGCCGCTATCGACCTCATTAAGAGTACTTGATGATTGAGAAGCGAATCGGACAGTCTGCTGAGGGA
GACAAAGCATGGCTTCGTTATGTTGCTGAGGATGGTAAGATTGATGGTTCTGTTAACCTAATGGAGCAGTTAC
GGGTCTGCGACCCATGCGTTCCCAAACCTTGCGCAAATTCCGGGTGTACGTTCTCCTTATGGAGAGCAGTGTC
GCGCTGCTTTTGGCGCTGAGCACCATTTGGATGGGATAACTGGTAAGCCTTGGGTTCAGGCTGGCATCGACGCA
TCCGGTCTTGAGCTACGCTGCTTGGCTCACTTCATGGCTCGCTTTGATAACGGCGAGTACGCTCACGAGATTCT
TAACGGCGACATCCACACTAAGAACCAGATAGCTGCTGAACTACCTACCCGAGATAACGCTAAGACGTTTCATCT
ATGGGTTCTCTATGGTGCTGGTGATGAGAAGATTGGACAGATTGTTGGTGCTGGTAAAGAGCGCGGTAAGGAA
CTCAAGAAGAAATTCTTGAGAACACCCCCGCGATTGCAGCACTCCGCGAGTCTATCCAACAGACACTTGTGCA
GTCCTCTCAATGGTAGCTGGTGAGCAACAAGTCAAGTGGAACGCCGCTGGATTAAGGCTCTGGATGGTCGTA
AGGTACACGTTCTAGTCCTCACGCTGCCTTGAATACCCTACTGCAATCTGCTGGTGCTCTCATCTGCAAACCTG
TGGATTATCAAGACCGAAGAGATGCTCGTAGAGAAAGGCTTGAAGCATGGCTGGGATGGGGACTTTGCGTACAT
GGCATGGGTACATGATGAAATCCAAGTAGGCTGCCGTACCGAAGAGATTGCTCAGGTGGTCATTGAGACCGCAC
AAGAAGCGATGCGCTGGGTGGAGACCACTGGAACCTCCGGTGCTTCTGGATACCGAAGGTAAGATGGGTCTCT
AATTGGGCGATTTGCCACTGATACAGGAGGCTACTCATGAACGAAAGACACTTAACAGGTGCTGCTTCTGAAAT
GCTAGTAGCCTACAAATTTACCAAAGCTGGGTACACTGTCTATTACCCTATGCTGACTCAGAGTAAAGAGGACT
TGGTTGTATGTAAGGATGGTAAATTTAGTAAGGTTGAGGTTAAACAGCCACAACGGTTCAAACCAACACAGGA
GATGCCAAGCAGGTTAGGCTAGGTGGATGCGGTAGGTCCGAATATAAGGATGGAGACTTTGACATTCTTGCGGT
TGTGGTTGACGAAGATGTGCTTATTTTACATGGGACGAAGTAAAAGGTAAGACATCCATGTGTGTGCGCAAGA
GAAACAAAGGCATAAACTATAGGAGAAATTATTATGGCTATGACAAAGAAATTTAAAGTGTCCTTCGACGTTA
CCGCAAGATGTGCTCTGACGTTTCAAGCAATCTTAGAGAAAGATATGCTGCATCTATGTAAGCAGGTCCGGCTCA
GGTGCGATTGTCCCCAATGGTAAACAGAAGGAAATGATTGTCCAGTTCTTGACACACGGTATGGAAGGATTGAT
GACATTCGTAGTACGTACATCATTTTCGTGAGGCCATTAAGGACATGCACGAAGAGTATGCAGATAAGGACTCTT
TCAAACAATCTCCTGCAACAGTACGGGAGGTGTTCTGATGTCTGACTACCTGAAAGTGCTGCAAGCAATCAAAA
GTTGCCCTAAGACTTTCCAGTCCAACATATGACGGAACAATGCGAGCCTCGTAGCGGAGGCCGCTTCCCGTGGT
CACATCTCGTGCTGACTACTAGTGGACGTAACGGTGGCGCTTGGGAAATCACTGCTTCCGGTACTCGCTTTCT
GAAACGAATGGGAGGATGTGTCTAATGTCTCGTGACCTTGTGACTATTCCACGCGATGTGTGGAACGATATACA
GGGCTACATCGACTCTCTGGAACGTGAGAACGATAGCCTTAAGAATCAACTAATGGAAGCTGACGAATACGTAG
CGGAAGTACAGGAGAACTTAATGGCACTTCTTGACCTTAACAATCTATGAGTTACGTGAAGGCTGCGACGA
CAAGGGTATCCTTGTGATGGACGGCGACTGGCTGGTCTTCCAAGCTATGAGTGCTGCTGAGTTTGATGCCTCTT
GGGAGGAAGAGATTTGGCACCGATGCTGTGACCACGCTAAGGCCCGTCAGATTCTTGAGGATTCCATTAAGTCC
TACGAGACCCGTAAGAAGGCTTGGGCAGGTGCTCCAATTGTCTTGCCTTACCGATAGTGTTAACTGGCGTAA
AGAAGTGGTTGACCCGAACTATAAGGCTAACCCTAAGGCCGTGAAGAAACCTGTAGGGTACTTTGAGTTCTCTG
ATGCTCTCTTTGAGCGCGAAGAGTTCTATTGCATCCGTGAGCCTATGCTTGAGGGTGATGACGTTATGGGAGTT
ATTGCTTCCAATCCGTCTGCCTTCGGTGCTCGTAAGGCTGTAATCATCTCTTGCGATAAGGACTTTAAGACCAT
CCCTAACTGTGACTTCTGTGGTGTAACCTGACTCAGACCGAAGAGTCCGCTGACTGGTGGC
ACCTCTTCCAGACCATCAAGGTGACATCACTGATGGTTACTCAGGGATTGCTGGATGGGGTGATACCGCCGAG
GACTTCTTGAATAACCCGTTTATAACCGAGCCTAAAACGTCTGTGCTTAAGTCCGGTAAGAACAAAGGCCAAGA
GGTTACTAAATGGGTAAACGCGACCCCTGAGCCTCATGAGACGCTTTGGGACTGCATTAAGTCCATTGGCGCGA
AGGCTGGTATGACCGAAGAGGATATTATCAAGCAGGGCCAAATGGCTCGAATCCTACGGTTCAACGAGTACAAC
TTTATTGACAAGGAGATTTACCTGTGGAGACCGTAGCGTATATTGGTCTGGGTCTTTGTGTTCTCGGAGTGTGC
CTCATTTCGTGGGGCCTTTGGGACTTAGCCAGAATAATCAAGTCGTTACACGACACTAAGTGATAAACTCAAGG
TCCCTAAATTAATACGACTCACTATAGGGAGATAGGGGCCTTTACGATTATTACTTTAAGATTTAACTCTAAGA
GGAATCTTTATTATGTTAACACCTATTAACCAATTACTTAAGAACCCTAACGATATTCCAGATGTACCTCGTGC
AACCGCTGAGTATCTACAGGTTGATTCAACTATGCGTACCTCGAAGCGTCTGGTCATATAGGACTTATGCGTG
CTAATGGTTGTAGTGAGGCCACATCTTGGGTTTCATTGAGGGCTACAGTATGCCTCTAACGTCATTGACGAG
ATTGAGTTACGCAAGGAACAATAAGAGATGATGGGGAGGATTGACACTATGTGTTTCTCACCAGAAATTAATA

Figure 10 (CONTD.)

CTCCGAAGATGGATACCAATCAGATTCGAGCCGTTGAGCCAGCGCCTCTGACCCAAGAAGTGTCAAGCGTGGAG
TTCGGTGGGTCTTCTGATGAGACGGATACCGAGGGCACC GAAGTGTCTGGACGCAAAGGCCTCAAGGTCGAACG
TGATGATTCCGTAGCGAAGTCTAAAGCCAGCGGCAATGGCTCCGCTCGTATGAAATCTTCCATCCGTAAGTCCG
CATTTGGAGGTAAGAAGTGATGTCTGAGTTCACATGTGTGGAGGCTAAGAGTCGCTTCCGTGCAATCCGGTGG
CTGTGGAACACCTTGGGTTGCCTAAAGGATTCTGAAGGACACTTTGTGGGCTACAGCCTCTACGTAGACGAAGTG
ATGGACATGTCTGGTTGCCGTGAAGAGTACATTCTGGACTCTACCGGAAAACATGTAGCGTACTTCGCGTGGTG
CGTAAGCTGTGACATTCACCACAAAGGAGACATTCTGGATGTAACGTCCGTTGTCATTAATCCTGAGGCAGACT
CTAAGGGCTTACAGCGATTCTAGCGAAACGCTTTAAGTACCTTGCGGAACCCACGATTGCGATTGGGTGTCT
CGTTGTAAGCATGAAGGCGAGACAATGCGTGTATACTTTAAGGAGGTATAAGTTATGGGTAAGAAAAGTTAAGAA
GGCCGTGAAGAAAAGTCACCAAGTCCGTTAAGAAAAGTCGTTAAGGAAGGGGCTCGTCCGGTTAAACAGGTTGCTG
GCGGTCTAGCTGGTCTGGCTGGTGGTACTGGTGAAGCACAGATGGTGGAAGTACCACAAGCTGCCGCACAGATT
GTTGACGTACCTGAGAAAGAGGTTTCCACTGAGGACGAAGCACAGACAGAAAGCGGACGCAAGAAAAGCTCGTGC
TGGCGGTAAGAAAATCCTTGAGTGTAGCCCGTAGCTCCGGTGGCGGTATCAACATTTAATCAGGAGGTTATCGTG
GAAGACTGCATTGAATGGACCGGAGGTGTCAACTCTAAGGGTTATGGTCGTAAGTGGGTTAATGGTAAACTTGT
GACTCCACATAGGCACATCTATGAGGAGACATATGGTCCAGTTCCAACAGGAATTGTGGTGATGCATATCTGCG
ATAACCTTAGGTGCTATAACATAAAGCACCTTACGCTTGGAACCTCAAAGGATAATTCCGAGGACATGGTTACC
AAAGGTAGACAGGCTAAAGGAGAGGAACCTAAGCAAGAACTTACAGAGTCAGACGTTCTCGCTATACGCTCTTC
AACCTTAAGCCACCGCTCCTTAGGAGAAGTGTATGGAGTCAGTCAATCAACCATAACGCGAATACTACAGCGTA
AGACATGGAGACACATTTAATGGCTGAGAAACGAACAGGACTTGCGGAGGATGGCGCAAAGTCTGTCTATGAGC
GTTTAAAGAACGACCGTGCTCCCTATGAGACACGCGCTCAGAATTGCGCTCAATATACCATCCCATCATTGTTTC
CCTAAGGACTCCGATAACGCCTCTACAGATTATCAAACCTCCGTGGCAAGCCGTGGGCGCTCGTGGTCTGAACAA
TCTAGCCTCTAAGCTCATGCTGGCTCTATTCCCTATGCAGACTTGATGCGACTTACTATATCTGAATATGAAG
CAAAGCAGTTACTGAGCGACCCCGATGGACTCGCTAAGGTCGATGAGGGCCTCTCGATGGTAGAGCGTATCATC
ATGAACCTACATTGAGTCTAACAGTTACCGCGTGACTCTCTTTGAGGCTCTCAAACAGTTAGTCGTAGCTGGTAA
CGTCCTGCTGTACCTACCGGAACCGGAAGGGTCAAACCTATAATCCCATGAAGCTGTACCGATTGTCTTCTTATG
TGGTCCAACGAGACGCATTCCGGCAACGTTCTGCAAATGGTGACTCGTGACCAGATAGCTTTTGGTGCTCTCCCT
GAGGACATCCGTAAGGCTGTAGAAGGTCAAGGTGGTGAGAAGAAAAGCTGATGAGACAATCGACGTGTACACTCA
CATCTATCTGGATGAGGACTCAGGTGAATACCTCCGATACGAAGAGGTTCGAGGGTATGGAAGTCCAAGGCTCCG
ATGGGACTTATCCTAAAGAGGCTTGCCCATACATCCCGATTCCGGATGGTTCAGACTAGATGGTGAATCCTACGGT
CGTTTCGTACATTGAGGAATACTTAGGTGACTTACGGTCCCTTGAAAATCTCCAAGAGGCTATCGTCAAGATGTC
CATGATTAGCTCTAAGGTTATCGGCTTAGTGAATCCTGCTGGTATCACCCAGCCACGCCGACTGACCAAAGCTC
AGACTGGTGACTTCGTTACTGGTTCGTCCAGAAGACATCTCGTTCCCTCCAAGTGGAGAAGCAAGCAGACTTTACT
GTAGCTAAAGCCGTAAGTGACGCTATCGAGGCTCGCCTTTTCGTTTGCCTTTATGTTGAACTCTGCGGTTTCAGCG
TACAGGTGAACGTGTGACCGCCGAAGAGATTTCGGTATGTAGCTTCTGAACTTGAAGATACTTTAGGTGGTGTCT
ACTCTATCCTTTCTCAAGAATTACAATTGCCTCTGGTACGAGTGCTCTTGAAGCAACTACAAGCCACGCAACAG
ATTCTTGAGTTACCTAAGGAAGCCGTAGAGCCAACCATTAGTACAGGTCTGGAAGCAATTGGTCGAGGACAAGA
CCTTGATAAGCTGGAGCGGTGTGTCACTGCGTGGGCTGCACTGGCACCTATGCGGGACGACCTGATATTAACC
TTGCGATGATTAAAGTTACGTATTGCCAACGCTATCGGTATTGACACTTCTGGTATTCTACTCACCGAAGAACAG
AAGCAACAGAAGATGGCCCAACAGTCTATGCAAATGGGTATGGATAATGGTGCTGCTGCGCTGGCTCAAGGTAT
GGCTGCACAAGCTACAGCTTCACCTGAGGCTATGGCTGCTGCCGCTGATTCGCTAGGTTTACAGCCGGGAATTT
AATACGACTCACTATAGGGAGACCTCATCTTTGAAATGAGCGATGACAAGAGGTTGGAGTCTCGGTCTTTCCTG
TAGTTCAACTTTAAGGAGACAATAATAATGGCTGAATCTAATGCAGACGTATATGCATCTTTTGGCGTGAACCTC
CGCTGTGATGTCTGGTGGTTCGGTTGAGGAACATGAGCAGAACATGCTGGCTCTTGATGTTGCTGCCCCTGATG
GCGATGATGCAATCGAGTTAGCGTCAGACGAAGTGGAAACAGAACGTGACCTGTATGACAACTCTGACCCGTTTC
GGTCAAGAGGATGACGAAGGCCGCATTACGGTTTCGTATCGGTGATGGCTCTGAGCCGACCGATGTGGACACTGG
AGAAGAAGGCGTTGAGGGCACCGAAGGTTCCGAAGAGTTTACCCCACTGGGCGAGACTCCAGAAGAACTGGTAG
CTGCCTCTGAGCAACTTGGTGAGCACGAAGAGGGCTTCCAAGAGATGATTAACATTGCTGCTGAGCGTGGCATG
AGTGTGAGACCATTGAGGCTATCCAGCGTGAGTACGAGGAGAACGAAGAGTTGTCCGCCGAGTCTACGCTAA
GCTGGCTGAAATTGGCTACACGAAGGCTTTCAATTGACTCGTATATCCGTGGTCAAGAAGCTCTGGTGGAGCAGT
ACGTAAACAGTGTCAATTGAGTACGCTGGTGGTCTGAACGTTTTGATGCACTGTATAACCACCTTGAGACGCAC
AACCCTGAGGCTGCACAGTCGCTGGATAATGCGTTGACCAATCGTGACTTAGCGACCGTTAAGGCTATCATCAA
CTTGGCTGGTGAGTCTCGCGCTAAGGCGTTCGGTCTGAAGCCAACCTCGTAGTGTGACTAATCGTGCTATTCCGG
CTAAACCTCAGGCTACCAAGCGTGAAGGCTTTGCGGACCGTAGCGAGATGATTAAAGCTATGAGTGACCCCTCGG
TATCGCACAGATGCCAACTATCGTCTGCAAGTCAACAGAAAAGTAATCGATTGCAACTTCTGATAGACTTCGAA

Figure 10 (CONTD.)

ATTAATACGACTCACTATAGGGAGACCACAACGGTTTCCCTCTAGAAATAATTTTGTTTAACTTTAAGAAGGAG
ATATACATATGGCTAGCATGACTGGTGGACAGCAAATGGGTACTAACCAAGGTAAAGGTGTAGTTGCTGCTGGA
GATAAACTGGCGTTGTTCTTGAAGGTATTTGGCGGTGAAGTCCTGACTGCGTTCGCTCGTACCTCCGTGACCAC
TTCTCGCCACATGGTACGTTCCATCTCCAGCGGTAAATCCGCTCAGTTCCCTGTTCTGGGTGCGACTCAGGCAG
CGTATCTGGCTCCGGGCGAGAACCTCGACGATAAACGTAAGGACATCAAACACACCGAGAAGGTAATCACCATT
GACGGTCTCCTGACGGCTGACGTTCTGATTTATGATATTGAGGACGCGATGAACCACTACGACGTTGCTCTGA
GTATACCTCTCAGTTGGGTGAATCTCTGGCGATGGCTGCGGATGGTGCGGTTCTGGCTGAGATTGCCGGTCTGT
GTAACGTGGAAGCAAATATAATGAGAACATCGAGGGCTTAGGTACTGCTACCGTAATTGAGACCACTCAGAAC
AAGGCCGCACTTACCGACCAAGTTGCGCTGGGTAAGGAGATTATTGCGGCTCTGACTAAGGCTCGTGCGGCTCT
GACCAAGAACTATGTTCCGGCTGCTGACCGTGTGTTCTACTGTGACCCAGATAGCTACTCTGCGATTCTGGCAG
CACTGATGCCGAACGACGAACTACGCTGCTCTGATTGACCCTGAGAAGGGTCTATCCGCAACGTTATGGGC
TTTGAGGTTGTAGAAGTTCCGCACCTCACCGCTGGTGGTGCTGGTACCGCTCGTGAGGGCACTACTGGTCAGAA
GCACGTCTTCCCTGCCAATAAAGGTGAGGGTAATGTCAAGGTTGCTAAGGACAACGTTATCGGCCTGTTTCATGC
ACCGCTCTGCGGTAGGTACTGTTAAGCTGCGTGACTTGGCTCTGGAGCGCGCTCGCCGTGCTAACTTCCAAGCG
GACCAGATTATCGCTAAGTACGCAATGGGCCACGGTGGTCTTCGCCCAGAAGCTGCTGGTGCAGTGGTTTTCAA
AGTGGAGTAATGCTGGGGGTGGCCTCAACGGTCGCTGCTAGTCCCAGAAGAGGCGAGTGTTACTTCAACAGAAGA
AACCTTAACGCCAGCACAGGAGGCCGACGACCCGCGCTGCTAACAAAGCCGAAAGGAAGCTGAGTTGGCTG
CTGCCACCGCTGAGCAATAACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGTTTTTTGCTGAAA
GGAGGAACATATATGCGCTCATACGATATGAACGTTGAGACTGCCGCTGAGTTATCAGCTGTGAACGACATTCTG
GCGTCTATCGGTGAACCTCCGGTATCAACGCTGGAAGGTGACGCTAACGCAGATGCAGCGAACGCTCGGCGTAT
TCTCAACAAGATTAACCGACAGATTCAATCTCGTGGATGGACGTTCAACATTGAGGAAGGCATAACGCTACTAC
CTGATGTTTACTCCAACCTGATTGTATACAGTGACGACTATTTATCCCTAATGTCTACTTCCGGTCAATCCATC
TACGTTAACCGAGGTGGCTATGTGTATGACCGAACGAGTCAATCAGACCGCTTTGACTCTGGTATTACTGTGAA
CATTATTTCGTCTCCGCGACTACGATGAGATGCCTGAGTGCTTCCGTTACTGGATTGTCACCAAGGCTTCCCGTC
AGTTCAACAACCGATTCTTTGGGGCACCGGAAGTAGAGGGTGTACTCCAAGAAGAGGAAGATGAGGCTAGACGT
CTCTGCATGGAGTATGAGATGGACTACGGTGGGTACAATATGCTGGATGGAGATGCGTTCACCTCTGGTCTACT
GACTCGCTAACATTAATAAATAAGGAGGCTCTAATGGCACTCATTAGCCAATCAATCAAGAACCTTGAAGGGTGG
TATCAGCCAACAGCTGACATCCTTCGTTATCCAGACCAAGGGTCACGCCAAGTTAACGGTTGGTCTTCGGAGA
CCGAGGGCCTCCAAAAGCGTCCACCTCTTGTTCCTTAAATACACTTGGAGACAACGGTGCGTTAGGTCAAGCT
CCGTACATCCACCTGATTAACCGAGATGAGCACGAACAGTATTACGCTGTGTTCACTGGTAGCGGAATCCGAGT
GTTTCGACCTTTCTGGTAACGAGAAGCAAGTTAGGTATCCTAACGGTTCCTAACCTACATCAAGACCGCTAATCCAC
GTAACGACCTGCGAATGGTTACTGTAGCAGACTATACGTTTCATCGTTAACCGTAACGTTGTTGCACAGAAGAAC
ACAAAGTCTGTCAACTTACCGAATTACAACCTAATCAAGACGGATTGATTAACGTTTCGTGGTGGTCAGTATGG
TAGGGAACATAATTGTACACATTAACGGTAAAGACGTTGCGAAGTATAAGATACCAGATGGTAGTCAACCTGAAC
ACGTAAACAATACGGATGCCAATGGTTAGCTGAAGAGTTAGCCAAGCAGATGCGCACTAACTTGTCTGATTGG
ACTGTAAATGTAGGGCAAGGGTTCATCCATGTGACCGCACCTAGTGGTCAACAGATTGACTCCTTCACGACTAA
AGATGGCTACGCAGACCAGTTGATTAACCTGTGACCCACTACGCTCAGTCGTTCTCTAAGCTGCCACCTAATG
CTCCTAACGGCTACATGGTGAAAATCGTAGGGGACGCCTCTAAGTCTGCCGACCAGTATTACGTTCCGGTATGAC
GCTGAGCGGAAAAGTTGGACTGAGACTTTAGGTTGGAACACTGAGGACCAAGTTCTATGGGAAACCATGCCACA
CGCTCTTGTGCGAGCCGCTGACGGTAATTCGACTTCAAGTGGCTTGAGTGGTCTCCTAAGTCTTGTGGTGACG
TTGACACCAACCTTGGCCTTCTTTTGTGGTTCAAGTATTAACGATGTGTTCTTCTTCCGTAACCGCTTAGGA
TTCCTTAGTGGGGAGAACATCATATTGAGTCGTACAGCCAAATACTTCAACTTCTACCCTGCGTCCATTGCGAA
CCTTAGTGATGACGACCCTATAGACGTAGCTGTGAGTACCAACCGAATAGCAATCCTTAAGTACGCCGTTCCGT
TCTCAGAAGAGTTACTCATCTGGTCCGATGAAGCACAATTCGTCTGACTGCCTCGGGTACTCTCACATCTAAG
TCGGTTGAGTTGAACCTAACGACCCAGTTTGACGTACAGGACCGAGCGAGACCTTTTGGGATTGGGCGTAATGT
CTACTTTGCTAGTCCGAGGTCCAGCTTCACGTCCATCCACAGGTACTACGCTGTGCAGGATGTCAGTTCCGTTA
AGAATGCTGAGGACATTACATCACACGTTCCCTAACTACATCCCTAATGGTGTGTTCACTATTTGCGGAAGTGGT
ACGGAAAACCTTCTGTTCCGGTACTATCTCACGGGGACCCTAGTAAAATCTTCATGTACAAATTCCTGTACCTGAA
CGAAGAGTTAAGGCAACAGTCGTGGTCTCATTTGGGACTTTGGGGAAAACGTACAGGTTCTAGCTTGTGAGAGTA
TCAGCTCAGATATGTATGTGATTCTTCGCAATGAGTTCAATACGTTCCCTAGCTAGAATCTCTTCACTAAGAAC
GCCATTGACTTACAGGGAGAACCCTATCGTGCCCTTTATGGACATGAAGATTGATACACGATTCCCTAGTGGAAC
ATACAACGATGACACATTCCTACCTCTATTCATATTCACAACATTTATGGTGCAAACCTTCGGGAGGGGCAAAA
TCACTGTATTGGAGCCTGATGGTAAGATAACCGTGTTTGAGCAACCTACGGCTGGGTGGAATAGCGACCCCTTG
CTGAGACTCAGCGGTAACCTTGAGGGGACGCATGGTGTACATTGGGTTCAACATTAACCTTCGTATATGAGTTCTC

Figure 10 (CONTD.)

TAAGTTCCTCATCAAGCAGACTGCCGACGACGGGTCTACCTCCACGGAAGACATTGGGCGCTTACAGTTACGCC
GAGCGTGGGTAACTACGAGAACTCTGGTACGTTTGACATTTATGTTGAGAACCAATCGTCTAACTGGAAGTAC
ACAATGGCTGGTGCCCGATTAGGCTCTAACACTCTGAGGGCTGGGAGACTGAACTTAGGGACCGGACAATATCG
ATTCCTGTGGTTGGTAACGCCAAGTTCAACACTGTATACATCTTGTGAGATGAGACTACCCCTCTGAACATCA
TTGGGTGTGGCTGGGAAGGTAACACTACTTACGGAGAAGTTCGGGTATTTAATTAAATATTCTCCCTGTGGTGGCT
CGAAATTAATACGACTCACTATAGGGAGAACAATACGACTACGGGAGGGTTTTCTTATGATGACTATAAGACCT
ACTAAAAGTACAGACTTTTGAGGTATTCCTCCGGCTCACCATGACATTCTTGAAGCTAAGGCTGCTGGTATTGA
GCCGAGTTTCCCTGATGCTTCCGAGTGTGTCACGTTGAGCCTCTATGGGTTCCTCTAGCTATCGGTGGTAACT
GCGGGGACCAGTGCTGGTTCGTTACGAGCGACCAAGTGTGGCGACTTAGTGGAAGGCTAAGCGAAAGTTCCGT
AAGTTAATCATGGAGTATCGCGATAAGATGCTTGAGAAGTATGATACTCTTTGGAATTACGTATGGGTAGGCAA
TACGTCCACATTCGTTTTCTCAAGACTATCGGTGCGGTATTCCATGAAGAGTACACACGAGATGGTCAATTTTC
AGTTATTTACAATCACGAAAGGAGGATAACCATATGTGTTGGGCGACCGCAATACCTATCGCTATATCTGGCGC
TCAGGCTATCAGTGGTCAGAACGCTCAGGCCAAAATGATTGCCGCTCAGACCGCTGCTGGTCTGTCGTCAAGCTA
TGGAATCATGAGGCAGACGAACATCCAGAATGCTGACCTATCGTTGCAAGCTCGAAGTAACTTGAGGAAGCG
TCCGCCGAGTTGACCTCACAGAACATGCAGAAGGTCCAAGCTATTGGGTCTATCCGAGCGGCTATCGGAGAGAG
TATGCTTGAAGGTTCTCAATGGACCGCATTAAGCGAGTCACAGAAGGACAGTTCATTCCGGGAAGCCAATATGG
TAACTGAGAATATCGCCGTGACTACCAAGCAATCTTCGCACAGCAACTTGGTGGTACTCAAAGTGCTGCAAGT
CAGATTGACGAAATCTATAAGAGCGAACAGAAACAGAAGAGTAAGCTACAGATGGTTCTGGACCCACTGGCTAT
CATGGGGTCTTCCGCTGCGAGTGCTTACGCATCCGGTGCCTTCGACTCTAAGTCCACAATAAGGCACCTATTG
TTGCCGCTAAAGGAACCAAGACGGGGAGGTAATGAGCTATGAGTAAAATTGAATCTGCCCTTCAAGCGGCACAA
CCGGGACTCTCTCGGTTACGTGGTGGTGCTGGAGGTATGGGCTATCGTGCAGCAACCACTCAGGCCGAACAGCC
AAGGTCAAGCCTATTGGACACCATTGGTCGGTTCGCTAAGGCTGGTGCCGATATGTATACCGCTAAGGAACAAC
GAGCACGAGACCTAGCTGATGAACGCTCTAACGAGATTATCCGTAAGCTGACCCCTGAGCAACGTCGAGAAGCT
CTCAACAACGGGACCCTTCTGTATCAGGATGACCATAACGCTATGGAAGCACTCCGAGTCAAGACTGGTCGTAA
CGCTGCGTATCTTGTGGACGATGACGTTATGCAGAAGATAAAAGAGGGTGTCTTCCGTACTCGCGAAGAGATGG
AAGAGTATCGCCATAGTCGCCTTCAAGAGGGCGCTAAGGTATACGCTGAGCAGTTCCGCATCGACCCTGAGGAC
GTTGATTATCAGCGTGGTTTTCAACGGGGACATTACCGAGCGTAACATCTCGCTGTATGGTGCGCATGATAACTT
CTTGAGCCAGCAAGCTCAGAAGGGCGCTATCATGAACAGCCGAGTGGAAGTCAACGGTGTCTTCAAGACCCTG
ATATGCTGCGTCTGCCAGACTCTGCTGACTTCTTTGAGAAGTATATCGACAACGGTCTGGTTACTGGCGCAATC
CCATCTGATGCTCAAGCCACACAGCTTATAAGCCAAGCGTTCAGTGACGCTTCTAGCCGTGCTGGTGGTGCTGA
CTTCTGATGCGGAGTCGGTGACAAGAAGGTAACACTTAACGGAGCCACTACGACTTACCGAGAGTTGATTGGTG
AGGAACAGTGGAACGCTCTCATGGTCACAGCACAAACGTTCTCAGTTTGAGACTGACGCGAAGCTGAACGAGCAG
TATCGCTTGAAGATTAACCTCTGCGCTGAACCAAGAGGACCCAAGGACAGCTTGGGAGATGCTTCAAGGTATCAA
GGCTGAACTAGATAAGGTCCAACCTGATGAGCAGATGACACCACAACGTGAGTGGCTAATCTCCGCACAGGAAC
AAGTTCAGAATCAGATGAACGCATGGACGAAAAGCTCAGGCCAAGGCTCTGGACGATTCCATGAAGTCAATGAAC
AACTTGACGTAATCGACAAGCAATTCCAGAAGCGAATCAACGGTGAGTGGGTCTCAACGGATTTTAAGGATAT
GCCAGTCAACGAGAACACTGGTGAGTTCAAGCATAGCGATATGGTTAACTACGCCAATAAGAAGCTCGCTGAGA
TTGACAGTATGGACATTCCAGACGGTGCCAAGGATGCTATGAAGTTGAAGTACCTTCAAGCGGACTCTAAGGAC
GGAGCATTCCGTACAGCCATCGGAACCATGGTCACTGACGCTGGTCAAGAGTGGTCTGCCGCTGTGATTAAACGG
TAAGTTACCAGAACGAACCCAGCTATGGATGCTCTGCGCAGAATCCGCAATGCTGACCCTCAGTTGATTGCTG
CGCTATACCCAGACCAAGCTGAGCTATTCTGACGATGGACATGATGGACAAGCAGGGTATTGACCCCTCAGGTT
ATTCCTGATGCCGACCGACTGACTGTTAAGCGGTCCAAAGAGCAACGCTTTGAGGATGATAAAGCATTCGAGTC
TGCACTGAATGCATCTAAGGCTCCTGAGATTGCCCGTATGCCAGCGTCACTGCGCGAATCTGCACGTAAGATTT
ATGACTCCGTAAAGTATCGCTCGGGGAACGAAAGCATGGCTATGGAGCAGATGACCAAGTTCCCTAAGGAATCT
ACCTACACGTTCACTGGTGATGATGTTGACGGTGATACCGTTGGTGTGATTCCTAAGAATATGATGCAGGTTAA
CTCTGACCCGAAATCATGGGAGCAAGGTCTGGGATATTCTGGAGGAAGCACGTAAGGGAATCATTCGAGCAACC
CTTGGATAACCAATAAGCAACTGACCATGTATTCTCAAGGTGACTCCATTTACCTTATGGACACCACAGGTCAA
GTCAGAGTCCGATACGACAAAGAGTTACTCTCGAAGGTCTGGAGTGAGAACCAGAAGAACTCGAAGAGAAAGC
TCGTGAGAAGGCTCTGGCTGATGTGAACAAGCGAGCACCTATAGTTGCCGCTACGAAGGCCCCGTGAAGCTGCTG
CTAAACGAGTCCGAGAGAAACGTAAACAGACTCCTAAGTTTCATCTACGGACGTAAGGAGTAACCTAAAGGCTACA
TAAGGAGGCCCTAAATGGATAAGTACGATAAGAAGCTACCAAGTGATTATGATGGTCTGTTCCAAAAGGCTGCT
GATGCCAACGGGGTCTCTTATGACCTTTTACGTAAAGTCGCTTGGACAGAATCACGATTTGTGCCTACAGCAAA
ATCTAAGACTGGACCATTAGGCATGATGCAATTTACCAAGGCAACCGCTAAGGCCCTCGGTCTGCGAGTTACCG
ATGGTCCAGACGACGACCGACTGAACCCTGAGTTAGCTATTAATGCTGCCGCTAAGCAACTTGCAGGTCTGGTA

Figure 10 (CONTD.)

GGGAAGTTTGATGGCGATGAACTCAAAGCTGCCCTTGCCTACAACCAAGGCGAGGGACGCTTGGGTAATCCACA
ACTTGAGGCGTACTCTAAGGGAGACTTCGCATCAATCTCTGAGGAGGGACGTAACCTACATGCGTAACCTTCTGG
ATGTTGCTAAGTCACCTATGGCTGGACAGTTGGAACCTTTTGGTGGCATAACCCCAAAGGGTAAAGGCATTCCG
GCTGAGGTAGGATTGGCTGGAATTGGTCACAAGCAGAAAGTAACACAGGAACCTCCTGAGTCCACAAGTTTTGA
CGTTAAGGGTATCGAACAGGAGGCTACGGCGAAACCATTGCGCAAGGACTTTTGGGAGACCCACGGAGAAACAC
TTGACGAGTACAACAGTCGTTCAACCTTCTTCGGATTCAAAAATGCTGCCGAAGCTGAACTCTCCAACCTCAGTC
GCTGGGATGGCTTTCCTGCTGGTCGTCTCGATAATGTTTTGATGTGTTTAAAGACACCATTACGCCGACTCG
CTGGAACCTCTCACATCTGGACTCCAGAGGAGTTAGAGAAGATTGGAACAGAGGTTAAGAACCCTGCGTACATCA
ACGTTGTAACCTGGTGGTTCCTTCCCTGAGAACCTCGATGACCTCATTAATTTGGCTAACGAGAACCTTGAGAATGAC
TCCCGCGCTGCCGAGGCTGGCCTAGGTGCCAACTGAGTGCTGGTATTATTGGTGCTGGTGTGGACCCGCTTAG
CTATGTTCTCTATGGTCGGTGTCACTGGTAAGGGCTTTAAGTTAATCAATAAGGCTCTTGATGTTGGTGCCGAAA
GTGCTGCTCTGAACGTTGCATCCGAAGGTCTCCGTACCTCCGTAGCTGGTGGTGACGCAGACTATGCGGGTGCT
GCCTTAGGTGGCTTTGTGTTTGGCGCAGGCATGTCTGCAATCAGTGACGCTGTAGCTGCTGGACTGAAACGCAG
TAAACCAGAAGCTGAGTTCGACAATGAGTTCATCGGTCTATGATGCGATTGGAAGCCCGTGAGACAGCACGAA
ACGCCAACTCTGCGGACCTCTCTCGGATGAACACTGAGAACATGAAGTTTGAAGGTGAACATAATGGTGTCCCT
TATGAGGACTTACCAACAGAGAGAGGTGCCGTGGTGTTACATGATGGCTCCGTTCTAAGTGCAAGCAACCCAAT
CAACCCTAAGACTCTAAAAGAGTTCTCCGAGGTTGACCCTGAGAAGGCTGCGCGAGGAATCAAACCTGGCTGGGT
TCACCGAGATTGGCTTGAAGACCTTGGGGTCTGACGATGCTGACATCCGTAGAGTGGCTATCGACCTCGTTCGC
TCTCCTACTGGTATGCACTGTGGTGCCTCAGGTAAGTTCCGTGCAACAGCTTCTGACATCCATGAGAGACTTCA
TGGTACTGACCAGCGTACTTATAATGACTTGTACAAAGCAATGTCTGACGCTATGAAAGACCCCTGAGTTCCTCA
CTGGCGGGCGCTAAGATGTCCCGTGAAGAACTCGATACACTATCTACCGTAGAGCGGCACTAGCTATTGAGCGT
CCAGAACTACAGAAGGCACCTCACTCCGTCTGAGAGAATCGTTATGGACATCATTAAAGCGTCACTTTGACACCAA
GCGTGAACCTTATGGAAGAACCCAGCAATATTCGGTAACACAAAGGCTGTGAGTATCTTCCCTGAGAGTCGCCACA
AAGGTACTTACGTTCTCACGTATATGACCGTCATGCCAAGGCGCTGATGATTCAACGCTACGGTGCCGAAGGT
TTGCAGGAAGGGATTGCCCGCTCATGGATGAACAGCTACGTCTCCAGACCTGAGGTCAAGGCCAGAGTCGATGA
GATGCTTAAGGAATTACACGGGGTGAAGGAAGTAACACCAGAGATGGTAGAGAAGTACGCTATGGATAAGGCTT
ATGGTATCTCCCACTCAGACCAGTTTACCAACAGTTCCATAATAGAAGAGAACATTGAGGGCTTAGTAGGTATC
GAGAATAACTCATTCTTGGAGGCACGTAACCTTGTGTTGATTCCGACCTATCCATCACTATGCCAGACGGACAGCA
ATTCTCAGTGAATGACCTAAGGGACTTCGATATGTTCCGCATCATGCCAGCGTATGACCGCCGTGTCAATGGTG
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GCTGAGGGGAGACGGTAAGAAGACTGGCGAGGTACATGCTTTAATGGATACCGTTAAGATTCTTACTGGTCGTGC
TAGACGCAATCAGGACACTGTGTGGGAAACCTCACTGCGTGCCATCAATGACCTAGGGTTCTTCGCTAAGAACG
CCTACATGGGTGCTCAGAACATTACGGAGATTGCTGGGATGATTGTCACTGGTAACGTTTCGTGCTCTAGGGCAT
GGTATCCCAATTCTGCGTGATACACTCTACAAGTCTAAACCAGTTTCAGCTAAGGAACTCAAGGAACTCCATGC
GTCTCTGTTCCGGGAAGGAGGTGGACCACTGATTCCGGCTAAACGTGCTGACATTGTGCAGCGCCTAAGGGAAG
CAACTGATACCGGACCTGCCGTGGCGAACATCGTAGGGACCTTGAAGTATTCAACACAGGAACTGGCTGCTCGC
TCTCCGTGGACTAAGCTACTGAACGGAACCACTAACTACCTTCTGGATGCTGCGCGTCAAGGTATGCTTGGGGA
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CTCCTGAGCAGATGGCTGGCATCAAGTCTCTCATCAAGGAACATATGGTACGCGGTGAGGACGGGAAGTTTACC
GTTAAGGACAAGCAAGCGTTCTCTATGGACCCACGGGCTATGGACTTATGGAGACTGGCTGACAAGGTAGCTGA
TGAGGCAATGCTGCGTCCACATAAGGTGTCTTACAGGATTCCCATGCGTTCCGAGCACTAGGTAAGATGGTTA
TGCAGTTTAAAGTCTTCACTATCAAGTCCCTTAACTCTAAGTTCCTGCGAACCTTCTATGATGGATACAAGAAC
AACCAGCGGATTGACGCTGCGCTGAGCATCATCACCTCTATGGGTCTCGCTGGTGGTTCCTATGCTATGGCTGC
ACACGTCAAAGCATACGCTCTGCCTAAGGAGAAACGTAAGGAGTACTTGGAGCGTGCACTGGACCCAAACCATGA
TTGCCCACGCTGCGTTATCTCGTAGTTCTCAATTGGGTGCTCCTTTGGCTATGGTTGACCTAGTTGGTGGTGT
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CAAACCGTACACCTCTAGAGAGGTAATGGGCGCTATGGGTTCAAACCTTCTGGAACAGATGCCTTCGGCTGGCT
TTGTGGCTAACGTAGGGGCTACCTTAATGAATGCTGCTGGCGTGGTCAACTCACCTAATAAAGCAACCGAGCAG
GACTTCATGACTGGTCTTATGAACTCCACAAAAGAGTTAGTACCGAACGACCCATTGACTCAACAGCTTGTGTT
GAAGATTTATGAGGCGAACGGTGTAACTTGAGGGAGCGTAGGAAATAATACGACTCACTATAGGGAGAGGCGA
AATAATCTTCTCCCTGTAGTCTCTTAGATTTACTTTAAGGAGGTCAAATGGCTAACGTAATTAACCCGTTTTG
ACTTACCAGTTAGATGGCTCCAATCGTGATTTAATATCCCGTTTGGTATCTAGCCCGTAAGTTCGTAGTGGT
AACTCTTATTGGTGTAGACCGAAAGGTCCTTACGATTAATACAGACTATCGCTTTGCTACACGTACTACTATCT
CTCTGACAAAGGCTTGGGGTCCAGCCGATGGCTACACGACCATCGAGTTACGTCGAGTAACCTCCACTACCGAC

Figure 10 (CONTD.)

CGATTGGTTGACTTTACGGATGGTTCAATCCTCCGCGCGTATGACCTTAACGTCGCTCAGATTCAAACGATGCA
CGTAGCGGAAGAGGCCCGTGACCTCACTACGGATACTATCGGTGTCAATAACGATGGTCACCTGGATGCTCGTG
GTCGTCGAATTGTGAACCTAGCGAACGCCGTGGATGACCGCGATGCTGTTCCGTTTGGTCAACTAAAGACCATG
AACCAGAATCATGGCAAGCACGTAATGAAGCCTTACAGTTCCGTAATGAGGCTGAGACTTTCAGAAACCAAGC
GGAGGGCTTTAAGAACGAGTCCAGTACCAACGCTACGAACACAAAGCAGTGGCGCGATGAGACCAAGGGTTTCC
GAGACGAAGCCAAGCGGTTCAAGAATACGGCTGGTCAATACGCTACATCTGCTGGGAACTCTGCTTCCGCTGCG
CATCAATCTGAGGTAAACGCTGAGAACTCTGCCACAGCATCCGCTAACTCTGCTCATTTGGCAGAACAGCAAGC
AGACCGTGCGGAACGTGAGGCAGACAAGCTGGAAAATTACAATGGATTGGCTGGTGCAATTGATAAGGTAGATG
GAACCAATGTGTACTGGAAAGGAAATATTCACGCTAACGGGCGCCTTTACATGACCACAAACGGTTTTGACTGT
GGCCAGTATCAACAGTTCTTTGGTGGTGTCACTAATCGTTACTCTGTCTATGGAGTGGGAGATGAGAACGGATG
GCTGATGTATGTTCAACGTAGAGAGTGGACAACAGCGATAGGCGGTAACATCCAGTTAGTAGTAAACGGACAGA
TCATCACCCAAGGTGGAGCCATGACCGGTCAGCTAAAATTGCAGAATGGGCATGTTCTTCAATTAGAGTCCGCA
TCCGACAAGGCGCACTATATTCTATCTAAAGATGGTAACAGGAATAACTGGTACATTGGTAGAGGGTCAGATAA
CAACAATGACTGTACCTTCCACTCCTATGTACATGGTACGACCTTAACACTCAAGCAGGACTATGCAGTAGTTA
ACAAACACTTCCACGTAGGTCAGGCCGTTGTGGCCACTGATGGTAATATTCAGGTACTAAGTGGGAGGTAA
TGGCTGGATGCTTACCTACGTGACAGCTTCGTTGCGAAGTCCAAGGCGTGGACTCAGGTGTGGTCTGGTAGTGC
TGGCGGTGGGGTAAGTGTGACTGTTTCACAGGATCTCCGCTTCCGCAATATCTGGATTAAGTGTCCAACAAC
CTTGGAACCTTCTCCGTACTGGCCCCGATGGAATCTACTTCATAGCCTCTGATGGTGGATGGTTACGATTCCAA
ATACACTCCAACGGTCTCGGATTCAAGAATATTGCAGACAGTCGTTTCACTACCTAATGCAATCATGGTGGAGAA
CGAGTAATTGGTAAATCACAAGGAAAGACGTGTAGTCCACGGATGGACTCTCAAGGAGGTACAAGGTGCTATCA
TTAGACTTTAAACAACGAATTGATTAAGGCTGCTCCAATTGTTGGGACGGGTGTAGCAGATGTTAGTGTCTGACT
GTTCTTTGGGTTAAGCCTTAACGAATGGTCTACGTTGCTGCTATCGCCTACACAGTGGTTCAGATTGGTGCCA
AGGTAGTCGATAAGATGATTGACTGGAAGAAAGCCAATAAGGAGTGATATGTATGGAAGAGGATAAGAGCCTTA
TTACATTCTTAGAGATGTTGGACACTGCGATGGCTCAGCGTATGCTTGGGACCTTTCGGACCATGAGCGTCGC
TCTCCGCAACTCTATAATGCTATTAACAACTGTTAGACCGCCACAAGTTCAGATTGGTAAGTTGCAGCCGGA
TGTTACATCTTAGGTGGCCTTGCTGGTGTCTTGAAGAGTACAAAGAGAAAGTCGGTGATAACGGTCTTACGG
ATGATGATATTTACACATTACAGTGATATACTCAAGGCCACTACAGATAGTGGTCTTTATGGATGTCATTGTCT
ATACGAGATGCTCCTACGTGAAATCTGAAAGTTAACGGGAGGCATTATGCTAGAATTTTTTACGTAAGCTAATCC
CTTGGGTTCTCGCTGGGATGCTATTCCGGTTAGGATGGCATCTAGGGTCAGACTCAATGGACGCTAAATGGAAA
CAGGAGGTACACAATGAGTACGTTAAGAGAGTTGAGGCTGCGAAGAGCACTCAAAGAGCAATCGATGCGGTATC
TGCTAAGTATCAAGAAGACCTTGCCGCGCTGGAAGGGAGCACTGATAGGATTATTTCTGATTTGCGTAGCGACA
ATAAGCGGTTGCGGTCAGAGTCAAACTACCGGAACCTCCGATGGTCAGTGTGGATTCGAGCCTGATGGTCGA
GCCGAACCTTGACGACCGAGATGCTAAACGTATTCTCGCAGTGACCCAGAAGGGTGACGCATGGATTCTGCGTT
ACAGGATACTATTCTGTAAGTGAACGTAAGTAGGAAATCAAGTAAGGAGGCAATGTGTCTACTCAATCCAATC
GTAATGCGCTCGTAGTGGCGCAACTGAAAGGAGACTTCGTGGCGTTCCCTATTCGTCTTATGGAAGGCGCTAAAC
CTACCGGTGCCCACTAAGTGTGAGATTGACATGGCTAAGGTGCTGGCGAATGGAGACAACAAGAAGTTCATCTT
ACAGGCTTTCCGTGGTATCGGTAAGTCGTTTATCACATGTGCGTTCTGTTGTGGTCTTATGGAGAGACCCTC
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GACCTGCTGCCATTCCCTATCTGAGTTAAAGCCAAGACCCGGACAGCGTGACTCGGTAATCAGCTTTGATGTAGG
CCCAGCCAATCCTGACCACTCTCCTAGTGTGAAATCAGTAGGTATCACTGGTCAGTTAACTGGTAGCCGTGCTG
ACATTATCATTGCGGATGACGTTGAGATTCCGTCTAACAGCGCAACTATGGGTGCCCCGTGAGAAGCTATGGACT
CTGGTTACAGGAGTTCGCTGCGTTACTTAAACCGCTGCCTTCCTCTCGCGTTATCTACCTTGGTACACCTCAGAC
AGAGATGACTCTCTATAAGGAACCTTGAGGATAACCGTGGGTACACAACCATTTATCTGGCCTGCTCTGTACCCAA
GGACACGTGAAGAGAACCTCTATTACTCACAGCGTCTTGCTCCTATGTTACGCGCTGAGTACGATGAGAACCCT
GAGGCACTTGCTGGGACTCCAACAGACCCAGTGCGCTTTGACCGTGATGACCTGCGCGAGCGTGAGTTGGAATA
CGGTAAGGCTGGCTTTACGCTACAGTTCATGCTTAACCCTAACCTTAGTGATGCCGAGAAGTACCCGCTGAGGC
TTCGTGACGCTATCGTAGCGCCTTAGACTTAGAGAAGGCCCAATGCATTACCAAGTGGCTTCCGAACCGTCAG
AACATCATTGAGGACCTTCCTAACGTTGGCCTTAAGGGTGATGACCTGCATACGTACCACGATTGTTCCAACAA
CTCAGGTCACTACCAACAGAAGATTCTGGTCATTGACCCTAGTGGTCGCGGTAAGGACGAAACAGGTTACGCTG
TGCTGTACACACTGAACGGTTACATCTACCTTATGGAAGCTGGAGGTTTCCGTGATGGCTACTCCGATAAGACC
CTTGAGTTACTCGCTAAGAAGGCAAAGCAATGGGGAGTCCAGACGGTGTCTACGAGAGTAACTTCGGTGACGG
TATGTTCCGTAAGGTATTCAGTCCTATCCTTCTTAAACACCACAACGTGCGATGGAAGAGATTCGTGCCCGTG
GTATGAAAGAGATGCGTATTTGCGATACCCTTGAGCCAGTCATGCAGACTCACCGCCTTGTAATTCGTGATGAG
GTCATTAGGGCCGACTACCAGTCCGCTCGTGACGTAGACGGTAAGCATGACGTTAAGTACTCGTTGTTCTACCA

Figure 10 (CONTD.)

GATGACCCGTATCACTCGTGAGAAAGGCGCTCTGGCTCATGATGACCGATTGGATGCCCTTGCGTTAGGCATTG
AGTATCTCCGTGAGTCCATGCAGTTGGATTCCGTTAAGGTCGAGGGTGAAGTACTTGCTGACTTCCTTGAGGAA
CACATGATGCGTCCTACGGTTGCTGCTACGCATATCATTGAGATGTCTGTGGGAGGAGTTGATGTGTACTCTGA
GGACGATGAGGGTTACGGTACGTCTTTCATTGAGTGGTGATTTATGCATTAGGACTGCATAGGGATGCACTATA
GACCACGGATGGTCAGTTCCTTTAAGTTACTGAAAAGACACGATAAATTAATACGACTCACTATAGGGAGAGGAG
GGACGAAAGGTTACTATATAGATACTGAATGAATACTTATAGAGTGCATAAAGTATGCATAATGGTGTACCTAG
AGTGACCTCTAAGAATGGTGATTATATTGTATTAGTATCACCTTAACTTAAGGACCAACATAAAGGGAGGAGAC
TCATGTTCCGCTTATTGTTGAACCTACTGCGGCATAGAGTCACCTACCGATTTCTTGTGGTACTTTGTGCTGCC
CTTGGGTACGCATCTCTTACTGGAGACCTCAGTTCCTGAGTCTGTGCTTTGCTCTATACTCACTTGTAGCGA
TTAGGGTCTTCCTGACCGACTGATGGCTCACCGAGGGATTGAGCGGTATGATTGCATCACACCACTTCATCCCT
ATAGAGTCAAGTCCTAAGGTATAACCCATAAAGAGCCTCTAATGGTCTATCCTAAGGTCTATACCTAAAGATAGG
CCATCCTATCAGTGTACCTAAAGAGGGTCTTAGAGAGGGCCTATGGAGTTCCTATAGGGTCCTTTAAAATATA
CCATAAAAATCTGAGTGACTATCTCACAGTGTACGGACCTAAAGTTCCCCCATAGGGGGTACCTAAAGCCCAGC
CAATCACCTAAAGTCAACCTTCGGTTGACCTTGAGGGTTCCTAAGGGTTGGGGATGACCCTTGGGTTTGTCTT
TGGGTGTTACCTTGAGTGTCTCTGTGTCCCT

Figure 11

>DLPECO2_Double_lumi Enterobacteria phage T7, complete genome (SEQ ID NO: 2)

TCTCACAGTGTACGGACCTAAAGTTCCCCCATAGGGGGTACCTAAAGCCCAGCCAATCACCTAAAGTCAACCTT
CGGTTGACCTTGAGGGTTCCCTAAGGGTTGGGGATGACCCTTGGGTTTGTCTTTGGGTGTTACCTTGAGTGTCT
CTCTGTGTCCCTATCTGTTACAGTCTCCTAAAGTATCCTCCTAAAGTCACCTCCTAACGTCCATCCTAAAGCCA
ACACCTAAAGCCTACACCTAAAGACCCATCAAGTCAACGCCTATCTTAAAGTTTAAACATAAAAGACCAGACCTA
AAGACCAGACCTAAAGACACTACATAAAAGACCAGACCTAAAGACGCCTTGTTGTTAGCCATAAAAGTGATAACCT
TTAATCATTGTCTTTATTAATACAACCTCACTATAAGGAGAGACAACCTTAAAGAGACTTAAAAGATTAATTTAAA
ATTTATCAAAAAGAGTATTGACTTAAAGTCTAACCTATAGGATACTTACAGCCATCGAGAGGGACACGGCGAAT
AGCCATCCCAATCGACACCGGGGTCAACCGGATAAGTAGACAGCCTGATAAGTCGCACGAAAAACAGGTATTGA
CAACATGAAGTAACATGCAGTAAGATACAAATCGCTAGGTAACACTAGCAGCGTCAACCGGGCGCACAGTGCCT
TCTAGGTGACTTAAAGCGCACCACGGCACATAAGGTGAAACAAAACGGTTGACAACATGAAGTAAACACGGTACG
ATGTACCACATGAAACGACAGTGAGTCACCACACTGAAAGGTGATGCGGTCTAACGAAACCTGACCTAAGACGC
TCTTTAACAATCTGGTAAATAGCTCTTGAGTGCATGACTAGCGGATAACTCAAGGGTATCGCAAGGTGCCCTTT
ATGATATTCACATAAAGTGCACGAGGTAACACAAGATGGCTATGTCTAACATGACTTACAACAACGTTTTTCGA
CCACGCTTACGAAATGCTGAAAGAAAACATCCGTTATGATGACATCCGTGACACTGATGACCTGCACGATGCTA
TTCACATGGCTGCCGATAATGCAGTTCGCGCACTACTACGCTGACATCTTTAGCGTAATGGCAAGTGAGGGCATT
GACCTTGAGTTCGAAGACTCTGGTCTGATGCCTGACACCAAGGACGTAATCCGCATCCTGCAAGCGCGTATCTA
TGAGCAATTAACGATTGACCTCTGGGAAGACGCGAGAAGACTTGCTCAATGAATACTTGAGGGAAGTCGAGGAGT
ACGAGGAGGATGAAGAGTAATGTCTACTACCAACGTGCAATACGGTCTGACCGCTCAAACGTACTTTTTCTATA
GCGACATGGTGCCTGTGGCTTTAACTGGTCACTCGCAATGGCACAGCTCAAAGAAGTGTACGAAAACAACAAG
GCAATAGCTTTAGAATCTGCTGAGTGATAGACTCAAGGTCGCTCCTAGCGAGTGGCCTTTATGATTATCACTTT
ACTTATGAGGGAGTAATGTATATGCTTACTATCGGTCTACTCACCGCTCTAGGTCTAGCTGTAGGTGCATCCTT
TGGGAAGGCTTTAGGTGTAGCTGTAGGTTCTTACTTTACCGCTTGATCATCATAGGAATCATCAAAGGGGCAC
TACGCAAATGATGAAGCACTACGTTATGCCAATCCACACGTCCAACGGGGCAACCGTATGTACACCTGATGGGT
TCGCAATGAAACAACGAATCGAACGCCTTAAGCGTGAACCTCCGCATTAACCGCAAGATTAACAAGATAGGTTCC
GGCTATGACAGAACGCACTGATGGCTTAAAGAAAGGTTATATGCCCAATGGCACACTATACGCTGCAAATCGGC
GAATAGTGAGAACTTGCGGAGAGAACAACCTCGAACGCCGCAAGGACAAGAGAGGGCGGGCTGGCATAGACGAA
AGGAAAAGGTTAAAGCCAAGAACTCGCCGCACTTGAACAGGCACTAGCCAACACACTGAACGCTATCTCATAA
CGAACATAAAGGACACAATGCAATGAACATTACCGACATCATGAACGCTATCGACGCAATCAAAGCACTGCCAA
TCTGTGAACCTTGACAAGCGTCAAGGTATGCTTATCGACTTACTGGTTCGAGATGGTCAACAGCGAGACGTGTGAT
GGCGAGCTAACCGAACTAAATCAGGCACTTGAGCATCAAGATTGGTGGACTACCTTGAAGTGTCTCACGGCTGA
CGCAGGGTTCAAGATGCTCGGTAATGGTCACTTCTCGGCTGCTTATAGTCACCCGCTGCTACCTAACAGAGTGA
TTAAGGTGGGCTTTAAGAAAGAGGATTCAAGGCGAGCCTATACCGCATCTGCGCGATGTATCAGGGTGCCTCT
GGTATCCCTAACGTCTACGATGTACAGCGCCACGCTGGATGCTATACGGTGGTACTTGACGCACTTAAGGATTG
CGAGCGTTTCAACAATGATGCCATTATAAATACGCTGAGATTGCAAGCGACATCATTGATTGCAATTCCGATG
AGCATGATGAGTTAACTGGATGGGATGGTGAGTTTGTGAACTTGTAACTAATCCGCAAGTTCTTTGAGGGC
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ATCATTCTCGCAGAAAGAAAGACGGTGGCGCATTCAGCATCGACCCTGAGGAACCTCATCAAGGAAGTCGAGGAAG
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TTCAAACGTGCAACCGCAAGGCACGTAAAGCACACAAAGCTAAGCGCGAAAGAATGCTTGCTGCGTGGCGATG
GGCTGAACGTCAAGAACGGCGTAACCATGAGGTAGCTGTAGATGTACTAGGAAGAACCAATAACGCTATGCTCT
GGGTCAACATGTTCTCTGGGGACTTTAAGGCGCTTGAGGAACGAATCGCGCTGCACTGGCGTAATGCTGACCGG
ATGGCTATCGCTAATGGTCTTACGCTCAACATTGATAAGCAACTTGACGCAATGTTAATGGGCTGATAGTCTTA
TCTTACAGGTCACTGCGGGTGGCCTGAATAGGTACGATTTACTAACTGGAAGAGGCACTAAATGAACACGATT
AACATCGCTAAGAACGACTTCTCTGACATCGAAGTGGCTGCTATCCCGTTCAACACTCTGGCTGACCATTACGG
TGAGCGTTTGTAGCTCGCGAACAGTTGGCCCTTGAGCATGAGTCTTACGAGATGGGTGAAGCACGCTTCCGCAAGA
TGTTTTGAGCGTCAACTTAAAGCTGGTGAGGTTGCGGATAACGCTGCCGCCAAGCCTCTCATCACTACCCTACTC
CCTAAGATGATTGCACGCATCAACGACTGGTTTGAGGAAGTGAAAGCTAAGCGCGGCAAGCGCCGACAGCCTT
CCAGTTCTGCAAGAAATCAAGCCGGAAGCCGTAGCGTACATCACCATTAAAGACCACTCTGGCTTGCCTAACCA
GTGCTGACAATACAACCGTTTCAGGCTGTAGCAAGCGCAATCGGTGCGGCCATTGAGGACGAGGCTCGCTTCGGT

Figure 11 (CONTD.)

CGTATCCGTGACCTTGAAGCTAAGCACTTCAAGAAAAACGTTGAGGAACAACCTCAACAAGCGCGTAGGGCACGT
CTACAAGAAAGCATTTATGCAAGTTGTGAGGCTGACATGCTCTCTAAGGGTCTACTCGGTGGCGAGGCGTGGT
CTTCGTGGCATAAGGAAGACTCTATTCATGTAGGAGTACGCTGCATCGAGATGCTCATTGAGTCAACCGGAATG
GTTAGCTTACACCGCCAAAATGCTGGCGTAGTAGGTCAAGACTCTGAGACTATCGAACTCGCACCTGAATACGC
TGAGGCTATCGCAACCCGTGCAGGTGCGCTGGCTGGCATCTCTCCGATGTTCCAACCTTGCCTAGTTCCCTCCTA
AGCCGTGGACTGGCATTACTGGTGGTGGCTATTGGGCTAACGGTTCGTCCTCTGGCGCTGGTGGTACTCAC
AGTAAGAAAGCACTGATGCGCTACGAAGACGTTTACATGCCTGAGGTGTACAAAGCGATTAACATTGCGCAAAA
CACCGCATGGAATAAACAAGAAAGTCTAGCGGTGCGCAACGTAATCACCAGTGGAAGCATTGTCCGGTTCG
AGGACATCCCTGCGATTGAGCGTGAAGAACTCCCGATGAAACCGGAAGACATCGACATGAATCCTGAGGCTCTC
ACCGCGTGGAAACGTGCTGCCGCTGCTGTGTACCGCAAGGACAAGGCTCGCAAGTCTCGCCGTATCAGCCTTGA
GTTTCATGCTTGAGCAAGCCAATAAGTTTGTAAACCATAAGGCCATCTGGTTCCCTTACAACATGGACTGGCGCG
GTCGTGTTTACGCTGTGTCAATGTTCAACCCGCAAGGTAACGATATGACCAAAGGACTGCTTACGCTGGCGAAA
GGTAAACCAATCGGTAAGGAAGGTTACTACTGGCTGAAAATCCACGGTGCAAACGTGCGGGTGTGATAAGGT
TCCGTTCCCTGAGCGCATCAAGTTCATTGAGGAAAACACGAGAACATCATGGCTTGCCTAAGTCTCCACTGG
AGAACACTTGGTGGGCTGAGCAAGATTCTCCGTTCTGCTTCCCTTGCCTTCTGCTTTGAGTACGCTGGGGTACAG
CACCACGGCCTGAGCTATAACTGCTCCCTTCCGCTGGCGTTTGACGGGTCTTGCTCTGGCATCCAGCACTTCTC
CGCGATGCTCCGAGATGAGGTAGGTGGTGCAGCGGTTAACTTGCTTCCCTAGTGAAACCGTTTACGGACATCTACG
GGATTGTTGCTAAGAAAGTCAACGAGATTCTACAAGCAGACGCAATCAATGGGACCGATAACGAAGTAGTTACC
GTGACCGATGAGAACACTGGTGAAATCTCTGAGAAAGTCAAGCTGGGCACTAAGGCACTGGCTGGTCAATGGCT
GGCTTACGGTGTTACTCGCAGTGTGACTAAGCGTTCAGTCATGACGCTGGCTTACGGGTCCAAAGAGTTCGGCT
TCCGTCAACAAGTGTGGAAGATACCATTACGCCAGCTATTGATTCCGGCAAGGGTCTGATGTTCACTCAGCCG
AATCAGGCTGCTGGATACATGGCTAAGCTGATTTGGGAATCTGTGAGCGTGACGGTGGTAGCTGCGGTTGAAGC
AATGAACCTGGCTTAAGTCTGCTGCTAAGCTGCTGGCTGCTGAGGTCAAAGATAAGAAGACTGGAGAGATTCTTC
GCAAGCGTTGCGCTGTGCATTGGGTAACCTCTGATGGTTTCCCTGTGTGGCAGGAATACAAGAAGCCTATTTCAG
ACGCGCTTGAACCTGATGTTCCCTCGGTGAGTTCGGCTTACAGCCTACCATTAAACACCAACAAAGATAGCGAGAT
TGATGCACACAAACAGGAGTCTGGTATCGCTCCTAACTTTGTACACAGCCAAGACGGTAGCCACCTTCGTAAGA
CTGTAGTGTGGGCACACGAGAAGTACGGAATCGAATCTTTTGCCTGATTCACGACTCCTTCGGTACCATTCCG
GCTGACGCTGCGAACCTGTTCAAAGCAGTGCGCGAACTATGGTTGACACATATGAGTCTTGTGATGTACTGGC
TGATTTCTACGACCAGTTCGCTGACCAGTTGCACGAGTCTCAATTGGACAAAATGCCAGCACTTCCGGCTAAAG
GTAACCTTGAACCTCCGTGACATCTTAGAGTCGGACTTCGCGTTTCGCGTAACGCCAAATCAATACGACTCACTAT
AGAGGGACAAACTCAAGGTCATTTCGCAAGAGTGGCCTTTATGATTGACCTTCTTCCGGTTAATACGACTCACTA
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ACACTCGAAGATTTTCGTTGGGGACTGGCGACAGACAGCCGGCTACAACCTGGACCAAGTCCCTTGAACAGGGAGG
TGTGTCCAGTTTGTTCAGAATCTCGGGGTGTCCGTAACCTCCGATCCAAAGGATTGTCCTGAGCGGTGAAAATG
GGCTGAAGATCGACATCCATGTCATCATCCCGTATGAAGGTCTGAGCGGCGACCAAATGGGCCAGATCGAAAAA
ATTTTTAAGGTGGTGTACCCTGTGGATGATCATCACTTTAAGGTGATCCTGCACTATGGCACACTGGTAATCGA
CGGGGTACGCCGAACATGATCGACTATTTCCGACGGCCGTATGAAGGCATCGCCGTGTTGACGGCAAAAAGA
TCACTGTAACAGGGACCTGTGGAACGGCAACAAATATCGACGAGCGCTGATCAACCCCGACGGCTCCCTG
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ATATGACCATGATTACGGATTCACTGGCCGTGTTTTTACAACGTCGTGACTGGGAAAACCTGGCGTTACCCAA
CTTAATCGCCTTGACGACATCCCCCTTTCCGCCAGCTGGCGTAATAGCGAAGAGGCCCCGACCGATCGCCCTTC
CCAACAGTTGCGCAGCCTGAATGGCGAATGGAAATTAAAGAATTACTAAGAGAGGACTTTAAGTATGCGTAACT
TCGAAAAGATGACCAACGTTCTAACCCTAATGCTCGTACTTCGAGGCAACCAAGGTGCGAAGTTGAATAAG
ACTAAGCGTGACCGCTCTCACAAGCGTAGCTGGGAGGGTCAGTAAGATGGGACGTTTATATAGTGGTAATCTGG
CAGCATTCAAGGCAGCAACAAACAAGCTGTCCAGTTAGACTTAGCGGTCAATTTATGATGACTGGTATGATGCC
TATACAAGAAAAGATTGCATACGGTTACGTATTGAGGACAGGAGTGGAAACCTGATTGATACTAGCACCTTCTA
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GGAAGTAATACGACTCAGTATAGGGACAATGCTTAAGGTGCTCTCTAGGAGTGGCCTTAGTCATTTAACCAAT
AGGAGATAAACATTATGATGAACATTAAGACTAACCCTTTAAAGCCGTGTCTTTCGTAGAGTCTGCCATTAAAG
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CAATACTGCTAACAGTTACTGGCTCTCTCGTGTATCTAAAACGATTCCGGCACTGGAGCACTTAAACGGGTTTG
ATGTTGCTGGAAGCGTCTACTGAACGATGACCGTTGCTTCTACAAAGATGGCTTTATGCTTGATGGGGAACCTC
ATGGTCAAGGGCGTAGACTTTAACACAGGGTCCGGCTACTGCGTACCAAATGGACTGACACGAAGAACCAAGA
GTTCCATGAAGAGTTATTCGTTGAACCAATCCGTAAGAAAGATAAAGTCCCTTTAAGCTGCACACTGGACACC

Figure 11 (CONTD.)

TTCACATAAACTGTACGCTATCCTCCCCTGCACATCGTGGAGTCTGGAGAAGACTGTGATGTCATGACGTTG
CTCATGCAGGAACACGTTAAGAACATGCTGCCTCTGCTACAGGAATACTTCCCTGAAATCGAATGGCAAGCGGC
TGAATCTTACGAGGTCTACGATATGGTAGAACTACAGCAACTGTACGAGCAGAAGCGAGCAGAAGGCCATGAGG
GTCTCATTGTGAAAGACCCGATGTGTATCTATAAGCGCGGTAAGAAATCTGGCTGGTGGAAAATGAAACCTGAG
AACGAAGCTGACGGTATCATTACAGGTCTGGTATGGGGTACAAAAGGTCTGGCTAATGAAGGTAAAGTGATTGG
TTTTGAGGTGCTTCTTGAGAGTGGTCGTTTAGTTAACGCCACGAATATCTCTCGCGCCTTAATGGATGAGTTCA
CTGAGACAGTAAAAGAGGCCACCCTAAGTCAATGGGGATTCTTTAGCCCATACGGTATTGGCGACAACGATGCT
TGTAATTAACCCCTTACGATGGCTGGGCGTGTCAAATTAGCTACATGGAGGAAACACCTGATGGCTCTTTGCG
GCACCCATCGTTCTGAATGTTCCGTGGCACCAGGACAAACCCTCAAGAGAAAATGTAATCACACTGGCTCACCT
TCGGGTGGGCCTTTCTGCGTTTATAAGGAGACACTTTATGTTTAAAGAGTTGGTAAATTCCTTGCGGCTTTGG
CAGCTATCCTGACGCTTGCCTATATTCTTGCGGTATACCCTCAAGTAGCACTAGTAGTAGTTGGCGCTTGTTAC
TTAGCGGCAGTGTGTGCTTGCCTGTGGAGTATAGTTAACTGGTAATACGACTCACTAAAGGAGGTACACACCAT
GATGTACTTAATGCCATTACTCATCGTCATTGTAGGATGCCTTGCGCTCCACTGTAGCGATGATGATATGCCAG
ATGGTCACGCTTAATACGACTCACTAAAGGAGACACTATATGTTTCGACTTCATTACAACAAAAGCGTTAAGAA
TTTCACGGTTCGCCGTGCTGACCGTTCAATCGTATGTGCGAGCGAGCGCCGAGCTAAGATACCTCTTATTGGTA
ACACAGTTCCTTTGGCACCAGCGTCCACATCATTATCACCCGTGGTGACTTTGAGAAAAGCAATAGACAAGAAA
CGTCCGGTTCTTAGTGTGGCAGTGACCCGCTTCCCGTTCGTCGCTCTGTTACTCAAACGAATCAAGGAGGTGTT
CTGATGGGACTGTTAGATGGTGAAGCCTGGGAAAAAGAAAACCCGCCAGTACAAGCAACTGGGTGTATAGCTTG
CTTAGAGAAAGATGACCGTTATCCACACACCTGTAACAAAGGAGCTAACGATATGACCGAACGTGAACAAGAGA
TGATCATTAAGTTGATAGACAATAATGAAGGTCGCCAGATGATTTGAATGGCTGCGGTATTCTCTGCTCCAAT
GTCCCTTGCCACCTCTGCCCCGAAATAACGATCAAAGATAACCTTAGGTGAAATCCGAGCGATGGACCCACG
TAAACCACATCTGAATAAACCTGAGGTAACCTACAGATGACCAGCCTTCCGCTGAGACAATCGAAGGTGTCA
CTAAGCCTTCCCACTACATGCTGTTTGACGACATTGAGGCTATCGAAGTGATTGCTCGTTCAATGACCGTTGAG
CAGTTCAAGGGATACTGCTTCGGTAACATCTTAAAGTACAGACTACGTGCTGGTAAGAAGTCAGAGTTAGCGTA
CTTAGAGAAAGACCTAGCGAAAGCAGACTTCTATAAAGAAGTCTTTGAGAAACATAAGGATAAATGTTATGCAT
AACTTCAAGTCAACCCACCTGCCGACAGCCTATCTGATGACTTCACATCTTGCTCAGAGTGGTGCCGAAAGAT
GTGGGAAGAGACATTCGACGATGCGTACATCAAGCTGTATGAACTTTGGAAATCGAGAGGTCAATGACTATGTC
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TCGAGGTTCCAATCTACGCTGAGACCCTAGACGAAGCTCTGGAGTTAGCCGAATGGCAATACGTTCCGGCTGGC
TTTGAGGTTACTCGTGTGCGTCCTTGTGTAGCACCGAAGTAATACGACTCACTATTAGGGAAGACTCCCTCTGA
GAAACCAAACGAAACCTAAAGGAGATTAACATTATGGCTAAGAAGATTTTCACCTCTGCGCTGGGTACCGCTGA
ACCTTACGCTTACATCGCCAAGCCGGACTACGGCAACGAAGAGCGTGGCTTTGGGAACCCCTCGTGGTGTCTATA
AAGTTGACCTGACTATTCCCAACAAAGACCCGCGCTGCCAGCGTATGGTCGATGAAATCGTGAAGTGTCACGAA
GAGGCTTATGCTGCTGCCGTTGAGGAATACGAAGCTAATCCACCTGCTGTAGCTCGTGGTAAGAAAACCGCTGAA
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CTTTCCAAGACAAGAAGACCAAGAGACCAAGCACATCAATCTGGTTGTGGTTGACTCAAAAAGGTAAGAAGATG
GAAGACGTTCCGATTATCGGTGGTGGCTCTAAGCTGAAAGTTAAATATTCTCTGGTTCCATACAAGTGGAACAC
TGCTGTAGGTGCGAGCGTTAAGCTGCAACTGGAATCCGTGATGCTGGTCGAAGTGGCTACCTTTGGTGGCGGTG
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GACGAAGAAAGCTGGGACGAAGACGACGAAGAGTCCGAGGAAGCAGACGAAGACGGAGACTTCTAAGTGGAAGT
GCGGGAGAAAATCCTTGAGCGAATCAAGGTGACTTCCTCTGGGTGTTGGGAGTGGCAGGGCGCTACGAACAATA
AAGGTTACGGGCAGGTGTGGTGCAGCAATACCGGAAAGGTTGTCTACTGTCATCGCGTAATGTCTAATGCTCCG
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AAAAGAGAACTCCACTGACATGGTAAATAAGGGTTCGCTCACACAAGGGGTATAAACTTTTCCAGACGAAGACGTAA
TGGCAATCATGGAGTCCAGCGAGTCCAATGTATCCTTAGCTCGCACCTATGGTGTCTCCCAACAGACTATTTGT
GATATACGCAAAGGGAGGCGACATGGCAGGTTACGGCGCTAAAGGAATCCGAAAGGTTGGAGCGTTTCGCTCTG
GCCTAGAGGACAAGGTTTCAAAGCAGTTGGAATCAAAGGTATTAAATTCGAGTATGAAGAGTGGAAGTGCCCT
TATGTAATTCCGGCGAGCAATCACACTTACACTCCAGACTTCTTACTTCCAAACGGTATATTCTGTTGAGACAAA
GGGTCTGTGGGAAAGCGATGATAGAAAGAAGCACTTATTAATTAGGGAGCAGCACCCCGAGCTAGACATCCGTA
TTGTCTTCTCAAGCTCACGTACTAAGTTATACAAAGGTTCTCCAACGTCTTATGGAGAGTTCTGCGAAAAGCAT
GGTATTAAGTTTCGCTGATAAACTGATACCTGCTGAGTGGATAAAGGAACCCAAAGAAGGAGGTCCCTTTGATAG
ATTAAGAAAGGAAAGGAGGAAAGAAATAATGGCTCGTGTACAGTTTAAACAACGTGAATCTACTGACGCAATCTT
TGTTCACTGCTCGGCTACCAAGCCAAGTCAGAATGTTGGTGTCCGTGAGATTCGCCAGTGGCACAAGAGCAGG
GTTGGCTCGATGTGGGATACCACTTTATCATCAAGCGAGACGGTACTGTGGAGGCAGGACGAGATGAGATGGCT

Figure 11 (CONTD.)

GTAGGCTCTCACGCTAAGGGTTACAACCACAACCTCTATCGGCGTCTGCCTTGTTGGTGGTATCGACGATAAAGG
TAAGTTCGACGCTAACTTTACGCCAGCCCAAATGCAATCCCTTCGCTCACTGCTTGTCACACTGCTGGCTAAGT
ACGAAGGCGCTGTGCTTCGCGCCCATCATGAGGTGGCGCCGAAGGCTTGCCCTTCGTTGACCTTAAGCGTTGG
TGGGAGAAGAACGAACTGGTCACCTTCTGACCGTGGATAATTAATTGAACTCACTAAAGGGAGACCACAGCGGTT
TCCCTTTGTTGCGATTGGAGGTCAAATAATGCGCAAGTCTTATAAACAATTCTATAAGGCTCCGAGGAGGCATA
TCCAAGTGTGGGAGGCAGCCAATGGGCCTATACCAAAGGTTATTATATAGACCACATTGACGGCAATCCACTC
AACGACGCCTTAGACAATCTCCGTCTGGCTCTCCCAAAAGAAAACCTCATGGAACATGAAGACTCCAAAGAGCAA
TACCTCAGGACTAAAGGGACTGAGTTGGAGCAAGGAAAGGGAGATGTGGAGAGGCACTGTAACAGCTGAGGGTA
AACAGCATAACTTTCGTAGTAGAGATCTATTGGAAGTCGTTGCGTGGATTTATAGAAGTAGGAGGGAATTGCAT
GGACAATTCGCACGATTCCGATAGTGTATTTCTTTACCACATTCTTGTGACAACCTGTGGGAGTAGTGATGGGA
ACTCGCTGTTCTCTGACGGACACACGTTCTGCTACGTATGCGAGAAGTGGACTGCTGGTAATGAAGACACTAAA
GAGAGGGCTTCAAACGGAAACCTCAGGAGGTAAACCAATGACTTACAACGTGTGGAACCTTCGGGAATCCAA
TGGACGCTACTCCGCGTTAACTGCGAGAGGAATCTCCAAGGAAACCTGTCAGAAGGCTGGCTACTGGATTGCCA
AAGTAGACGGTGTGATGTACCAAGTGGCTGACTATCGGGACCAGAACGGCAACATTGTGAGTCAGAAGGTTTCA
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TGGTAAGAAGATTGTCGTTACAGAAGGTGAAATCGACATGCTTACCGTGATGGAACCTTCAAGACTGTAAGTATC
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TTCGAACAGATTATCTTAATGTTTCGATATGGACGAAGCAGGGCGCAAAGCAGTCGAAGAGGCTGCACAGGTTCT
ACCTGCTGGTAAGGTACGAGTGGCAGTCTTCCGTGTAAGGATGCAAACGAGTGTACCTAAATGGTCACGACC
GTGAAATCATGGAGCAAGTGTGGAATGCTGGTCTTGGATTCTTGATGGTGTGGTATCGGCTCTTTCGTTACGT
GAACGAATCCGTGAGCACCTATCGTCCGAGGAATCAGTAGGTTTACTTTTCAGTGGCTGCACTGGTATCAACGA
TAAGACCTTAGGTGCCCCTGGTGGTGAAGTCATTATGGTCACCTCCGCTTCCGGTATGGGTAAGTCAACGTTTCG
TCCGTCAACAAGCTCTACAATGGGGCACAGCGATGGGCAAGAAGGTAGGCTTAGCGATGCTTGAGGAGTCCGTT
GAGGAGACCGCTGAGGACCTTATAGGTCTACACAACCGTGTCCGACTGAGACAATCCGACTCACTAAAGAGAGA
GATTATTGAGAACGGTAAGTTCGACCAATGGTTCGATGAACTGTTTCGGCAACGATACGTTCCATCTATATGACT
CATTCGCCGAGGCTGAGACGGATAGACTGCTCGCTAAGCTGGCCTACATGCGCTCAGGCTTGGGCTGTGACGTA
ATCATTCTAGACCACATCTCAATCGTCGTATCCGCTTCTGGTGAATCCGATGAGCGTAAGATGATTGACAACCT
GATGACCAAGCTCAAAGGGTTTCGCTAAGTCAACTGGGGTGGTGCTGGTTCGTAATTTGTACCTTAAGAACCCAG
ACAAAGGTAAAGCACATGAGGAAGGTGCCCCGTTTCTATTACTGACCTACGTGGTTCTGGCGCACTACGCCAA
CTATCTGATACTATTATTGCCCTTGAGCGTAATCAGCAAGGCGATATGCCTAACCTTGTCTCGTTCTGATTCT
CAAGTGCCGCTTTACTGGTGATACTGGTATCGCTGGCTACATGGAATACAACAAGGAAACCGGATGGCTTGAAC
CATCAAGTTACTCAGGGGAAGAAGAGTCACACTCAGAGTCAACAGACTGGTCCAACGACACTGACTTCTGACAG
GATTCTTGATGACTTTCCAGACGACTACGAGAAGTTTCGCTGGAGAGTCCCATTCTAATACGACTCACTAAAGG
AGACACACCATGTTCAAACCTGATTAAGAAGTTAGGCCAACTGCTGGTTCGTATGTACAACGTGGAAGCCAAGCG
ACTGAACGATGAGGCTCGTAAAGAGGCCACACAGTCACGCGCTCTGGCGATTTCGCTCCAACGAACTGGCTGACA
GTGCATCCACTAAAGTTACCGAGGCTGCCCCGTGTGGCAAACCAAGCTCAACAGCTTTCCAAATCTTTGAGTAA
TCAAACAGGAGAAAACCATATGTCTAACGTAGCTGAACTATCCGTCTATCCGATACAGCTGACCAGTGAACCC
GTCGAGTCCACATCAACGTTTCGCAACGGTAAGGCGACTATGGTTTACCGCTGGAAGGACTCTAAGTCTCTAAG
AATCACACTCAGCGTATGACGTTGACAGATGAGCAAGCACTGCGTCTGGTCAATGCGCTTACCAAAGCTGCCGT
GACAGCAATTCATGAAGCTGGTCGCGTCAATGAAGCTATGGCTATCCTCGACAAGATTGATAACTAAGAGTGGT
ATCCTCAAGGTCGCCAAAGTGGTGGCCTTCATGAATACTATTGCACTCACTATAGGAGATATTACCATGCGTGA
CCCTAAAGTTATCCAAGCAGAAATCGCTAAACTGGAAGCTGAACTGGAGGACGTTAAGTACCATGAAGCTAAGA
CTCGCTCCGCTGTTACATCTTGAAGAACTTAGGCTGGACTTGGACAAGACAGACTGGCTGGAAGAAACCAGAA
GTTACCAAGCTGAGTCATAAGGTGTTGATAAGGACACTATGACCCACATCAAGGCTGGTGAATTGGGTTAAGGT
TGACATGGGAGTTGTTGGTGGATACGGCTACGTCGCTCAGTTAGTGGCAAATATGCACAAGTGTACATACATCA
CAGGTGTTACTCCACGCGGTGCAATCGTTGCCGATAAGACCAACATGATTCACACAGGTTTCTTGACAGTTGTT
TCATATGAAGAGATTGTTAAGTCACGATAATCAATAGGAGAAATCAATATGATCGTTTCTGACATCGAAGCTAA
CGCCCTCTTAGAGAGCGTCACTAAGTTCCACTGCGGGGTTATCTACGACTACTCCACCGCTGAGTACGTAAGCT
ACCGTCCGAGTGACTTCGGTGCATCTGATGACCAAACCTGGCAAAGTTGCAATTGAACCGAGAGTTCCACCT
TCCTCGTGAGAACTGTATTGACACCCTTGTGTTGTACGTTTGATTCAATCCAACCTCAAGGACACCGATATGG
GTCTTCTGCGTTCCGGCAAGTTGCCCCGAAAACGCTTTGGGTCTCACGCTTTGGAGGCGTGGGGTTATCGCTTA
GGCGAGATGAAGGGTGAATACAAAGACGACTTTAAGCGTATGCTTGAAGAGCAGGCTGAAGAATACGTTGACGG
AATGGAGTGGTGAACCTTCAACGAAGAGATGATGGACTATAACGTTTCAAGGACGTTGTGGTAACCTAAAGCTCTCC

Figure 11 (CONTD.)

TTGAGAAGCTACTCTCTGACAAACATTACTTCCCTCCTGAGATTGACTTTACGGACGTAGGATACACTACGTTCTGGTGCAGAATCCCTTGAGGCCGTTGACATTGAACATCGTGCTGCATGGCTGCTCGCTAAACAAGAGCGCAACGGGTTCCCGTTTGACACAAAAGCAATCGAAGAGTTGTACGTAGAGTTAGCTGCTCGCCGCTCTGAGTTGCTCCGTA AATTGACCGAAACGTTTCGGCTCGTGGTATCAGCCTAAAGGTGGCACTGAGATGTTCTGCCATCCGCGAACAGGT AAGCCACTACCTAAATACCCTCGCATTAAAGACACCTAAAGTTGGTGGTATCTTTAAGAAGCCTAAGAACAAGGC ACAGCGAGAAGGCCGTGAGCCTTGCGAACTTGATACCCGCGAGTACGTTGCTGGTGTCTCTTACACCCCAGTTG AACATGTTGTGTTAACCCTTCGTCTCGTGACCACATTGAGAAGAACTCCAAGAGGCTGGGTGGGTCGCGACC AAGTACACCGATAAGGGTGTCTGTGGTGGACGATGAGGTACTCGAAGGAGTACGTGTAGATGACCCTGAGAA GCAAGCCGCTATCGACCTCATTAAAGAGTACTTGATGATTGAGAAGCGAATCGGACAGTCTGCTGAGGGAGACA AAGCATGGCTTCGTTATGTTGCTGAGGATGGTAAGATTGATGGTTCTGTTAACCCTAATGGAGCAGTTACGGGT CGTGCGACCCATGCGTTCCCAAACCTTGCGCAAATTCGGGTGTACGTTCTCCTTATGGAGAGCAGTGTGCGGC TGCTTTTGGCGCTGAGCACCATTGGATGGGATAACTGGTAAGCCTTGGGTTTCAGGCTGGCATCGACGCATCCG GTCTTGAGCTACGCTGCTTGGCTCACTTCATGGCTCGCTTTGATAACGGCGAGTACGCTCACGAGATTCTTAAC GCGCAGATCCACACTAAGAACCAGATAGCTGCTGAACCTACCTACCCGAGATAACGCTAAGACGTTTCATCTATGG GTTCTCTATGGTGTGGTGTGATGAGAAGATTGGACAGATTGTTGGTGTGGTAAAGAGCGCGGTAAGGAACTCA AGAAGAAATTCCTTGAGAACACCCCCGCGATTGCAGCACTCCGCGAGTCTATCCAACAGACACTTGTCGAGTCC TCTCAATGGGTAGCTGGTGAGCAACAAGTCAAGTGGAACGCCGCTGGATTAAAGGTCTGGATGGTCGTAAGGT ACACGTTTCGTAGTCTCACGCTGCCTTGAATACCCTACTGCAATCTGCTGGTGTCTCATCTGCAAACGTGTGGA TTATCAAGACCGAAGAGATGCTCGTAGAGAAAAGGCTTGAAGCATGGCTGGGATGGGGACTTTGCGTACATGGCA TGGGTACATGATGAAATCCAAGTAGGCTGCCGTACCGAAGAGATTGCTCAGGTGGTCATTGAGACCGCACAAGA AGCGATGCGCTGGTTGGAGACCACTGGAACCTCCGGTGTCTTCTGGATACCGAAGGTAAGATGGTCCCTAATT GGGCGATTTGCCACTGATACAGGAGGCTACTCATGAACGAAAGACACTTAACAGGTGCTGCTTCTGAAATGCTA GTAGCCTACAAATTTACCAAAGCTGGGTACACTGTCTATTACCCTATGCTGACTCAGAGTAAAGAGGACTTGGT TGTATGTAAGGATGGTAAATTTAGTAAGGTTTCAGGTTAAACAGCCACAACGGTTCAAACCAACACAGGAGATG CCAAGCAGGTTAGGCTAGGTGGATGCGGTAGGTCCGAATATAAGGATGGAGACTTTGACATTCTTGCGGTTGTG GTTGACGAAGATGTGCTTATTTTACATGGGACGAAGTAAAAGGTAAGACATCCATGTGTGTGCGGCAAGAGAAA CAAAGGCATAAAACTATAGGAGAAATTATTATGGCTATGACAAAGAAATTTAAAGTGTCTTCGACGTTACCGC AAAGATGTGCTCTGACGTTTCAGGCAATCTTAGAGAAAGATATGCTGCATCTATGTAAGCAGGTTCGGCTCAGGTG CGATTGTCCCCAATGGTAAACAGAAGGAAATGATTGTCCAGTTCTTGACACACGGTATGGAAGGATTGATGACA TTCGTAGTACGTACATCATTTTCGTGAGGCCATTAAGGACATGCACGAAGAGTATGCAGATAAGGACTCTTTCAA ACAATCTCCTGCAACAGTACGGGAGGTGTTCTGATGTCTGACTACCTGAAAGTGCTGCAAGCAATCAAAAGTTG CCCTAAGACTTTCCAGTCCAACCTATGTACGGAACAATGCGAGCCTCGTAGCGGAGGCCGCTTCCCGTGGTCACA TCTCGTGCTGACTACTAGTGGACGTAACGGTGGCGCTTGGGAAATCACTGCTTCCGGTACTCGCTTTCTGAAA CGAATGGGAGGATGTGTCTAATGTCTCGTGACCTTGTGACTATTCCACGCGATGTGTGGAACGATATACAGGGC TACATCGACTCTCTGGAACGTGAGAACGATAGCCTTAAGAATCAACTAATGGAAGCTGACGAATACGTAGCGGA ACTAGAGGAGAACTTAATGGCACTTCTTGACCTTAACAATTTCTATGAGTTACGTGAAGGCTGCGACGACAAG GGTATCCTTGTGATGGACGGCGACTGGCTGGTCTTCCAAGCTATGAGTGCTGCTGAGTTTGATGCCTCTTGGGA GGAAGAGATTTGGCACCAGTGTGTGACCACGCTAAGGCCCGTCAGATTCTTGAGGATTCCATTAAGTCCTACG AGACCCGTAAGAAGGCTTGGGCAGGTGCTCCAATTGTCTTGCCTTACCGATAGTGTTAACTGGCGTAAAGAA CTGGTTGACCCGAACTATAAGGCTAACCGTAAGGCCGTGAAGAAACCTGTAGGGTACTTTGAGTTCCCTTGATGC TCTCTTTGAGCGCGAAGAGTTCTATTGCATCCGTGAGCCTATGCTTGAGGGTGATGACGTTATGGGAGTTATTG CTTCCAATCCGTCTGCCTTCGGTGTCTGTAAGGCTGTAATCATCTCTTGCATAAGGACTTTAAGACCATCCCT AACTGTGACTTCTGTGGTGTACCACTGGTAACATCCTGACTCAGACCGAAGAGTCCGCTGACTGGTGGCACCT CTTCCAGACCATCAAGGTTGACATCACTGATGGTTACTCAGGGATTGCTGGATGGGGTGATACCGCCGAGGACT TCTTGAATAACCCGTTTATAACCGAGCCTAAAACGTCTGTGCTTAAAGTCCGGTAAGAACAAAGGCCAAGAGGTT ACTAAATGGGTAAACGCGACCCCTGAGCCTCATGAGACGCTTTGGGACTGCATTAAGTCCATTGGCGCGAAGGC TGGTATGACCGAAGAGGATATTATCAAGCAGGGCCAAATGGCTCGAATCCTACGGTTCAACGAGTACAACCTTA TTGACAAGGAGATTTACCTGTGGAGACCGTAGCGTATATTGGTCTGGGTCTTTGTGTTCTCGGAGTGTGCCTCA TTTCTGTTGGGCTTTGGGACTTAGCCAGAATAATCAAGTCGTTACACGACACTAAGTGATAAACTCAAGGTCCC TAAATTAATACGACTCACTATAGGGAGATAGGGGCCCTTACGATTATTACTTTAAGATTTAACTCTAAGAGGAA TCTTTATTATGTTAACACCTATTAAACCAATTACTTAAGAACCCTAACGATATTCCAGATGTACCTCGTGCAACC GCTGAGTATCTACAGGTTTCGATTCAACTATGCGTACCTCGAAGCGTCTGGTCATATAGGACTTATGCGTGCTAA TGGTTGTAGTGAGGCCACATCTTGGGTTTCATTGAGGCCCTACAGTATGCCTCTAACGTCATTGACGAGATTG AGTTACGCAAGGAACAACCTAAGAGATGATGGGGAGGATTGACACTATGTGTTTCTCACCAGAAATTAACCTCC

Figure 11 (CONTD.)

GAAGATGGATACCAATCAGATTCGAGCCGTTGAGCCAGCGCCTCTGACCCAAGAAGTGTCAAGCGTGGAGTTCTG
GTGGGTCTTCTGATGAGACGGATACCGAGGGCACC GAAGTGTCTGGACGCAAAGGCCTCAAGGTGCAACGTGAT
GATTCCGTAGCGAAGTCTAAAGCCAGCGGCAATGGCTCCGCTCGTATGAAATCTTCCATCCGTAAAGTCCGCATT
TGGAGGTAAGAAGTGATGTCTGAGTTCACATGTGTGGAGGCTAAGAGTCGCTTCCGTGCAATCCGGTGGACTGT
GGAACACCTTGGGTTGCCCTAAAGGATTCTGAAGGACACTTTGTGGGCTACAGCCTCTACGTAGACGAAGTGATGG
ACATGTCTGGTTGCCGTGAAGAGTACATTCTGGACTCTACCGGAAAACATGTAGCGTACTTTCGCGTGGTGCGTA
AGCTGTGACATTACCCACAAAGGAGACATTCTGGATGTAACGTCCGTTGTCATTAATCCTGAGGCAGACTCTAA
GGGCTTACAGCGATTCCCTAGCGAAACGCTTTAAGTACCTTGCAGAACTCCACGATTGCGATTGGGTGTCTCGTT
GTAAGCATGAAGGCGAGACAATGCGTGTATACTTTAAGGAGGTATAAGTTATGGGTAAGAAAGTTAAGAAGGCC
GTGAAGAAAGTCACCAAGTCCGTTAAGAAAGTCGTTAAGGAAGGGGCTCGTCCGGTTAAACAGGTTGCTGGCGG
TCTAGCTGGTCTGGCTGGTGGTACTGGTGAAGCACAGATGGTGGAAGTACCACAAGCTGCCGCACAGATTGTTG
ACGTACCTGAGAAAGAGGTTTCCACTGAGGACGAAGCACAGACAGAAAGCGGACGCAAGAAAGCTCGTGCTGGC
GGTAAGAAATCCTTGAGTGTAGCCCGTAGCTCCGGTGGCGGTATCAACATTTAATCAGGAGGTTATCGTGGAAG
ACTGCATTGAATGGACCGGAGGTGTCAACTCTAAGGGTTATGGTCGTAAGTGGGTAAATGGTAAACTTGTGACT
CCACATAGGCACATCTATGAGGAGACATATGGTCCAGTTCACACAGGAATTGTGGTGATGCATATCTGCGATAA
CCCTAGGTGCTATAACATAAAGCACCTTACGCTTGGAACTCCAAAGGATAATTCCGAGGACATGGTTACCAAAG
GTAGACAGGCTAAAGGAGAGGAACCTAAGCAAGAACTTACAGAGTCAGACGTTCTCGCTATACGCTCTTCAACC
TTAAGCCACCGCTCCTTAGGAGAAGTGTATGGAGTCAGTCAATCAACCATAACGCGAATACTACAGCGTAAGAC
ATGGAGACACATTTAATGGCTGAGAAACGAACAGGACTTGCAGGAGGATGGCGCAAAGTCTGTCTATGAGCGTTT
AAAGAACGACCGTGCTCCCTATGAGACACGCGCTCAGAATTGCGCTCAATATAACCATCCCATCATTTGTTCCCTA
AGGACTCCGATAACGCCTCTACAGATTATCAAACCTCCGTGGCAAGCCGTGGGCGCTCGTGGTCTGAACAATCTA
GCCTCTAAGCTCATGCTGGCTCTATTCCCTATGCAGACTTGGATGCGACTTACTATATCTGAATATGAAGCAAA
GCAGTTACTGAGCGACCCCGATGGACTCGCTAAGGTGCGATGAGGGCCCTCTCGATGGTAGAGCGTATCATCATGA
ACTACATTGAGTCTAACAGTTACCGCGTGACTCTCTTTGAGGCTCTCAAACAGTTAGTCGTAGCTGGTAACGTC
CTGCTGTACCTACCGGAACCGGAAGGGTCAAACCTATAATCCCATGAAGCTGTACCGATTGTCTTCTTATGTGGT
CCAACGAGACGCATTCCGCAACGTTCTGCAAATGGTGACTCGTGACCAGATAGCTTTTGGTGCTCTCCCTGAGG
ACATCCGTAAGGCTGTAGAAGGTCAAGGTGGTGAGAAGAAAGCTGATGAGACAATCGACGTGTACACTCACATC
TATCTGGATGAGGACTCAGGTGAATACCTCCGATACGAAGAGGTGAGGGTATGGAAGTCCAAGGCTCCGATGG
GACTTATCCTAAAGAGGCTTGCCCATACATCCCGATTCCGGATGGTCAGACTAGATGGTGAATCCTACGGTCTGTT
CGTACATTGAGGAATACTTAGGTGACTTACGGTCCCTTGAAAATCTCCAAGAGGCTATCGTCAAGATGTCCATG
ATTAGCTCTAAGGTTATCGGCTTAGTGAATCCTGCTGGTATCACCCAGCCACGCCGACTGACCAAAGCTCAGAC
TGGTGACTTCGTTACTGGTTCGTCAGAAAGACATCTCGTTCCCTCCAACCTGGAGAAGCAAGCAGACTTTACTGTAG
CTAAAGCCGTAAGTGACGCTATCGAGGCTCGCCTTTGCTTTGCCTTTATGTTGAACTCTGCGGTTTCAGCGTACA
GGTGAACGTGTGACCGCCGAAGAGATTCCGTATGTAGCTTCTGAACTTGAAGATACTTTAGGTGGTGTCTACTC
TATCCTTTCTCAAGAATTACAATTGCCTCTGGTACGAGTGCTCTTGAAGCAACTACAAGCCACGCAACAGATTC
CTGAGTTACCTAAGGAAGCCGTAGAGCCAACCATTAGTACAGGTCTGGAAGCAATTGGTCGAGGACAAGACCTT
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AACAGAAGATGGCCCAACAGTCTATGCAAATGGGTATGGATAATGGTGCTGCTGCGCTGGCTCAAGGTATGGCT
GCACAAGCTACAGCTTCACCTGAGGCTATGGCTGCTGCCGCTGATTCCGTAGGTTTACAGCCGGGAATTTAATA
CGACTCACTATAGGGAGACCTCATCTTTGAAATGAGCGATGACAAGAGGTTGGAGTCCTCGGTCTTCCCTGTAGT
TCAACTTTAAGGAGACAATAATAATGGCTGAATCTAATGCAGACGTATATGCATCTTTTGGCGTGAACCTCCGCT
GTGATGTCTGGTGGTTCCGTTGAGGAACATGAGCAGAACATGCTGGCTCTTGATGTTGCTGCCCCGTGATGGCGA
TGATGCAATCGAGTTAGCGTCAGACGAAGTGGAACAGAAGCTGACCTGTATGACAACCTTGACCCGTTCCGGTC
AAGAGGATGACGAAGGCCGCATTACAGGTTTCGTATCGGTGATGGCTCTGAGCCGACCGATGTGGACACTGGAGAA
GAAGGCGTTGAGGGCACC GAAGGTTCCGAAGAGTTTACCCCACTGGGCGAGACTCCAGAAGAACTGGTAGCTGC
CTCTGAGCAACTTGGTGAGCACGAAGAGGGCTTCCAAGAGATGATTAACATTGCTGCTGAGCGTGGCATGAGTG
TCGAGACCATTGAGGCTATCCAGCGTGAGTACGAGGAGAACGAAGAGTTGTCCGCCGAGTCTACGCTAAGCTG
GCTGAAATTGGCTACACGAAGGCTTTTCAATTGACTCGTATATCCGTGGTCAAGAAGCTCTGGTGGAGCAGTACGT
AAACAGTGTCAATTGAGTACGCTGGTGGTCTGTAACGTTTTGATGCACTGTATAACCACCTTGAGACGCACAACC
CTGAGGCTGCACAGTCGCTGGATAATGCGTTGACCAATCGTGACTTAGCGACCGTTAAGGCTATCATCAACTTG
GCTGGTGAGTCTCGCGCTAAGGCGTTCCGGTCGTAAGCCAACCTCGTAGTGTGACTAATCGTGCTATTCGGGCTAA
ACCTCAGGCTACCAAGCGTGAAGGCTTTGCGGACCGTAGCGAGATGATTAAAGCTATGAGTGACCCCTCGGTATC
GCACAGATGCCAACTATCGTCGTCAAGTCGAACAGAAAGTAATCGATTGCAACTTCTGATAGACTTCGAAATTA

Figure 11 (CONTD.)

ATACGACTCACTATAGGGAGACCACAACGGTTTCCCTCTAGAAATAATTTTGTTTAACTTTAAGAAGGAGATAT
ACATATGGAGGAGATTCAACATGGTCTTCACACTCGAAGATTTTCGTTGGGGACTGGCGACAGACAGCCGGCTAC
AACCTGGACCAAGTCCTTGAACAGGGAGGTGTGTCCAGTTTGTTCAGAATCTCGGGGTGTCCGTAACCTCCGAT
CCAAAGGATTGTCTGAGCGGTGAAAATGGGCTGAAGATCGACATCCATGTCATCATCCCCTATGAAGGTCTGA
GCGGCGACCAAATGGGCCAGATCGAAAAAATTTTTAAGGTGGTGTACCCTGTGGATGATCATCACTTTAAGGTG
ATCCTGCACTATGGCACACTGGTAATCGACGGGGTTACGCCGAACATGATCGACTATTTTCGGACGGCCGTATGA
AGGCATCGCCGTGTTTCGACGGCAAAAAGATCACTGTAACAGGGACCCTGTGGAACGGCAACAAAATTATCGACG
AGCGCCTGATCAACCCCGACGGCTCCCTGCTGTTCCGAGTAACCATCAACGGAGTGACCGGCTGGCGGCTGTGC
GAACGCATTCTGGCGTAAAGGAGGTAAACATATGACCATGATTACGGATTCACCTGGCCGTCGTTTACAACGTC
GTGACTGGGAAAACCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCCGACGCTGGCGTAAT
AGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGCATGACTGGTGGAC
AGCAAATGGGTACTAACCAAGGTAAAGGTGTAGTTGCTGCTGGAGATAAACTGGCGTTGTTCTTGAAGGTATTT
GGCGGTGAAGTCCTGACTGCGTTTCGCTCGTACCTCCGTGACCACTTCTCGCCACATGGTACGTTCCATCTCCAG
CGGTAAATCCGCTCAGTTCCCTGTTCTGGGTGCACTCAGGCAGCGTATCTGGCTCCGGGCGAGAACCCTCGACG
ATAAACGTAAGGACATCAAACACACCGAGAAGGTAATCACCATTGACGGTCTCCTGACGGCTGACGTTCTGATT
TATGATATTGAGGACGCGATGAACCACTACGACGTTTCGCTCTGAGTATACCTCTCAGTTGGGTGAATCTCTGGC
GATGGCTGCGGATGGTGCAGTTCTGGCTGAGATTGCCGGTCTGTGTAACGTGGAAAGCAAATATAATGAGAACA
TCGAGGGCTTAGGTACTGCTACCGTAATTGAGACCACTCAGAACAAGGCCGCACTTACCGACCAAGTTGCGCTG
GGTAAGGAGATTATTGCGGCTCTGACTAAGGCTCGTGCGGCTCTGACCAAGAACTATGTTCCGGCTGCTGACCG
TGTGTTCTACTGTGACCCAGATAGCTACTCTGCGATTCTGGCAGCACTGATGCCGAACGCAGCAAACTACGCTG
CTCTGATTGACCCTGAGAAGGGTCTATCCGCAACGTTATGGGCTTTGAGGTTGTAGAAGTTCCGCACCTCACC
GCTGGTGGTCTGGTACCGCTCGTGAGGGCACTACTGGTCAGAAGCACGCTCTCCCTGCCAATAAAGGTGAGGG
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GTGACTTGGCTCTGGAGCGCGCTCGCCGTGCTAACTTCCAAGCGGACCAGATTATCGCTAAGTACGCAATGGGC
CACGGTGGTCTTCGCCCAGAAGCTGCTGGTGCAGTGGTTTTTCAAAGTGGAGTAATGCTGGGGGTGGCCTCAACG
GTCGCTGCTAGTCCCAGAGGGCGAGTGTTACTTCAACAGAAGAAACCTTAACGCCAGCACAGGAGGCCGCACG
CACCCGCGCTGCTAACAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAAC
CCCTTGGGGCTCTAAACGGGTCTTGAGGGGTTTTTTGTGAAAGGAGGAACCTATATGCGCTCATACGATATGA
ACGTTGAGACTGCCGCTGAGTTATCAGCTGTGAACGACATTCTGGCGTCTATCGGTGAACCTCCGGTATCAACG
CTGGAAGGTGACGCTAACGCAGATGCAGCGAACGCTCGGCGTATTCTCAACAAGATTAACCGACAGATTCAATC
TCGTGGATGGACGTTCAACATTGAGGAAGGCATAACGCTACTACCTGATGTTTACTCCAACCTGATTGTATACA
GTGACGACTATTTATCCCTAATGTCTACTTCCGGTCAATCCATCTACGTTAACCGAGGTGGCTATGTGTATGAC
CGAACGAGTCAATCAGACCGCTTTGACTCTGGTATTACTGTGAACATTATTCTGCTCTCCGCGACTACGATGAGAT
GCCTGAGTGCTTCCGTTACTGGATTGTACCAAGGCTTCCCGTCAGTTCAACAACCGATTCTTTGGGGCACCGG
AAGTAGAGGGTGTACTCCAAGAAGAGGAAGATGAGGCTAGACGCTCTGTCATGGAGTATGAGATGGACTACGGT
GGGTACAATATGCTGGATGGAGATGCGTTCACTTCTGGTCTACTGACTCGCTAACATTAATAAAATAAGGAGGCT
CTAATGGCACTCATTAGCCAATCAATCAAGAACTTGAAGGGTGGTATCAGCCAACAGCCTGACATCCTTCGTTA
TCCAGACCAAGGGTCACGCCAAGTTAACGGTTGGTCTTCGGAGACCGAGGGCCTCCAAAAGCGTCCACCTCTTG
TTTTCTTAAATACACTTGGAGACAACGGTGCCTTAGGTCAAGCTCCGTACATCCACCTGATTAAACCGAGATGAG
CACGAACAGTATTACGCTGTGTTCACTGGTAGCGGAATCCGAGTGTTTCGACCTTTCTGGTAACGAGAAGCAAGT
TAGGTATCCTAACGGTTCCAACCTACATCAAGACCGCTAATCCACGTAACGACCTGCGAATGGTTACTGTAGCAG
ACTATACGTTTCATCGTTAACCGTAACGTTGTTGCACAGAAGAACACAAAGTCTGTCAACTTACCGAATTACAAC
CCTAATCAAGACGGATTGATTAACGTTTCGTGGTGGTCACTATGGTAGGGAACCTAATTGTACACATTAACGGTAA
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CTGAAGAGTTAGCCAAGCAGATGCGCACTAACTTGTCTGATTGGACTGTAAATGTAGGGCAAGGGTTCATCCAT
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GGTTGGAACACTGAGGACCAAGTTCTATGGGAAACCATGCCACACGCTCTTGTGCGAGCCGCTGACGGTAATTT
CGACTTCAAGTGGCTTGAAGTGGTCTCCTAAGTCTTGTGGTGACGTTGACACCAACCCCTTGGCCTCTTTTGTG
GTTCAAGTATTAACGATGTGTTCTTCTTCCGTAACCGCTTAGGATTCCCTAGTGGGGAGAACATCATATTGAGT
CGTACAGCCAAATACTTCAACTTCTACCCTGCGTCCATTGCGAACCTTAGTGATGACGACCTATAGACGTAGC
TGTGAGTACCAACCGAATAGCAATCCTTAAGTACGCCGTTCCGTTCTCAGAAGAGTTACTCATCTGGTCCGATG
AAGCACAATTCGTCTGACTGCCTCGGGTACTCTCACATCTAAGTCGGTTGAGTTGAACCTAACGACCCAGTTT

Figure 11 (CONTD.)

GACGTACAGGACCGAGCGAGACCTTTTGGGATTGGGCGTAATGTCTACTTTGCTAGTCCGAGGTCCAGCTTCAC
GTCCATCCACAGGTACTACGCTGTGCAGGATGTCAGTTCCGTTAAGAATGCTGAGGACATTACATCACACGTTT
CTAACTACATCCCTAATGGTGTGTTTCAGTATTTGCGGAAGTGGTACGGAAAACCTTCTGTTCCGTACTATCTCAC
GGGGACCCTAGTAAAATCTTCATGTACAAATTCCTGTACCTGAACGAAGAGTTAAGGCAACAGTCGTGGTCTCA
TTGGGACTTTGGGAAAACGTACAGGTTCTAGCTTGTGAGAGTATCAGCTCAGATATGTATGTGATTCTTCGCA
ATGAGTTCAATACGTTCCCTAGCTAGAATCTCTTTCTACTAAGAACGCCATTGACTTACAGGGAGAACCCTATCGT
GCCTTTTATGGACATGAAGATTGATACACGATTCCCTAGTGGAACATACAACGATGACACATTCACTACCTCTAT
TCATATTCCAACAATTTATGGTGCAAACCTTCGGGAGGGGCAAATCACTGTATTGGAGCCTGATGGTAAGATAA
CCGTGTTTGAGCAACCTACGGCTGGGTGGAATAGCGACCCTTGGCTGAGACTCAGCGGTAACCTGGAGGGACGC
ATGGTGTACATTGGGTTCAACATTAACTTCGTATATGAGTTCTCTAAGTTCCTCATCAAGCAGACTGCCGACGA
CGGTCTACCTCCACGGAAGACATTGGGCGCTTACAGTTACGCCGAGCGTGGGTTAACTACGAGAACTCTGGTA
CGTTTGACATTTATGTTGAGAACCAATCGTCTAACTGGAAGTACACAATGGCTGGTGCCCGATTAGGCTCTAAC
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CACTGTATACATCTTGTGAGATGAGACTACCCCTCTGAACATCATTGGGTGTGGCTGGGAAGGTAACACTACTTAC
GGAGAAGTTCCGGTATTTAATTAAATATTCTCCCTGTGGTGGCTCGAAATTAATACGACTCACTATAGGGAGAA
CAATACGACTACGGGAGGGTTTTCTTATGATGACTATAAGACCTACTAAAAGTACAGACTTTGAGGTATTCACT
CCGGCTCACCATGACATTCTTGAAGCTAAGGCTGCTGGTATTGAGCCGAGTTTCCCTGATGCTTCCGAGTGTGT
CACGTTGAGCCTCTATGGGTTCCCTCTAGCTATCGGTGGTAACGCGGGGACCAGTGCTGGTTCTTACGAGCG
ACCAAGTGTGGCGACTTAGTGGAAGGCTAAGCGAAAGTTCCGTAAGTTAATCATGGAGTATCGCGATAAGATG
CTTGAGAAGTATGATACTCTTTGGAATTACGTATGGGTAGGCAATACGTCCACATTCTGTTTCTCAAGACTAT
CGGTGCGGTATTCCATGAAGAGTACACACGAGATGGTCAATTTCAGTATTTACAATCACGAAAGGAGGATAAC
CATATGTGTTGGGCAGCCGCAATACCTATCGCTATATCTGGCGCTCAGGCTATCAGTGGTCAGAACGCTCAGGC
CAAATGATTGCCGCTCAGACCCTGCTGGTCTGCTCAAGCTATGGAAATCATGAGGCAGACGAACATCCAGA
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ACGAGATTATCCGTAAGCTGACCCCTGAGCAACGTGAGAAAGCTCTCAACAACGGGACCCTTCTGTATCAGGAT
GACCCATACGCTATGGAAGCACTCCGAGTCAAGACTGGTTCGTAACGCTGCGTATCTTGTGGACGATGACGTTAT
GCAGAAGATAAAAAGAGGGTGTCTTCCGTACTCGCGAAGAGATGGAAGAGTATCGCCATAGTCGCCTTCAAGAGG
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CATGAACAGCCGAGTGGAACCTCAACGGTGTCTTCAAGACCCTGATATGCTGCGTCTGTCAGACTCTGCTGACT
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TGACGATGGACATGATGGACAAGCAGGGTATTGACCCTCAGGTTATTCTTGATGCCGACCGACTGACTGTTAAG
CGGTCCAAAGAGCAACGCTTTGAGGATGATAAAGCATTCGAGTCTGCACTGAATGCATCTAAGGCTCCTGAGAT
TGCCCGTATGCCAGCGTCACTGCGCGAATCTGCACGTAAGATTTATGACTCCGTTAAGTATCGCTCGGGGAACG
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Figure 11 (CONTD.)

GGTGATACCGTTGGTGTGATTCCCTAAGAATATGATGCAGGTTAACTCTGACCCGAAATCATGGGAGCAAGGTCG
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CTCCTAAGTTTCATCTACGGACGTAAGGAGTAACATAAGGAGGCCCTAAATGGATAAGTACGATA
AGAACGTACCAAGTGATTATGATGGTCTGTTCCAAAAGGCTGCTGATGCCAACGGGGTCTCTTATGACCTTTTA
CGTAAAGTCGCTTGGACAGAATCACGATTTGTGCCTACAGCAAAATCTAAGACTGGACCATTAGGCATGATGCA
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GCCCTTGGCTACAACCAAGGCGAGGGACGCTTGGGTAATCCACAACCTGAGGCGTACTCTAAGGGAGACTTCGC
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CCACTAAGGAACTTAAGGATGAGATTTTGGCTCTCAAAGCGAAAGCTGAGGGAGACGGTAAGAAGACTGGCGAG
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CTCACTGCGTGCCATCAATGACCTAGGGTCTTCGCTAAGAACGCCTACATGGGTGCTCAGAACATTACGGAGA
TTGCTGGGATGATTGTCACTGGTAACGTTCTGTCTAGGGCATGGTATCCCAATTCTGCGTGATACACTCTAC
AAGTCTAAACCAGTTTCAGCTAAGGAACTCAAGGAACTCCATGCGTCTCTGTTCCGGGAAGGAGGTGGACCAGTT
GATTCCGGCTAAACGTGCTGACATTGTGCAGCGCCTAAGGGAAGCAACTGATACCGGACCTGCCGTGGCGAACA
TCGTAGGGACCTTGAAGTATTCAACACAGGAACTGGCTGCTCGCTCTCCGTGGACTAAGCTACTGAACGGAACC
ACTAACTACCTTCTGGATGCTGCGCGTCAAGGTATGCTTGGGGATGTATTAGTGCCACCCTAACAGGTAAGAC
TACCCGCTGGGAGAAAGAAGGCTTCCTTCGTGGTGCCTCCGTAACCTCCTGAGCAGATGGCTGGCATCAAGTCTC
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CCACGGGCTATGGACTTATGGAGACTGGCTGACAAGGTAGCTGATGAGGCAATGCTGCGTCCACATAAGGTGTC
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TTAACTCTAAGTTCTGCGAACCTTCTATGATGGATACAAGAACAACCGAGCGATTGACGCTGCGCTGAGCATC
ATCACCTCTATGGGTCTCGCTGGTGGTTTCTATGCTATGGCTGCACACGTCAAAGCATAACGCTCTGCCTAAGGA
GAAACGTAAGGAGTACTTGGAGCGTGCACTGGACCCAACCATGATTGCCACGCTGCGTTATCTCGTAGTTCTC

Figure 11 (CONTD.)

AATTGGGTGCTCCTTTGGCTATGGTTGACCTAGTTGGTGGTGT TTTAGGGTTCGAGTCCTCCAAGATGGCTCGC
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CGCTATGGGTTCAAACCTTCTGGAACAGATGCCTTCGGCTGGCTTTGTGGCTAACGTAGGGGCTACCTTAATGA
ATGCTGCTGGCGTGGTCAACTCACCTAATAAAGCAACCGAGCAGGACTTCATGACTGGTCTTATGAACTCCACA
AAAGAGTTAGTACCGAACGACCCATTGACTCAACAGCTTGTGTTGAAGATTTATGAGGCGAACGGTGTAACTT
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TACTTTAAGGAGGTCAAATGGCTAACGTAATTAAAACCGTTTTGACTTACCAGTTAGATGGCTCCAATCGTGAT
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TACGATTAATACAGACTATCGCTTTGCTACACGTACTACTATCTCTCTGACAAAGGCTTGGGGTCCAGCCGATG
GCTACACGACCATCGAGTTACGTGAGTAACCTCCACTACCGACCGATTGGTTGACTTTACGGATGGTTCAATC
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GGATCTCCGCTTCCGCAATATCTGGATTAAGTGTGCCAACAACTCTTGGAACTTCTTCCGTACTGGCCCCGATG
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GCTCCAATTGTTGGGACGGGTGTAGCAGATGTTAGTGCTCGACTGTTCTTTGGGTAAAGCCTTAACGAATGGTT
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CGTCTAACAGCGCAACTATGGGTGCCCCGTGAGAAGCTATGGACTCTGGTTCAGGAGTTCGCTGCGTTACTTAA
CCGCTGCCTTCCCTCTCGCGTTATCTACCTTGGTACACCTCAGACAGAGATGACTCTCTATAAGGAACCTTGAGGA
TAACCGTGGGTACACAACCATTATCTGGCCTGCTCTGTACCCAAGGACACGTGAAGAGAACCTCTATTACTCAC
AGCGTCTTGCTCCTATGTTACGCGCTGAGTACGATGAGAACCCTGAGGCACCTTGCTGGGACTCCAACAGACCCA

Figure 11 (CONTD.)

GTGCGCTTTGACCGTGATGACCTGCGCGAGCGTGAGTTGGAATACGGTAAGGCTGGCTTTACGCTACAGTTCAT
GCTTAACCCTAACCTTAGTGATGCCGAGAAGTACCCGCTGAGGCTTCGTGACGCTATCGTAGCGGCCTTAGACT
TAGAGAAGGCCCAATGCATTACCAGTGGCTTCCGAACCGTCAGAACATCATTGAGGACCTTCCTAACGTTGGC
CTTAAGGGTGATGACCTGCATACGTACCACGATTGTTCCAACAACCTCAGGTCAGTACCAACAGAAGATTCTGGT
CATTGACCCTAGTGGTCGCGGTAAGGACGAAACAGGTTACGCTGTGCTGTACACACTGAACGGTTACATCTACC
TTATGGAAGCTGGAGGTTTCCGTGATGGCTACTCCGATAAGACCCTTGAGTTACTCGCTAAGAAGGCAAAGCAA
TGGGGAGTCCAGACGGTTGTCTACGAGAGTAACCTTCGGTGACGGTATGTTCCGTAAGGTATTCAGTCCTATCCT
TCTTAAACACCACAACCTGTGCGATGGAAGAGATTCTGTCCTGATGAAAGAGATGCGTATTTGCGATACCC
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TGAGTGGTGATTTATGCATTAGGACTGCATAGGGATGCACTATAGACCACGGATGGTCAGTTCTTTAAGTTACT
GAAAAGACACGATAAATTAATACGACTCACTATAGGGAGAGGAGGGACGAAAGGTTACTATATAGATACTGAAT
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ATTAGTATCACCTTAACCTAAGGACCAACATAAAGGGAGGAGACTCATGTTCCGCTTATTGTTGAACCTACTGC
GGCATAGAGTCACCTACCGATTTCTTGTTGTTACTTTGTGCTGCCCTTGGGTACGCATCTCTTACTGGAGACCTC
AGTTCACTGGAGTCTGTCGTTTGTCTATACTCACTTGTAGCGATTAGGGTCTTCCTGACCGACTGATGGCTCA
CCGAGGGATTACAGCGGTATGATTGCATCACACCACTTCATCCCTATAGAGTCAAGTCCTAAGGTATACCCATAA
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TTAGAGAGGGCCTATGGAGTTCCTATAGGGTCCTTTAAAATATACCATAAAAATCTGAGTGACTATCTCACAGT
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CCT

Figure 12

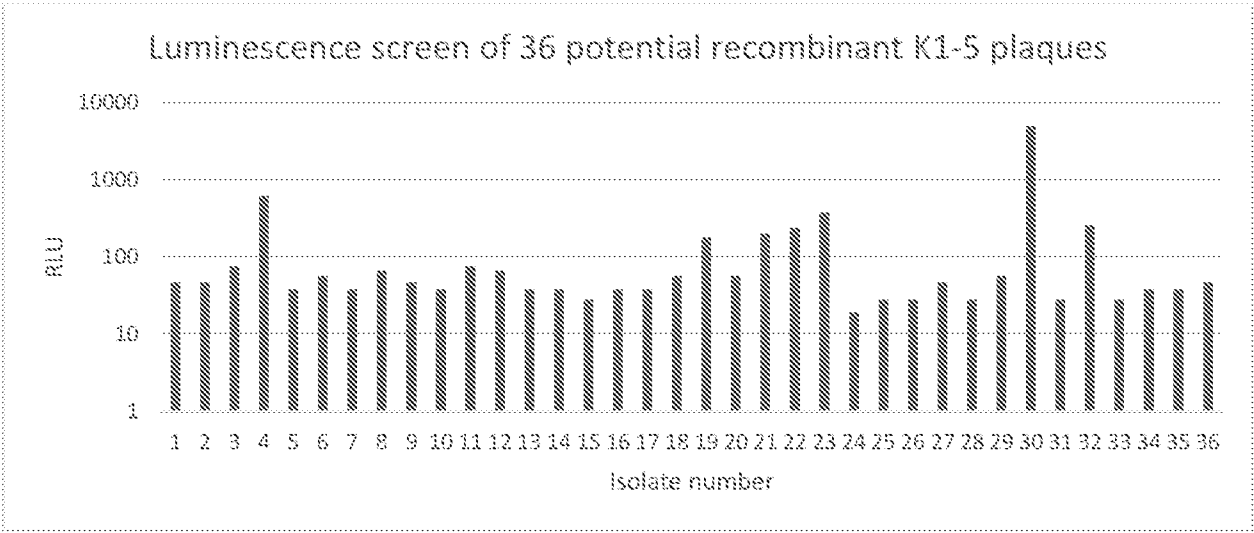


Figure 13

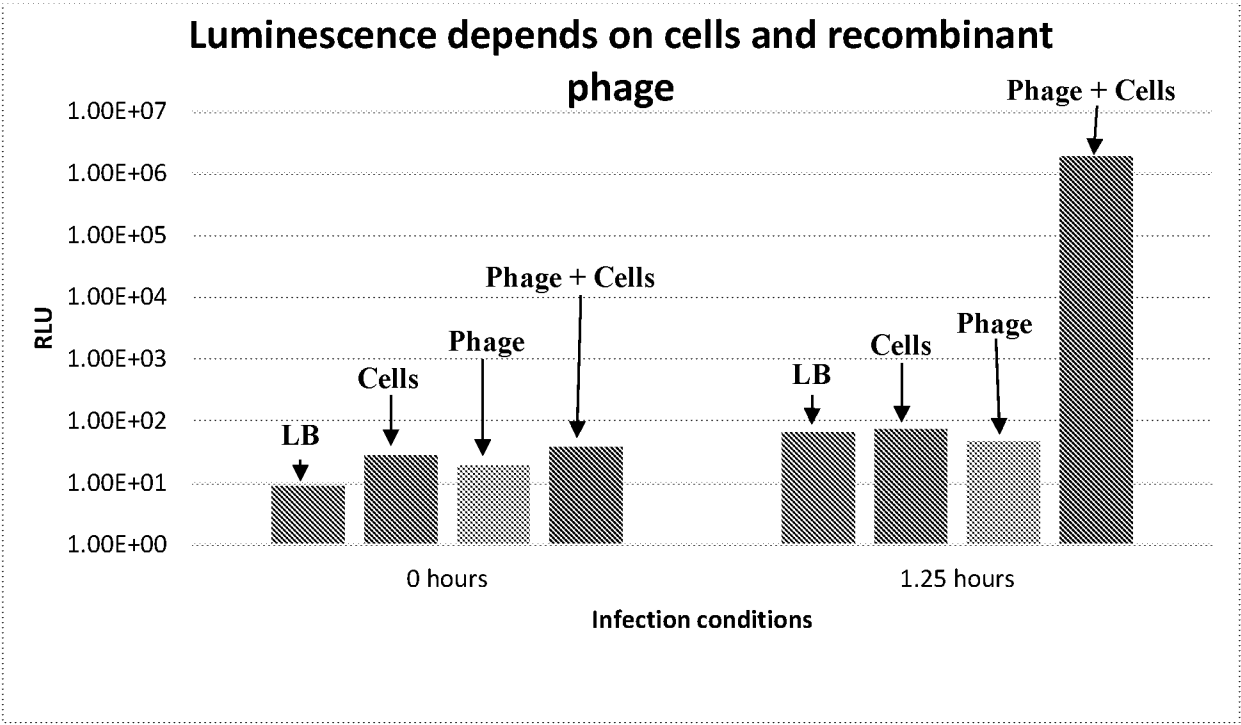


Figure 14

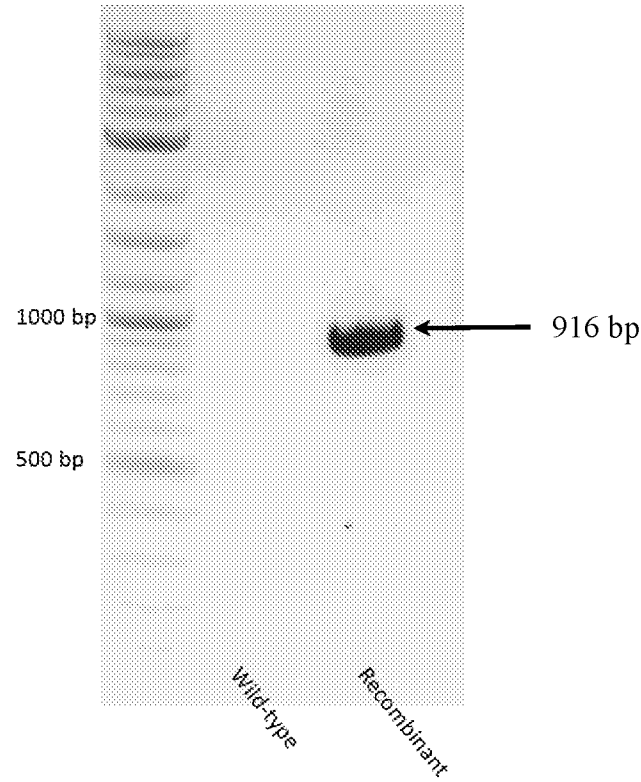


Figure 15

>K1-5 BAR 3.0 Insert DNA (SEQ ID NO: 3)

CAACGTCGTGCCATGAAGAAACCTTCTGCATCTTCTGCGTAAAGAGGAGATATACAATGGTCTTCACACTCGAAGA
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GTTTCAGAATCTCGGGGTGTCCGTAACCTCCGATCCAAAGGATTGTCCTGAGCGGTGAAAATGGGCTGAAGATCGA
CATCCATGTCATCATCCCGTATGAAGGTCTGAGCGGCGACCAAATGGGCCAGATCGAAAAATTTTAAAGGTGGT
GTACCCTGTGGATGATCATCACTTTAAGGTGATCCTGCACTATGGCACACTGGTAATCGACGGGGTTACGCCGAAC
ATGATCGACTATTTTCGGACGGCCGTATGAAGGCATCGCCGTGTTTCGACGGCAAAAAGATCACTGTAACAGGGACC
CTGTGGAACGGCAACAAAATTATCGACGAGCGCCTGATCAACCCCGACGGCTCCCTGCTGTTCCGAGTAACCATCA
ACGGAGTGACCGGCTGGCGGCTGTGCGAACGCATTCTGGCGTAAGCAGGTTAATATCTTAGTATAAACAAGGGCA
GACTTAGGTTTGTCTTAGTGATTCCAAAGGAGGTAACATGCTGAAAGATGGTTGGGTTTCATATGACCCTACAG
ACCCTAAGAATTGGCTACAGGTTATCGCTATAGCTTGTGCAGGTAGCCTATTGGCTGCCCTGATGTATTCATTATGG
ATGTACACAAAGTAACCAAAGTCAAAATTTTGATGTAGGCGTGTGTCAGCTCTCTCGCCCTCGCCCTCGCCGGGTT
GTCCCATAGGGTGGCCTGAGGGAATCCGTCTTCGACGGGCAGGGCTGATGTACTCCTTGTCTAGTACAAGGGAG
GCGGAGGGAACGCCTAGGGAGGCCTAGGAATGGCTTAGTGGTGGACAAGGTGATTACCTTAGTGAAGCCTCTTA
GTGCATTCTGAGGCCATTAGGGCGTTTATGAGGGATTGACAGGGTGTGAGGGCGTGGGCTA

Figure 16

>K1-5 BAR 3.0_(SEQ ID NO:4)

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GGCCATTAGGGCGTTTATGAGGGATTGACAGGGTGTGAGGGCGTGGGCTATCTGTTCTTTGCTCCTCACTTCGTTCTGCTGCGGTAGCC
TGATGTGTACCTTAGGTTATTCCTTGATGGATAGCTTAGGTTAGCCTTAGTGGATTACCTTAGTTAAAGCCTTAGTGCTTCACTTAGTATCAGCT
TAGTAGTGTACCTTAGTAAGTCTTAGTGTCTTCTTAGTGATTGCACATGCAAGCATGTAAGATGCTAATAGGTGCGGGTCGGCAGACCGCT
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GTGCTGAGGCACCTAGTAGCCAGCTAGTAAGGCATACGAAGAGACTAGCGCTTACATTGCTCTTAAACAATTTGCTTAGTGTAACCTATGTAT
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GTCATTACTGAGTATCTAGGCAGTGAAGATTACGATTACGATGAAGTAATCACGACAAATCTCTAAATTAAGTGTGACAGCCACGGCATACA
AGGTTACATTAAGCATCAAGACGGCGACGCTTTAAACATCCCGCTTTTAAACAATACGTTTGTGCTTGATAGGCTAACTAACTAACTAAGG
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GAGGATGCTGGTTTGATTCTGACACGAAGGATGTAACCAAGATTCTACAAGCTCGCATCTATGAAGCTCTTATAATGATGTACCAATGAC
AGCGATGTAGTTTGGTGTGAAGGCGAAGAAGAGGAAGAATAAGGATGGAAGCAATATAACTTTATCTTTTACAGCGGTGAACCCGTGAA
GTGTTCCCTACGATTTCGCACAAATTCGTGAGGAAGTACTAGGCACTACATACAACTATTTAGCTGACACTATAAGAGAAGGCTTAACAAGGC
GTTACTAAGGTAGCGCTGATTAACTTTCCTTACTAGGAGTTGAGATTATGAAAACCTTGATTGGATGCTTCTGTTGGCTTCTCTGCTCT
GGCATTTACCGCTAAAGCTGGTTATGACGCTTATAAAGTGAACAAGCCAGCAAGACTGGGCCAAAAAAAGTTCAACTTGTGCAGCAAGA
GCAACACCTACGAGTACTGCAACAAACACTAAGACACTTATGGAAGAGTAAGTACGCTATAGCCACCTGAGTGGGCTATGTGATATTTAC
TTAACTATATAAGGTGATTACTATGACTACTGAAAACACCCCTCGTGTCTGTCGCTGAAGCTGCAACCGCTGAAATCAAGCAACATTTAGAC
AATATCGGCACCTCTTACATCAAAGTAGGGGCTTGTCTGAATGAGTTACGCGGAGACTTTGAAGGTCAAAAAGAGTTTTTAGCCTATGTTGAA
GCAGAGTTTGCCATTAAGAAGGCACAATGTTACAAGCTGATGAGTGTAGCCGTGTCTTTGAAGGCGATGATCGCTTTAAAGGCGTGGCGAT
GCGTGTAATGCTGGCGCTTGTCTTTCGCTGATGAAAATATAATCATGGAGAAGGCCGAGAACTCGCCGCAATGGCAAGCTGGACACTA
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Figure 16 (CONTD.)

CTGGATAGTGAATTTCAAGACATGTGCCGCGACATTGCAGCGGATCCGCTGACCTTCACTCAATGGGTAAATGCCGACTCCCCTTACGGCTTC
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GGACCTCATAAATGCTATGCAGTTGTAGCACCAATGGTGTTAAGCCTTATCGTACTTCAAAAAGATTGGCATTAAATAGGTGCTAGTAGT
GCAAGTTTCCAAATGGAACCTTTTGGTCATTGGACTGAAAGGCCAATTCGGTGAGGATTAAAGTCAATGGCAGTTTCAAGTCAATGTTGAAATGCA
GAATAAACATAAGTCTAGAATGTTCTGATGGTCATGAAACCTGCAAGGCCAAGATTACTAACCAAGCCTTCTGTTCCGACAGTTAACTATGGC
TGAGGCTAAGAAGAATAGTCTCACTCGTGAACAGGTTATCAAGGAGGCCATTTGGGAACCAACCAAGGTAATATATGGGACCAAAATTA
CTGTAACACGCAAGTCGATAAGTCAAGGGTTGTCCAACGTGTTGGACAGCCTTTCATCATATTGATTGGGAGGTATTAATGACTAAGTTTACT
ATGCAAGACCTCATTAATTAACGTGATGAAATAGAAATCACCGGAAGTTAATACAGAGTTTCACTACATTGATCCACGAGATAAACGAGAGATT

Figure 16 (CONTD.)

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CATTGCTCAGGTTGAAGAGGAAGGTCTGTCTATGACAGGTCACATTACCTTCGACAAGCTGACCAAGAAATCCTTGATGACATCCCAGCCAA
CTTGGTGGTCAATACTTCTGAACGAGACGCTCGTGGTAAGAACCTGTCTGTTGCTGTTCTCACGTAGAAGCAATCATTAAAGCTGCTCG
TGAAGAAGACCCAGAATGGAAGAAGGCTAAGAAGAAAGACGAGGAAGATGCTACCCAGCTAATCGTAAATCTCTGGATACTGGTGAGTCT
GTTCCACAGGAAGTACCTGAAGCAGAAGATACTCTGCACCGGAGATGGATGAGGACGCGGAATATTAAGGAGAAAAGGATGAAAGTACAA
ATCGTAACCCCTGCACTGAAGAAAGGAATTACAACCTTGGCGGCAACACTTTTCACTCCTTCTGAAGGGGACACATATGCCGACCTGCAC
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Figure 16 (CONTD.)

TTGAGTCTTTCATTATCGTCGATGAAACTGATCAACTGGTAGCTGGTACTAAGGCTTACGATACCCGTGAAGAAGCTCAGGCTAAGATTGACA
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GTGACCGTGTGAACCTCTTGCTTAACCTCTGGGTGTATGCAGCAGAATGTGATGCAGCTAAGTTGTTTCATGACGAAATCAGAAGCTAAGTCC
GTGTCCGCTAGCATTACCAAGCCTTATAAAGGTCAACGTAAAGCCGAGAAGCCTCCATTCTTCTATGAATTGCGAGAGCATCTCTTAGAGG
TTCACGGTGCAATCTTGGCAGATGGAGAGGAAGCAGATGACCTCATGAGTATCGACAATGGGACAGCCACCGCGCTTCCAGCAAGATACA
GGTAACGAGTTCCTATCGGTAGTCCAGAGCATAAAGCATTCTCTGATACTTGTCATCGTTTCTTGATAAGGATTGATGATTGTTCCCGTT
GGCATCTACAGCCGGGTCAAGAGAAAGAAATGGGTAGAGCCTATGGGTTGGCTGAGCTACGCCGTAAAGCTAATGGGCAAGTCAAAGATCT
AAAAGGTGCTGGCCTCATGTTCCACTATGCACAGATGATTATCGGTGATGATTGATAACTATGCTGGCATAACAGGTCTGTTGCTAAATA
TGCCTATGATCTTCTCAAAGATTGTAAGACAGAGAAAGAGTTGTACATGGCAGTGCTGGGTGCTTACAAGGCTAAGTTCGGGCATGGACAAG
TTAAATTAAGAATTACCGAGGTGGTTATCGTATCGGCAAGCCTTTGACCTAATGCTTGAGTGTGGTCGCTTATCTCACATGGCAAGATTCA
AGGGTGATATATGGCGAGCCGATAAGAACCCAATCTGTGGGGAGATGATGCGGAATGGTTAGCAAATTAATCATCGGAGGTGGCAGCT
TATAAGAAGGAATTGCTAGATAAGCAAGGATGGAAATGCCCTCTGTGTGGCGGCAGTCTCAAAGCTGTACACCTGTAAACCGTGACTTGA
CCATGACCATGAGACAGGATTCTGCCGCGCTGTTGATGCCGAGGCTGCAATGGTGCAGGAAGGGAAGATTAAAGGTGTTATCTCTGTTATG
GTAAGGCTGGTAACAACCGTTACTTCCAGCTTCAATGGTTAGAGCGACTATATGAATACTGGAAGTTACATAGTACGCTCAGACAGATAAGT
TATATCAAAACATCAAACGGAGGCAGAGAAGCGCGAGGCTAAGAACCCTAAGGCACGCCTTGCTTATGCAAGAAAGAAGGAGGTTAAAGT
TGGGTAAGCTGCGCAGCTTGTAACAAGACTCCGAGGTACTTGATGCAATCGAGCAAGCTACCGACGAGAAAGGTAATGTTAACTACAATGAG
ATGGCACGTGTATTATCGTGTCTACTGTGGGTAAGAAGATTACCCGCCAGTTGGCTCGATACTGGCATGGTCAATTAAGAAGACCAAGAA
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TGCAGCCGTGGCAGCACGTTACCGTCCAGACACAGTGGTACACCTAGGAGATGAGGCAGACAAACATGCCCTGTCTTCCAGATTCCGACC
CAAATCTGGATAGTGCTGGCATGGAGTTAGAGAAGGCTCGTATCTTCATGCACAAATTGCACAAGATGTTCCCTGTGATGCGCCTGTGCTACT
CTAACCCAGGCTCTATGCACCTCCGTAAGGCAAGCGCCAAAGGCATCCCTGTGCAATACCTGCGCACCTATCGTGAAGTCTTCTTCCCGCAGG
GAGGTGGCGACCAGTGGGATTGGCAACATACGCACGTCCTTGAGTTGCCGAATGGTGAACAAGTGGCATTCAAGCATCAACCTGCTGGCTCT
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ACAGTATTGGGCTGTGCAAGGTGGCTGCTTAATTGATGAGTCATCCCGTGCAATTGCTATGGTCTGAGTCTAAATACAAGCCAGCATTAGG
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GAACAAAGGGCTAGGTAAGACTTATCGGCTGGCGTATCCAATGATATTGCACTAGCCCTTGATTGTATAGTGAATGGAGGATTCAATATGT
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GTAATGAAAAAGATTGATTCTTGGGAATCAATACTGCAAGAAGCTGGTATTGACCCTGATAGCCCTGTAAACCATAGATGATATTGATGGCA
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GTTCCACGACATTAACATGGTGGACGATTGAATGTCAATTGGTAAATCTTTGAAGTCAAAGGTCTTCAGGATTCAAGCAAGGGCAACATTTCG
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AGAAGGTTGACGAATTTATGTTACAGACGAAGAAGAAACCGACGATTTTCAATTGAAGGAATGGAGATGCTTGAGATGTTCTCAAGCTTC
TTCTCCTAAGGTGACTAAGACTCATGAAGAGTTAATCGTTGATGAAGTAAAGCGTTACATCATGGATTGTGTCAGAGCACAACCTGGTGGTCCA
ATGATACGTCCAGCCTCCTTCTAGATATTCCTGAGATTATAAACCTTGGGAATAAATATGTGGAAGAGGAAGTCAAGGTTGTAGCCACCAC

Figure 16 (CONTD.)

TCAGCCTCATGGAATGCAGAACAAAGTGCCATAACCTTTGTGCATCTCTTAATAGAGACCCACCACTCAGCCTCATGGAATGCAGAACAAAGT
GCACATAACCTTTGTGCATCTCTTAGTAGAGAAGATTTATCCCTATGGGTTGCTGTAGATGAAGGGCAGATTGTAGGGTTCCTGTGGGCTGGC
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GACGTATGTATAAGCGACTTGGCTTTGAACCGTTGGCACTGTGTATAACCTGAAGTTCTAAGGAGATAACATGGGTGTTGTAAGAAAGCA
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AATATGAAACAGAGCATAGATTTGGAGTATGGAGGTAAGCGGTCTAAGATACCTAAGCTATGGGAGAAGTTCTCAAATAACGTAGCTCTTT
CCTTGATAGGGCGAAGCATTACTCAAATTAACCTTGCCCTATCTGATGAATGACAAAGGTGATAACGAGACTTCGCAGAATGGATGGCAAG
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ACAAGGTGAGAAGGTTCTTAATCAGCGTGGCCTGAAGAAGACAGAGCTAGCTACCATCTTCGCTCAAGTGAAACACGGGCAATGAAAGAG
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GTACCTTTGACCAGCTACACGTGCGGTAGTAGAGTTGGCCTGAAAGGTAAGAAGTGCAAGGAAGATGACAGCGTTAAGCTGTACACACA
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TACCTTTTCATCCCATTAACCTTGAAGCGAAGCTATGGTGAGGATTGGGGTCGACCTCTTGACAGAGGATTACTCCGGTGATTTATTCTGTTATCCA
ATTCTTATCTGAAGCGTTGCCCCGTGGTGCTGCGCTGATGGCAGATATCAAGTACCTGATTCTGCTGGTGCTCAAAGTATGTTGACCACTTT
GTTAACTCTGGCACTGGTGAGGTTGTCACTGGTGATAGAAGAAGCATCCATATTGTACAGTTAGGTAAGTACGCGAGACCTCACACCTATTAGC
GCGGTTCTAGAGGTATACACTCGCCGTATCGGTGTTGTCTTCATGATGGAGACAATGACACGCCGTGACGCCGAACGTGTTACTGCTGTAGA
AATCCAGCGAGATGCGTTAGAGATTGAGCAGAACATGGGTGGTGATACTCCCTCTTGCTACTACTATGCAATCGCCAGTAGCGATGTGGG
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GTATCTGCGTCCGTGAGGTTGACAGCCTTCTCATTGAGAAGTTAATGGTAAGGTCAATGAGCAGTACCTGAAAGGTGAGAACATTCTGTC
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GAGTGAAGCACTGGCTAACCTCAGTATGTTATGGCTGCGGTAGAGTATGCTCTGGAGCAACAGCTTGAGCAGGAAGTGACATCTCTGATG
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CGTGACAGCGTAAGGCTGTATATGTCAAAACCGAAGGTGCTGCGGCTGCATTCTCTGCTGCCCCAGCAGGTATCCAAGCGGAAGACCTTGT
AGCGGCGGTACGTGCTGAATGGCAAATGACATTAAGCCGACTGCAATGAAACCTACTGAGTAACACCTATGCCCTATCTACCTTGCCTAGGT
AGGTTCTTTTTGTTAGGAGGATTGATGCTGTAATTAGACAAACCAAGGAGGTTGGTGGTCACTGAGTGGTCACTGAGGCTGAGGCGAGAAGT
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GCAAGCAAAATGATCGACATCTCCAGCGGTTCCAGTACCAACAAAGGAGGTTGGTGGTCACTGTAACCAAACTGGCAACTTGC
ACGACAGACTAACGGTGGAAGTTAATTTACCTAACCACTGCCTAGCAGTATTGAGTGTATGCTTTAGGTGAAAGAAAGTACCTATGACTAT
GCGAGCAGGTAAGCTCTACTCTACTTGGAGTCAACCTTTGATATGCGTAAGCATGTTAATGCTAATGGTATGATTCTGCTTACCTTACTCACC
TTACTACCCTACGAGCATCTACCTACAAGTGTAATGCAGGCTATTGCCTATCAAGCTGCTGTAGAGTTATTGTGTCTAAGGATGCAGATCAGA

Figure 16 (CONTD.)

CTAAGCTAGCCACTGCGCAGCAGATAGCCACTCAGCTTCTTATGGATGTACAATCTGAGCAAATGTCACAGAAGCGATTAAACATGCTGGTAC
ATAACCCTACTCAGCGTCAGTTTGGTATCATGGCTGGTGGCTCTCAGAATGTACCTGCTTACTCTCATTACCTTATGAGAGTTGGGCGCTCCG
TCCGTGGGAGGATCGTTAATGGAAGTACAAGGTTCAATAGGTAGACAAATCCAAGGGATTAGCCAGCAGCCGCCAGCGGTACGCTTGATG
GTCAGTGACAGCTATGGTTAATATGATACCTGATGTAGTGAATGGTACTCAATCACGCATGGGTACAACCTCATATTGCAAAGATACTTGATG
CGGGGACTGATGACATGGCTACTCATCATTATCGCAGAGGTGATGGTGATGAAGAGTATTTCTTACGTTGAAGAAAGGACAAGTTCCTGAG
ATATTTGATAAGTATGGGCGCAAATGTAATGTGACTTCACAAGATGCACCTATGACCTACCTCTCTGAGGTTGTTAATCCAAGGGAAGATGTG
CAATTCATGACGATAGCTGATGTTACTTTTCATGCTTAATCGTAGGAAAGTAGTTAAAGCTAGTAGCAGGAAGTACCTAAAGTTGGAACAAA
GCCATTGTGTTTTGTGCGTATGGTCAATATGGTACATCTTATTCATTGTAATTAATGGGGCCAACGCTGCTAGTTTTAAAACACCGGATGGT
GAAGTGCAGACCATGTTGAACAAATTCGAAGTGAACGTATCACTTCTGAATTGTAAGTCTAAGTTGCAGCAATGGAGCGGTGTGAGTGACTAT
GAAATACAAAGAGACGGTACTAGTATATTTATCGAGAGACGGGATGGTGCTAGCTTTACAATAACAACACCGGATGGTGCAAAAGGTAAGG
ACTTAGTGGCTATCAAGAATAAAGTTAGCTCTACTGACCTACTCCCTTCTCGTGCGCCTGCTGGTTATAAAGTACAAGTGTGGCCTACTGGCA
CAAACCTGAGTCTCGTTACTGGCTGCAAGCTGAGCCTAAAGAGGGAAACCTTGTGTCTTGAAAGAAACAATAGCTGCTGATGTATTACTTG
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GATCGTAAAGTAGGGGATGACTTGAACCTATGCCCTCTTTATTGATGAGGAAGTACCCAGACAATAGGTGGAATGTTTCATGGTGCA
GAACCGCTATGCTTACAGCAGGTGAAGCGGTTATTGCTTCTGTACATCATACTTCTTCGATTCTTTCGTTATACGGTTATCTCTGCATTGG
CAACTGACCCCTTTGATATTTCTCAGATGCTAGTGAAGTCTACCAGCTAAAACATGCAGTGACCTTAGATGGCGCTACCGTGTTGTTCTCTGA
TAAGTCAACAATCATACTGCCAGGCGATAAGCCTTTAGAGAAGTCAAATGCAGTCTTAAGCCTGTTACAACATTTGAAGTGAACAATAAAGT
GAAGCCAGTAGTAAGTGGTGAATCGGTAATGTTTGCCACTAATGATGTTTCTACTCTGGTGTACGAGAGTCTATACAGACTCTTATAGTGA
CACTAAGAAGGCACAAGCAATCAAGTCAATGTAATAAAGTCAATGTAAGGTAACATTACCAACATGGCAGCAAGCACCATGTCAACAGGT
TACTTGTCACTACCGATAAGTATCGTAACATAATCTACTGCTACGATTGGTTATGGCAAGGAACAGACCGTGTAACATCAGCATGGCATGTAT
GGAAGTGGCCTATAGGTACAAAGGTGCGAGGTATGTTTTATTCTGGTGAATTACTTTACCTGCTCCTTGAGCGAGGAGATGGCGTGTATCTG
GAGAAGATGGACATGGGTGATGCACTAACCTACGGTTTGAATGACCGCATCAGAATGGATAGGCAAGCAGAGTTAGTCTTCAAGCATTTCAA
AGCAGAAGATGAATGGGTATCTGAGCCGCTCCCTTGGGTTCTACTAACCCAGAACTTTAGATTGCATCTTAATCGAGGGTTGGGATTCTA
TATTGGCGGCTCTTTCTTATTCAAGTACAACCTAGTGACAATACTTTGTCTACAACCTTTGATATGTATGATGACAGCCATGTAAAGCGAAG
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AGGGTCTAATGGCTATAGGTTAGCCGTTATGGCTGGTATGTCTTCTATTGGTAGCATGTTTGCAGGCAGTGGTGACAGAGCCGCTGCTGGA
GGTGCTGCCGAGGTGGCGGAGGTTTGTAGGTTCACTAGGTGGATTCTAAGTGGCTCTACTGCTGGTTTCTAATGCTGGCCTTCTTGGT
GCTGGCCTTCAAGGTTAGGCTTATTGGTGATCTATTGGTGGAAGTGATGAAGCCAAGGCGATGAAGAAAGCACAAGAAGAGCAATGGC
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AATCAGGCTTCACTGCTACAGCAGCGAGCACAGGTTGCACTTACTTCTGGGGCTACTGGTACTGGTGGTAAATCTGTGTCCTCTATGCTTAAT
GACTTAGCAGCAGATGGCGGCAGGAACAGAGTACTATCATTGATAACTATGAGAATCAGAAGATTAATTTACCAACACAGCTTAAGTCTATC
CAACGTGGTGGTCAGATGCAGATGCGTGAGTTAAGAAGCCTTCTGCTATGAATACCTTGGTTAAAGGTATTCCAAGTCTGGCATCTGCCTAT
GTAAGTGGTAGTAAGTCTGGCAAGGCATTGGGTAAAGCCTTAAGTATTCTCGACATATTATCTGGAACAAGAGGTATTAAATGGCAATTG
AGCGACAAGCAGTACAAGGTCTGCCACAAGTGACGGCCACTTCTCCTAATGTCATGACCTTGCACCTCAACAAGTGGGAGGTGTGGAGGCT
GGCGTGGCTTCTACCTCCGGTAGTAGGTTTATCGAAGACCTTATTCGTGCAGCAAGCAGCGTGGCTGATGTTACCACTGGTATCCTTAATCAG
AAGATTGAGGAAGATAAGGTTGTTCAAATGGAACGGGCATATAACGGATTAATGCCTTCTGAGGATGCAACTCGTGGTGGCGCTCGTGCTAA
CATGCTTGTCAAAGCTCAACTGCTAGCTAATGATGAAGCAGCAGCAATGAAAGACATGGCTACTCGTTTCAAGGAACGGATGACGAATGGA
CACAACCTATGGTTGACTCTCGTAATGAGATGCAGAATAAGCTGTTCCAGCAATACCTGAGTTGCAAGGTGACAAAGATACTATGCGTATGG
TCACTAATGTCTTCAAGAACAGCAGCCTCAGATTTGGGCTACACGAACCCAGCATAAACTTGACCGTGAACAAGCAGACCGTGAGGATACTT
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CAGCACATTAATAATCTGACAGGTAAGTCTGCTTCTCTAATCCAGAACTAGAGGCACTGATGCGCCAACGGGCTAAGCAGAATGCAGAGCTA
GGTGCAATGCAGGATATGCGACGTGAGCTTTACTCCGACCGCTGACTGGCTTCCAAGGTAAAGACTGATAAAGAGAAGAAGGCTTACATTGA
TGTTATCAAACAGGATAGCCAACCTTATGCAGACCAGCAAATCAAACAACGTGGCTTGGACCCTTACAGTCAAGAGGCTGAAGCTATTCTGT
GTGCACTGGGAAGTACGCGCTGCAATTCATGAAGTCCAAAGGCTAGTGATGACTATTGCGCAAGTTGTGGGAACAGTTACCAAGAGAGCGGAGGT
TATCGCTGAGACTTTGCAAGGCGCAACACAGGAGTGTGATGACTATTGCGCAAGTTGTGGGAACAGTTACCAAGAGAGAGCGGAGGTGT
CTTTGGTGACACGTTGAATGGCTACATGGATAACTAGCAACTGACTACAAATGGGAGAGACACCTTTGACGGCTGCAAGGTTTGGCGGTA
AAGCACAGCAGAAATCTCTGCTACTGAGAAGGAAACCAAGAAGTTCAACTCAGCTATTGGAGATGCACTGGATGAGGTATCTGGTGCTGGC
TGGTTTGATGGTAAACCGAAGTGTGAGCTTAGGTAAAGCTATTGCGGAAGAAGAGTTACGAGCTAAGGCCAATATGTTGTGGTCTAGTGG

Figure 16 (CONTD.)

TATGCGTAACATGGATTCCATCAAGAAGGCTTTAATTACTTGGGGCAATAAACGCTACACTCAATCAGAGGATGCAAAGACTTCCGGTGGCTA
TTTCATTAAAGGTGATTACACTTCTGCATCTGATATGCTTATGTCAGTTGGGAAAGGCGTAAACCCTACCGATGTACCTCTGGCGCTTGGTAGG
TATGTAGAAACACAGATGCCAGAATTGAAGAAGGAGCTTCAAGAGGGGAAACTAAAGATGATATATACATTGATTACAATGAACAGAAAG
GTACTTTCGTGATTCTGCTGGTGCAGCAGGTGCGCCTCTTCTGGAGTAATCCCTGTAACCTCTTAGATACCACTTCACTACTAGATTCTGCC
TATCAGAAGAAAGTAGAGGAACGAGATAAAGGCGAGTATGTTACCCGTATCGTACAGATATTGGTGCACAAGAGCCTATGCCAGCTAAACC
AACTGCCAAAGATATTGGTAAATTTGGACTAGCTAACTTCTCATGTCTTCTGCTTTTCTTCTGGTGAAGATCTGCCTTCTAACTTCGAGATTA
ACTATCGAGGTAATATGCAACAATTCTATGACAAGCTAGCTATGGATGAGAATAAAGATAAAGTTGGCTTTAATAAGGCAACTGGAACCTTTA
CTCCATATAAAGACGCTCACGGTGAGTCTATCGGTTACGGTCATTTCTTAACGGAAGAAGAGAAGCGAAACGGGTATATTAAGATTGGCGAT
GAACTAGTTCCTATCGAGGGTCTATGTCTCAGCTTACAGAGAGCAAGGCTCGCGCTCTTATGGAGCAAGATGCTAAGAAGCATGTGCCTCCT
ACTCGTGACTGGAAGATTCCGTTTGACCAGATGCACCCTGCACAGCAACGTGGCTTGATGGATTTAAGCTACAATTTAGGTAAAGGTGGAAT
CCAGAACTCACCGCTGCTCTTGCTGCATTCAAAGCTGGTAAGCTTACGGAGGGCTTTATCGAAATGCTGGGCACTGCATCAAGTGAAGGTA
AGCGTATTCTGGCCTACTGAAGCGACGCGCTGAGGCATACAATATGGCATCTGCTGGTGGTGTGCCTAAGATTACCGAAGTGGAGACTCGT
GAAGATGGCTCCATGTGGGTTAGTTTGGTGGACCTATGCCAGCAGGTTCTGTCTCGGCATGGACTCATAACGTATTGGCGCGGATGGTTG
GTATCAGGTTTATGAGGCTGCACCTACCAAGTTAGCTAAAGATTCTAAGGTAGGTAAAGTTAAGTTGTAGTACCTAACTCAAGGCTTGCTCA
CATGTGAGACAGGTCTTTATGATAGGCACTATGGAGGAATTATGGAACAAGACATTAAGACTAATTGGGCTGGATATGTCCAGTCTACTCCT
GAGCCGTTTTCTATTGAGGCGGCTCCGGTATCGGCTCCTACGATACGCCAGCGTAATGAGTTACAAGAGCAAGTTCTTGAAGCTAAAGCTGA
CGCTGATATCTTAGGTGCTGTAGGTGCTGCCTTCAGAATGAGTGGTTGGCATTTCGGAGGCAAGCGGTGGTATGACCGTGCCACTGCTGATT
TCACACCTCAACCAGACTTTGAGATACAACCTGAGCAACGTGAAGCACTACGTTTCAAATATGGTACGGATATGATGCAGACAATCACTGAGG
GTGTTCTGTTCTGAGGATGAATTGAACCTCCGTATTCAGAATGCGGATGAAGACCTTGAGCGCAATAAGCGCATTGCTCAGGCTGGCTGGGTT
GGCTCTGTGGCGACGATTGGCGCTGCTGTGCTTGACCCTGTGGGATGGGTTGCCTCTATTCGAACCGGTGGTGGCGCTAAAGTTGGACTCGT
AGGCCGTGCTGTGCGTGGCGCTATCGCCGTGGCGTGAGTAATGCCGCTATTGAATCCGTATTGGTCCAAGGTGACATGACTCGTGATTAG
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GGTGATGACAGGGCTGTAGCATTGTGCGCAGTGACAGCGCAGGGGACCGCTATGTTCTGTGCTGTTGCCGATGACAGTATCGGTGCGATGC
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CGTAAGATTCCAAAGGAAGCAGCAGATGAGATTGCACGAGCACAGGTAAATCGCGTTGCTGATGTACCTTAACTGGAAAGCTTAGTTTTGA
AAAGGCAATGTCAGGTGAGCTAAGGCAGAGTATGAAGTATCATGCGTAAGGCAGGCTTCAGTGATGAAGAAATTGAAAAGATGATAGAA
GCTCTGGATAACAAAGAAACCAGAGATAACATCTTAACCGAGCTAAATGAGTTTAGGATTAGATGTTACTCAAGAATACAATGGCATTGCT
ATGCGTGACTTCATGAATACCAACGTGGAAGAGCTAACAGATAACTATATGAAGGAAGCAGCAGGTGGCGCTGCATTGGCTCGCCAAGGCTT
CTCTACCTATCAGGCTGCACCTTAATGCAATTGACCTTGTAGAGCGAAATGCACGAAACGCGGCTAAGGATAGCAAGGCTAGTTTGGCATTAG
ATGAAGAGATTCTGATGATGCGAGAAGGTCTTGCCTGATTATGGGCAAGTCGATTGATGCAGACCCACAGGCTATATCTACTAAGATGATG
CGTCTGGTCTGATATCAGAGGTGTGCTTGCCTTAGGTCAAATGGGCTTCGCACAGCTAGGTGAACCTGCCAATTTATGGGTGAATTTGGT
ATTGCTGCAACTACTATGGCTTTAGGTAAAGCAATTCGCTTACCTTAAGGCGTTGCGTAATGGCGATGGCTTCTCCGAGATAAGAACTTA
GCTGAGGTTGAGAGAATGGTGGGGTACATTGGTGAGGATAACTGGCTAACAACTAAGGGTGCACGCTCTGATGAATTTGGTGATGTAACCA
CAGTAAGAGGGATGATGGCTCACTTTGACCAATCCATGAACCTCAATACGTCGTCTCAAACCACTATCACTCTCCGCATGGCACAGGGTT
CTCTGGAGCGAATGACTAATAGGCAAATAGCTTTGCTTTTATTGACCACCTGAAGGCAAGAAGATTATCTCAGAAGAACTGGAGGAAC
TTGGTCTTACTCAGGAGTTCATGACTAACCTACAGAAGCACTATGATGCTAACTTAAAGGTTCTGGCTTCTTGGCTTTGATACAATGCCTTA
TGCCATGGGTGAACTTTAGCTAATGCTATTCGTCGTAAGTCAGGTCTAATCATCCAACGTAACTTCATTGGTGATGAAGGTATCTGGATGAA
CAAAGCACTAGGTAAAGACATTTGCACAGCTTAAGTCATTCTCTTGTATCTGGTGAGAAGCAATTTGGTCGAGGGATTGCCACGATAAAAT
TGGTCTTGCTAAGAAGACAGCTTACGGGTTTGTCTTGGGTTCAATAGTGTATGCGGCAAAAGCCTATGTGAACCTATTGGGCGAGAAGACC
AAGATGAATATTTGGAAGAGAAGTTATCGCCTAAAGGGTTGGCCTTTGGTGCAATGGGTATGATGAGTACAACCTGCTGTATTTAGTCTAGGT
GGAGATTTCTAGGTGGCCTAGGTGTTCTACCTCCGAACCTATTCAATCACGCTATGAAGCAGGTTTCCAAAGTAAGGGTCTGATTGACCAA
ATACCTCTGGTTGGCGTTGGTGACAGTGCAGTAAATCTGGCTAACTCAATCAAGAAGTATGCAGAAGGTGACACAGAAGGTAGATATCGC
TAAGCGAGCACTCCGCTTGTGCCACTTACCAATATAATAGGTGTCCAAAACGCATTGCGTTATGGCTTAGATGAAGTGAAGGATTGATGAGT
TATACTTTACAGAACATACAGCCAATGGTACGCAAGTACCTATCCTTTAGCTTTGCTGGTAGGGATAAAGGTTATCTTCGTCCTCAGATG
TGATAGTGGAGTCTCTTCAAGGTAACACTTGGATTGAAGTTACATCTGGCTGCAACTAAGTGCACGACGACCAAGGCTTTTGTGCTAGCAC
CAGTTGACGAGTTTGAAGTCCGATTTCGAAGGGAAGTACAAAAGAATATCCATACGCTGAGTTTGACCGTGGTGTACTTTGGATATGAAG
TCTTTAAATGGTTCTTTCACTCATATACTGGAGATTACACAGGAGTTACTTGACGGGTTTTATCCAGAAGGATACCTTATTAACAGAAATGTAA
GCTGGGGCGGCAATAAGATTACTGATTTGGCTGATGGCACAAATCCGGGAGATGCAGTAAATAAAGGGCAGCTTGATGCCATCGACAAGAA

Figure 16 (CONTD.)

GCATACAGATTGGAACGCCAAACAGGACATTGAGATTGCTGGCCTTAAGGCTGGTATGACTTCTGGTATTGCGCACAGAACTGTTCTTGTTA
CACGATAGCCCAAGGTGGTGAGATTTCCGTAACCAACCTTATGAATTTCAAGATGCACTAGTTTTCTTAATGGGGTATTGCAGCACCAAT
TGTAGGCGCATACTCTATAAGCAACAACACTATCACTTTGCGAGAGCCGCTTGTTGGCTGGTACAGAGGTGTATGTGCTGATTGGTAGTCGTGT
GGCTACATCTGAACCTAATATTCAAGTTGAGTTGAACCTTGACTTAGTAGAAGGCCAACAGTAGTACAGATTGGCTCTGCATTTAAGTACAT
TGAGGTCTACCTTGATGGATTATTACAACCTAACTTGCTTATCAGGTAGACGGTGACATTGTTACTTTCTCAGAAAGAGTACCAGAATGCCG
GATGACTGCTAAGATTATCACAGCATAAGGAGGTGGGATGATTAACCTCGAACTGGTAGATAGTGGTGTGAAGCTTGCGCCACCTGCACTCA
TATCAGGTGGGTACTTCTCGGTATCAGTTGGGATAATTGGGTGTTAATAGCAACATTCAATTTATACCGTGTGCAAAATGGGGACTGGTTTT
ATAATAAGTTCAAGATTTGGAGGGAGAAGCGTGAGCGTACACAATAAATCATGCAGCTACAGAGGACGAGGTTGGCATTCTGCATGGTGCTA
TTACCAAAATCTTCAATAAGAAAGCACAGGCAATACTGGACACTATAGAAGAAGACCCTGATGCAGCATTACATTTAGTGTCTGGTAAGGATA
TTGGTGCGATGTGTAAGTGGGTCTTGATAACGGCATTACCGCCACACCTGCTGCACAGCAGGAAGAGTCCAAGTTATCTAAGCGCCTCAAG
GCTATCCGAGAGGCATCCAGTGGAAGATAATTCAATTCATAAGGAGGATTGATGGCTAAGGCAAGAGAATCACAAGCGGAGGCTCTTGC
CAGATGGGAGATGCTACAGGAGTTACAGCAGACCTTTCTTACCCGCGGAAGGTTTGCTTCTTTGCAGATACAGTTATTCATAACTTAATT
GCAGGCAACCCCTCATCTGATTCGTATGCAGGCGGATATCTGAAGTTCCTATTTTACGGACACAAGTACCGCCTCATCGAAGCGCCTCGTGGT
ATCGCTAAGACAACACTATCAGCAATCTATACGGTATTCGGTATTATTCATGAACCGCATAAGCGTATCATGGTTGTGTCCCAAAACGCCAAGC
GAGCAGAGGAAATCGCAGGTTGGGTAGTTAAATCTTCCGTGGCTTAGACTTTCTTGAGTTTATGCTGCCGGATATCTACGCTGGGGACCGT
GCATCCGTTAAGGCGTTTGAGATTCAATACCCCTACGTGGTAGTGATAAGTCTCCTTCTGTATCCTGTTACTCAATCGAAGCAGGTATGCAGG
GTGCTCGTGCTGATATTATTCTAGCGGATGACGTAGAGTCGATGCAGAATGCTCGTACGGCAGCGGGCGGTGCCTTGCTTGAGGAGCTGACT
AAGGAGTTTGAATCTATCAACCAGTTTGGGGATATCATTTACCTTGGTACACCTCAGAACGTAACCTCTATCTACAACAACCTACCTGCTCGTG
GTTACTCTGTTCTGATCTGGAAGTGCAGGTTACCTTTCAGTAGAGCAAGAGCAATGTTATGGCGACTTCTTGACCTATGATTGTTCAAGATAT
GAAGGACAACCCAGCACTTCGCTCAGGGTACGGGTTGGATGGTAATAGTGGTGACCTTGTGCCCTGAAATGTATGATGATGAAGTCCTGA
TTGAGAAGGAAATCTCTCAGGGTGTCTGAAGTTCAGCTTCAGTTTCATGCTTAACACTCGCATGATGGATGCTGCAGATACCCATTACGCC
TGAACAATCTAATCTTACCTCGTTTGGTACAGAGGAAGTCCCTGTGATGCCTACGTGGAGTAATGATTCCATAAACATCATTGGTGATGCAC
CTAAGTATGGTAACAAGCCTACGGATTCATGTACAGACCTGTAGCTCGCCCATATGAATGGGGTGCTGTCTCCGCAAGATTATGTATATTG
ACCCTGCGGGTGGTGGTAAGAACGGAGATGAGACGGGTGTAGCCATCGTATTCTGCACGGCACATTCATTTATGTGTATCAGTGCTTTGGT
GTACCTGCGGATACCGAGAGTCGTCCCTGAATCGCATTGTGCAGGCCGCAAGCAGGCGGGTGTAAAGAGGTATTCAATGAGAAGAACT
TTGGTCATGGCGCTTTGAGGCGGTAATTAAGCCGTACTTTGAACGAGAGTGGCCTGTAACCTCTGGAAGAGGATTACGCCACCGGACAGAA
AGAGTTGCGTATCATTGAGACGCTGGAGCCGCTCATGGCAGCCCATAGGCTTATCTTCAATGCAGAGATGGTGAAGTCAGACTTTGAGTCGG
TACAGCACTATCCGCTTGAATACGCATGTCTACAGTCTTTTCAATCAATGTGCAACATAACGATTGAGAAGAACAGCCTCCGGCACGATG
ACCGCTAGACGCCCTGTATGGCGCTATACGGCAATTAACCTTCTCAGATAGACTATGACGAGGTTACACGGATTAATCGCCTCAGAGCGCAG
GAGATGCGCGATTACATCCATGCTATGAACACACCTCATCTACGCAGGGCAATGCTATATGGAGATTACGGTACTGAGCGAAGAGTGACCAA
CACTTCCGTAGCGATGCAGCAGCGAGTTACGGGCAGAACTACCGAAATAAATCGGCAAGCAGAAATACACTTTCTGCAAGGATTTCAAGGA
CTTATTAATTAAGTGGACACTATAGAAGGAAGGCCAGATAATAAGAGAAAATAATAGGTAATATATATAGGTTAACCTAGGTTATATAGGT
ATGCCTTAGTATGGGTGACTCCTGTACACCCTATTCCTTACTACCTTACTATATTTACATAATAGGAGAGAGACAAATGGCTAATGATTATAGT
AGTCAACCATTAAACAGGTAAGTCTAAGAGAAAGCAGGTACAACCTGTAAGTGAAGAACTAATGCTTCCGGTGCTCAAAAAGAGGAAGTTA
GTAAGAAAAGCAATGTTATTAATGATGCCACCAATCAGGTAAACAGAAAGGGGCCATGGTGTGCCTTGAAGTGAAGGTGGTGTATTGAA
GATTGCTATCGCGTTGATGGCAAGAAGATTACAGTGGAAGTTAGTAACAGTGGAACCACTGTTAACCCAGTTTAAGATAAGGAGGAA
GATTACATGGCTAAATATGGTACTACAGGTTCTGTTACTGGTCAGGCTTTTCGAGTAAAAGCAGTACAACTATTGCAACGGCAATCCCGATG
CCTGTTGTTAAGAAGAAGACCTTAAGAGTAAAGACCACCTATCAACATCAACATTTATCAGGTAAACAGAAAGGTGCAATGGTTGCTCTT
GAGAAAGGTGACACAACCTTACATATTGCTGTTGCAGTGGTAGTGAACCCACAGACCCTTGGGATGTAACCTGGTATGGAAGGACGCTGT
TACTCCAGCAGGGGTATAATAATGCTTAATAAATACTTCAAGCGTAAAGAGTTTGCTTGCCGTTGTGGGTGCGGTACATCCACTGTTGATGCT
GAATTAACAGGTAGTCACAGATGTGCGTGAGCACTTTGGTTCTCCTGTAGTTATCACTTCGGGTATCGCTGTGCTAAGCACAATGCCAAT
GTAGGTGGCGCTAAGAACTCCATGCATCTTACTGGTAAGGCTGCTGACATTAAGTGTCTGGCATATTACCTTCTGAAGTGCATAAGTATCTT
ACTAGCAAAATACCAAGGCAAGTATGGTATAGGTAAGTATAACTCCTTCACTCACATCGATGTACGGGATGGTTGTGCGCGATGGTAAGATGT
GTTGAATGGTGTGAGCGTATGGTTGCCAAGCTGCCGAGGATGGCAACTATGATGACTGGAAGAACTACTCTGACTTGTTAGCTCAATGGAA
AGGGAGATGCAATGAAAAAGCTGTTAAGTCTAAGAAGGTTGTAGGTGCACTGGTTGCACTTGTTATTGCTCTTGTTCTGTAGGTCTTGGTG
TAGACCTTGGCTCTGGCACGGAATCCTCTGTGACAGATGTGGTCTGCCAAGTGATCACCTGTGAATAAGTTTCTAGAAGTTCTGGCAGGTCTT
ATTGGCCTGCTTGTCTGTCTAAGAAGAAACAAGAAGAGAAGGAGGCACAAAGTGAAGCGAATCATGTTAGTGACAACCTTCTGATTGGTT
CGCTGACCACTTCCGGGTGTACAGGCGTTACCAGAGAAAGCAATGGTGAAACCTCTGAGGCCGACGCTGACGGCAGTTTACGAGGTAGA
CGATAAGGTCTGCTTATAGTAAGCCTGACGCTACAAAACCTTGTTTGTACATTCTCTCGCTAGAACCGGATACAATTAATACATAGCTTTATGT
ATCAGTGTCTTACGATTACTGGACACTATAGAAGAGGTAAAGATAGCGCCGTTCTTTGAGCGGCTATTACTAGCCAATCTTATAGTACCTTG
GTTGGAAGTAAATAGGAGATGACATGGCTAAATTAACCAACCTAACTGAAGGAATCTTGCAATAAGGACAATCTTGTATAGTACCTTG
ATGCGAGAGTTTTAATCAAGCCGTTTGGTGCTGACGAGTGACGCCACTACTGATGATACGGAGGTTATAGCTGCTTCAATTAACCTCTCAGA
AAGCTGTACAGTCTCAGATGGTGTATTCTAGCTCTGGTATTAACAGTAATTAAGTGAACCTAGACGGCAGGGGTAGTGGCGTGCTAAGTC
ACCGTTCAAGTACAGGTAACCTACTTAGTATTTAACAATCTACGTGCAGGTCGCTAAGTAATATTACGGTAGAAAGTAATAAGGCGACTGATA

Figure 16 (CONTD.)

CAACTCAGGGACAGCAGGTATCCCTTGCTGGTGAAGTGATGTTACTGTAAGTGACGTTAACTTCTCAAACGTTAAAGGTAAGTGGTTTCAGTT
TAATCGCATACCCTAATGATGCGCCACCTGATGGACTTATGATTAAAGGCATTGAGGTAGCTATTCGGCTATGCTACTAATAAGGCAGCCG
GATGCGTACTTGCTGATTCTCAGTTAACTCCCTCATAGATAACGTCATTGCTAAGAACTACCCTCAGTTCGGAGCAGTAGAGTTGAAAGGTA
CAGCCAGTTACAACATAGTCAGTAATGTTATAGGGACAGATTGCCAGCATGTAACCTACAACGGCACTGAAGGGCCAATAGCTCCTTCTAATA
ACCTTATCAAGGGGGTGATGGCTAATAACCTAAGTATGCAGCGGTTGTTGCAGGCAAAGGAAGTACGAACCTAATCTCAGACGTGCTCGTA
GATTACTCAACTTCTGATGCTAGGCAGGCTCATGGTGTACAGTAGAGGGTCTGATAACGTCATAAATAATGTGCTTATGTCAGGATGTGAT
GGTACTAACTCTTATAGGACAAGGGCAGACTGCTACAATTGCACGCTTATAGGTACAGCTAATAACAACCTATGCGTCTGTATTTCTAGCTACA
GTGCTACAGGTGTTATTACTTTGAATCCGGCTCTACCCGTAACCTCGTAGAGGTAAAGCACCTGGCAGGAGAAACGACCTTCTCAGTTCTG
CTAGTACTATTGACGGTGCAGCTACTATTGACGGCACTAGTAATAGTAACGTAGTGACGCACCTGCCTTAGGGCAGTACATAGGTAGTATGT
CAGGTAGGTTGCAATGGCGGATTAAGTCCATGTCACTCCCTCAGGCGTCTTACTTCTGCTGATAAGTACAGAATGCTTGGAGATGGTGCTG
TGTCATTAGCTGTAGGTGGGGGCACTTCTTCTCAAGTTCGCTATTTACTTCTGATGGTACTTCTCGGACAGTGTCCCTACCAACGGTAACGT
GCGTCTTTCTACAGTAGCACAGGCTTTTTGCAGTTAGGTGCTGATGCAATGACCCAGACAGTACTGGTACATACGATTAGGTTCCGCCAG
CCGAGCATGGTCTGGCGGTTTTACTCAAGCAGCATTCACTGTTACCTCAGATGCTCGGTGTAACAGAACCTCTTACTATCTCAGATGCCTTA
CTGGATGCTTGGTCTGAAGTTGACTTTGTGCAGTTTCAGTATTTGGATCGTGTTGAGGAGAAGGGTGCAGACTCAGCTAGATGGCACTTCGG
TATCATCGCTCAGCGAGCTAAGGAGGCTTTGCAACGTACCGTATAGATGCACATCGCTATGGCTTCTGTGCTTCGACAGTTGGGATGATGT
ATACGAGGAAGATGCCAATGGCTCTCGTAACTGATTACACCAGCAGGTTCCCGCTACGGTATTCGTTACGAGGAAGTACTGATATTAGAGG
CTGCGTTGATGCGGCGGACTATTAAAGCGTATGCAGGAAGCACTAGCTTCCCTGCCTAAGTAAGCAACAGGCAGTGCCTAAGCACTGCTTTTA
GCGCAACTTTTTCTAAAGGTTATCACGGTGGTAGCCTTTCAGAAAAGGAGGTTACATGATTCAAGACTAGGTTCTTCATTAGTTAAATTCAA
GAGTAAATAGCAGGTGCAATCTGGCGTAACCTGGATGACAAGCTACCCAGGTTGTATCGCTTAAAGATTTTGAGCCAAAGGTGATGGTA
AGACAAACGACCAAGATGCAGTAATGCAGCGATGGCTTCAGGTAAGAGAATTGACGGTGCTGGTGCTACTTACAAAGTATCATCTTACCT
GATATGGAGCGATTCTATAACACCCGCTTCGTATGGGAACGTTTAGCAGGTCAACCTCTTACTATGTGAGTAAAGGTTTTATCAATGGTGAA
CTATATAAAATCACGGATAACCTTATTACAATGCTTGGCCTCAAGACAAAGCGTTTGATATGAGAACGTGATATATGCACCTTACATGGGTA
GTGACCGTCATGGTGTAGTCGTCTGCATGTATCATGGGTTAAGTCTGGTGACGATGGTCAAACATGGTCTACTCCAGAGTGGTTAACTGATC
TGCATCCAGATTACCTACAGTGAATATCATTGTATGAGTATGGGTGTATGTGCGAACCGTCTGTTTGCCATGATTGAAACACGTACTTTAGC
CAAGAACAACTAACCAATTGTGCATTGTGGGATCGCCCTATGTCTCGTAGTCTGCATCTTACTGGTGGTATCACTAAGGCTGCAATCAGCA
ATATGCAACAATACATGTACCAGATCACGACTATTCGTGGGCGATTTTGTTAACTTCTCTAATTCGCGGTAAACAGGTGTATCAGGTGATATG
ACTGTTGCAACGGTAATAGATAAGGACAACCTCACGGTCTTACACCTAACCCAGCAGACTTCAGATTTGAATAACGCTGGAAGAGTTGGCAC
ATGGGTACTTCTTCCATAAGTCTCATGGCGTAAGACAGATCTTGGTCTAATCCCTAGTGTACAGAGGTGCATAGCTTTGCTACTATTGATA
ACAATGGCTTTGTTATGGGCTATCATCAAGGTGATGTAGTCCACGAGAAGTTGGTCTTTTCTACTTCCCTGATGCTTTCAATAGCCCCATCTAAT
TATGTTCTGTCGTCAGATACCATCTGAGTATGAACCAGATGCGTCAGAGCCATGCATCAAGTACTATGACGGTGATTATACCTTATCACTCGTG
GCACTCTTGGTGACAGACTTGAAGCTCTTGCATCGTAGTAGAGATATAGGTGCACTTGGGAGTCACTGAGATTTCCACATAATGTTTCATC
ATACTACCTACCTTTTGTAAAGTAGGAGATGACCTTATTATGTTGGTTCAGAACGTGCAGAAAATGAATGGGAAGCAGGTGCACCAGAT
GATCGTTACAAGGCATCTTATCCTCGTACCTTCTATGCAGGATTGAATGTAAACAATTGGAATGCAGATGATATTGAATGGGTTAACATCACA
GACCAATCTATCAAGGTGACATTGTGAACCTAGTGTAGGTGTAGGTTGCGTAGTAGTTAAAGACAGCTACATTTACTATATCTTTGGTGGC
GAAAACCATTTCAACCAATGACTTATGGTGACAACAAAGGTAAAGACCCATTTAAAGGTGATGGACACCTACTGATATATACTGCTATAAG
ATGCAGATTGCAATGACAATCGTGTATCTCGTAAGTTACATATGGTGCAACTCCGGGTCAAGCTATACCTACTTTCATGGGTACTGATGGA
ATACGAAATATCCCTGCACCTTTGATTTCTCAGATAACATTGTTACAGAGGATACTAAAGTTGGACACTTAACACTTAAAGCAAGCACAAGTT
CCAATATACGATCTGAAGTGACAGATGGAAGGTGAATATGGCTTTATTGGCAAGTCTGTTCCAAAGGACAACCAACTGGTCAACGTTTGATTA
TTTGTGGTGGAGAAGAGACTTCGTCTCTCAGGTGCACAGATAACTTGCACGGCTCTAATTCAAGTAAGGCTAATCGTATCACTTATAACG
GAAATGAGCACCTATTCAAGGTGCACCAATCATGCCTGCTGTAGATAACCAAGTTTGTGCTGGTGACCTAGTAACCGATTCACTACCATCT
ACCTAGGTAGTGACCCTGTTACAACCTCAGATGCTGACCACAAGTACAGTATCTCTAGTATTAATACCAAGGTGTTAAAGGCTTGGAGCAGGG
TTGGTTTTAAACAGTATGGTTGAATAGTGAAGCAGAGAGGGACCTTGATAGCATACACTTCGGTGCTTGGCTCAGGATATTGTAGCTGCTT
TTGAAGCTGAAGGGTTGGATGCCATTAAAGTATGGAATTGTGTCCTTCAAGAAGGTAGGTACGGTGTGAGGTATAGTGAAGTTCTAATACTA
GAGGCTGCTTATACTCGTTATCGTTTAGACAAGTTAGAGGAGATGTATGCCACTAATAAAATCAGTTAAGCAAGCTGCTGTACTCCAGAACAC
AGAAGAGCTTATCAATCAGGACGTGACCCTAAGCAGGCTTATGCCATTGCCAAGGATGTTCAACGTCGTGCCATGAAGAAACCTTCTGCATC
TTCTGCGTAAAGAGGAGATATACAATGGTCTTCACTCGAAGATTTGTTGGGGACTGGCGACAGACAGCCGGCTACAACCTGGACCAAGT
CCTTGAACAGGGAGGTGTGTCAGTTTGTTCAGAATCTCGGGGTGTCCGTAACCTCCGATCCAAAGGATTGCTTGGAGCGGTGAAAAATGGGC
TGAAGATCGACATCCATGTATCATCCCGTATGAAGGTCTGAGCGGCGACCAAAATGGGCCAGATCGAAAAATTTTAAAGGTGGTGTACCT
GTGGATGATCATCACTTTAAGGTGATCCTGCACTATGGCACACTGGTAATCGACGGGTTACGCCGAACATGATCGACTATTTCCGACGGCC
GTATGAAGGCATCGCGTGTTCGACGGCAAAAAGTACTGTAAACGAGGACCCCTGTGGAACGGCAACAAAATTCGACGACGCGCTGATC
AACCCCGACGGCTCCCTGCTGTTCCGAGTAACCATCAACGGAGTGACCGGCTGGCGGCTGTGCGAACGCACTTCAAGCAAGCTTAAATA
TCTTAGTATAAACAAGGGCAGACTTAGGTTTGTCTTATGTGATTCCAAAGGAGGTAACATGCTGAAAGATGTTGGGTTTCATATGACCCTA
CAGACCCTAAGAATTGGCTACAGGTTATCGCTATAGCTTGTGAGGTAGCCTATTGGCTGCCCTGATGTATTATTATGGATGTACACAAAGT
AACCAAAGTCAAAATTTTGTATGTAGGCGTGTGTGACGCTCTCTCGCCCTCGCCCTCGCCGGGTTGTCCCATAGGGTGGCCTGAGGGAAATCCGT

Figure 16 (CONTD.)

CTTCGACGGGCAGGGCTGATGTACTCCTTGTCTAGTACAAGGGAGGCGGAGGGGAACGCCTAGGGAGGCCTAGGAATGGCTTAGTGGTGGA
CAAGGTGATTACCTTAGTGAAGCCTCTAGTGCATTCTGAGGCCATTCAGGGCGTTTATGAGGGATTGACAGGGTGTGAGGGCGTGGGCTA

Figure 17

T7_10A_NheI_Nluc_LacZa_phage T7, (SEQ ID NO: 6)

CCTCTAGAAATAATTTTGTTTAACTTTAAGAAGGAGATATACATATGGTCTTCACAC
TCGAAGATTTTCGTTGGGGACTGGCGACAGACAGCCGGCTACAACCTGGACCAAGTC
CTTGAACAGGGAGGTGTGTCCAGTTTGTTCAGAAATCTCGGGGTGTCCGTAACCTCCG
ATCCAAAGGATTGTCCTGAGCGGTGAAAATGGGCTGAAGATCGACATCCATGTCAT
CATCCCGTATGAAGGTCTGAGCGGCGACCAAATGGGCCAGATCGAAAAAATTTTTA
AGGTGGTGTACCCTGTGGATGATCATCACTTTAAGGTGATCCTGCACTATGGCACAC
TGGTAATCGACGGGGTTACGCCGAACATGATCGACTATTTTCGGACGGCCGTATGAA
GGCATCGCCGTGTTTCGACGGCAAAAAGATCACTGTAACAGGGACCCTGTGGAACGG
CAACAAAATTATCGACGAGCGCCTGATCAACCCCGACGGCTCCCTGCTGTTCCGAGT
AACCATCAACGGAGTGACCGGCTGGCGGCTGTGCGAACGCATTCTGGCGTAAAGGA
GGTAAACATATGACCATGATTACGGATTCACTGGCCGTCGTTTTACAACGTCGTGAC
TGGGAAAACCCTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCC
AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAG
CCTGAATGGCGAATGGTAAAAAGAGGAGGTATACAATGGCTAGCATGACTGGTGGA
CAGCAAATGGGTACTAACCAAGGT

Figure 18

T7_SwaI_Nanoluc_Insert_sequence Enterobacteria phage T7, (SEQ ID NO: 7)

CTTTAAGACCCTTAAGTGTTAATTAGAGATTTAAGGAGATTCAACATGGTCTTCACA
CTCGAAGATTTTCGTTGGGGACTGGCGACAGACAGCCGGCTACAACCTGGACCAAGT
CCTTGAACAGGGAGGTGTGTCCAGTTTGTTCAGAAATCTCGGGGTGTCCGTAACCTCC
GATCCAAAGGATTGTCCTGAGCGGTGAAAATGGGCTGAAGATCGACATCCATGTCA
TCATCCCGTATGAAGGTCTGAGCGGCGACCAAATGGGCCAGATCGAAAAAATTTTT
AAGGTGGTGTACCCTGTGGATGATCATCACTTTAAGGTGATCCTGCACTATGGCACA
CTGGTAATCGACGGGGTTACGCCGAACATGATCGACTATTTTCGGACGGCCGTATGAA
GGCATCGCCGTGTTTCGACGGCAAAAAGATCACTGTAACAGGGACCCTGTGGAACGG
CAACAAAATTATCGACGAGCGCCTGATCAACCCCGACGGCTCCCTGCTGTTCCGAGT
AACCATCAACGGAGTGACCGGCTGGCGGCTGTGCGAACGCATTCTGGCGTAAAGGA
GGTAAACATATGACCATGATTACGGATTCACTGGCCGTCGTTTTACAACGTCGTGAC
TGGGAAAACCCTGGCGTTACCCAACCTTAATCGCCTTGCAGCACATCCCCCTTTCGCC
AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAG
CCTGAATGGCGAATGGTAAAAATTAAAGAATTACTAAGAGAGGACTTTAAGTATGC
GTAAC