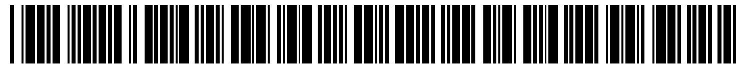


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(54) **ENGINEERED MICROBIAL POPULATION**

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**Publication Classification**

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| ***A23K 50/90*** | (2006.01) |
| ***C12N 15/74*** | (2006.01) |
| ***C12N 1/20*** | (2006.01) |

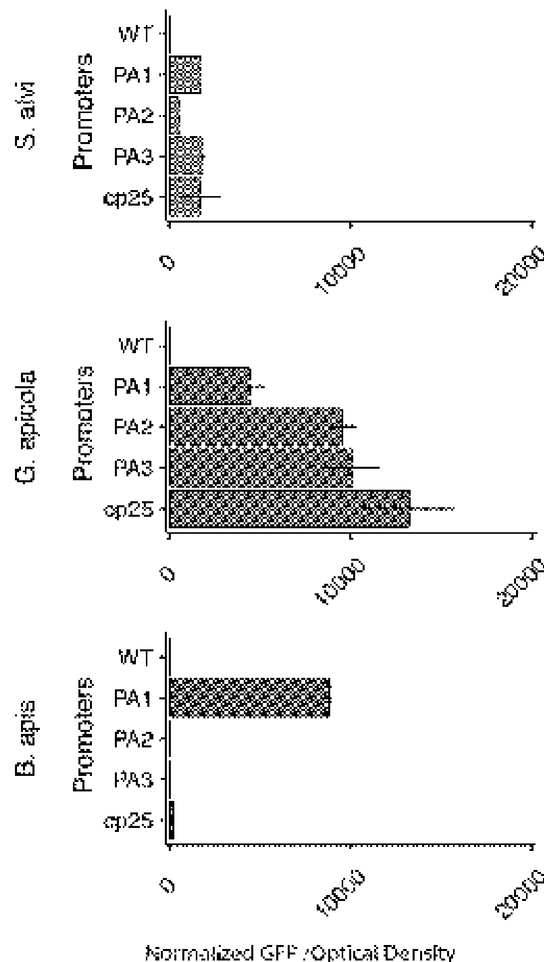
(52) **U.S. Cl.**

CPC ........ ***A61K 48/005*** (2013.01); ***A61K 9/0053*** (2013.01); ***A23K 50/90*** (2016.05); *C12N 2310/141* (2013.01); ***C12N 1/20*** (2013.01); *A01K 2227/706* (2013.01); *C12N 2310/20* (2017.05); ***C12N 15/746*** (2013.01)

(57) **ABSTRACT**

Provided herein are genetically engineered bacteria that are native to a host insect microbiome. Further provided are methods of inducing RNA interference in an insect, such as a bee, by administering the genetically engineered bacteria.

**Specification includes a Sequence Listing.**



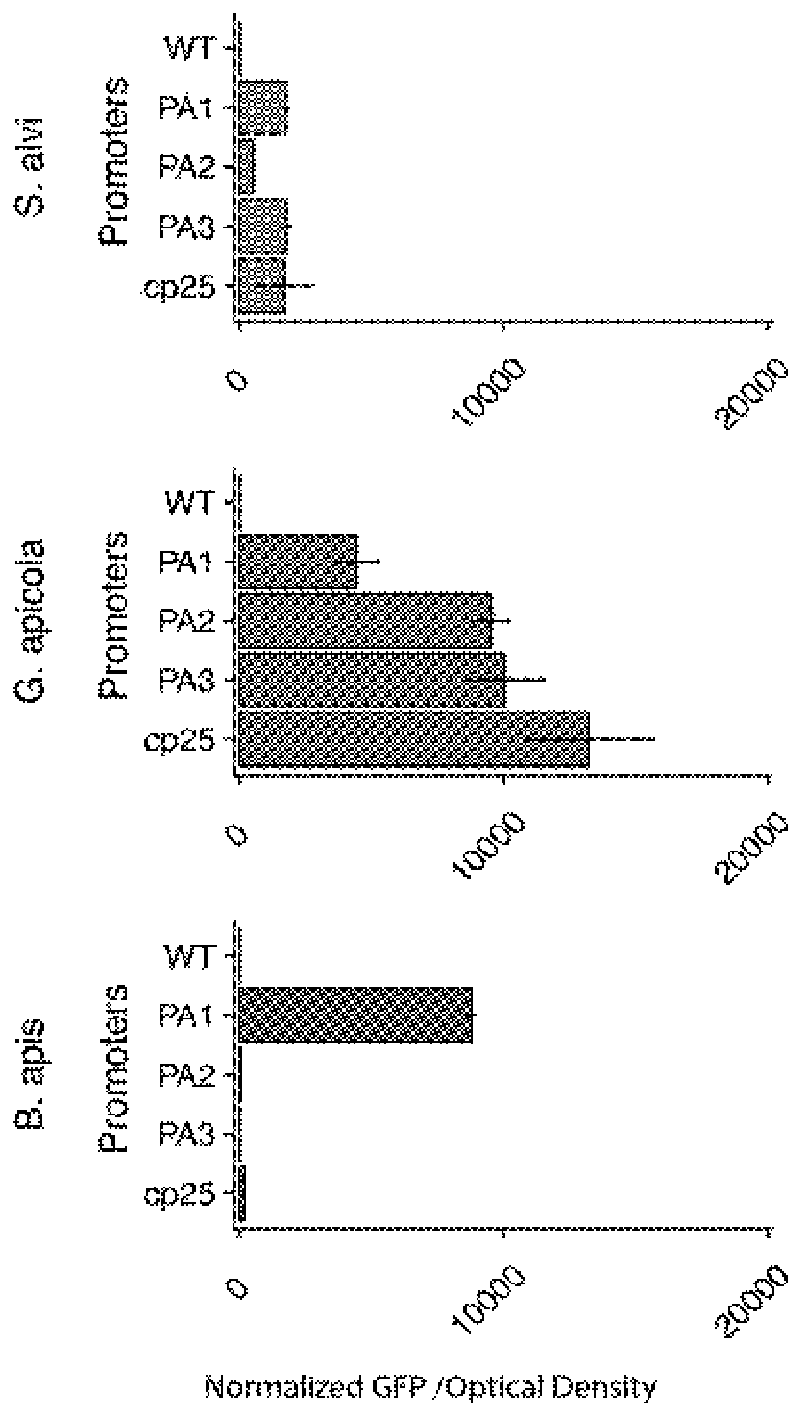



Figure 1

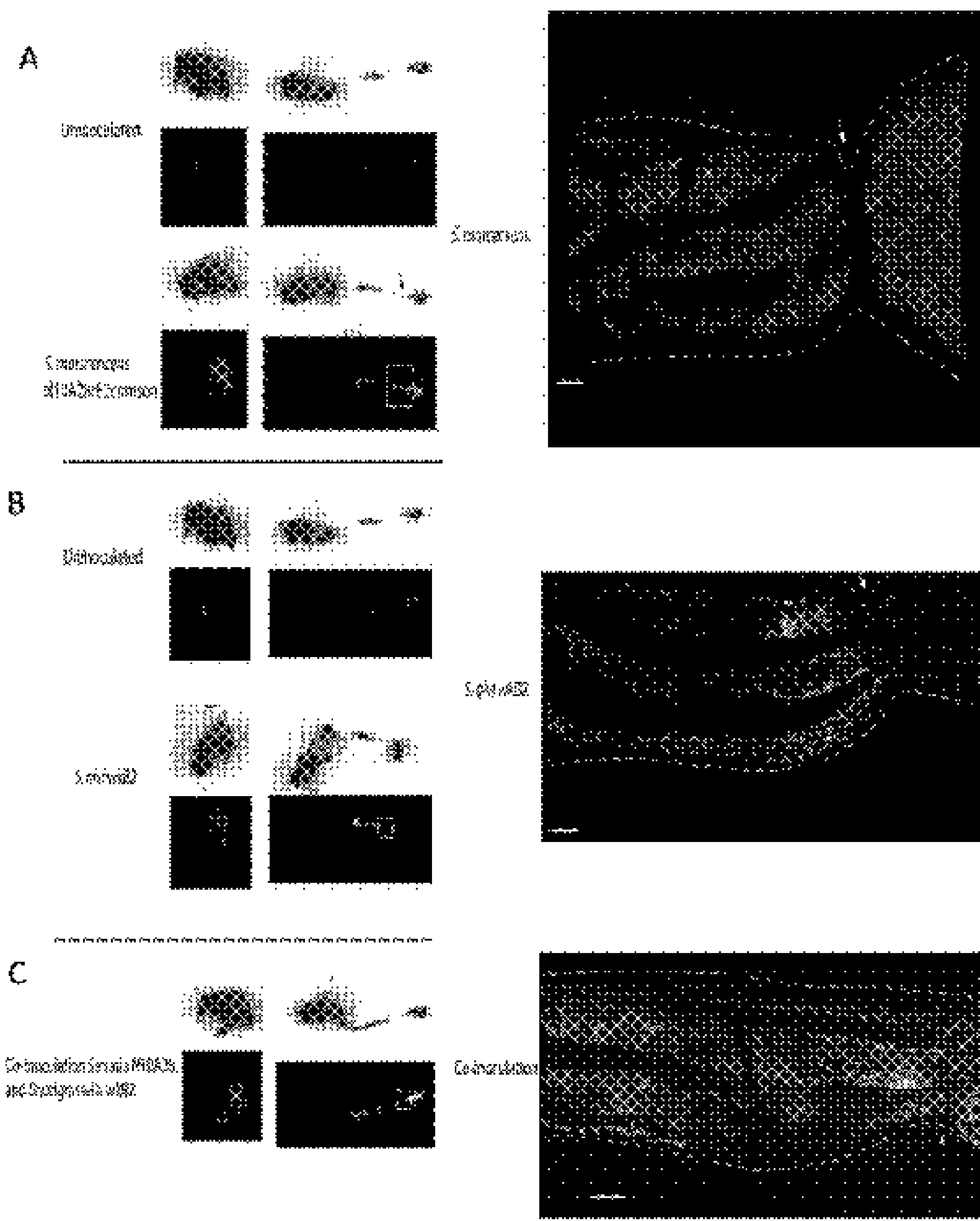



Figure 2A-Figure 2C

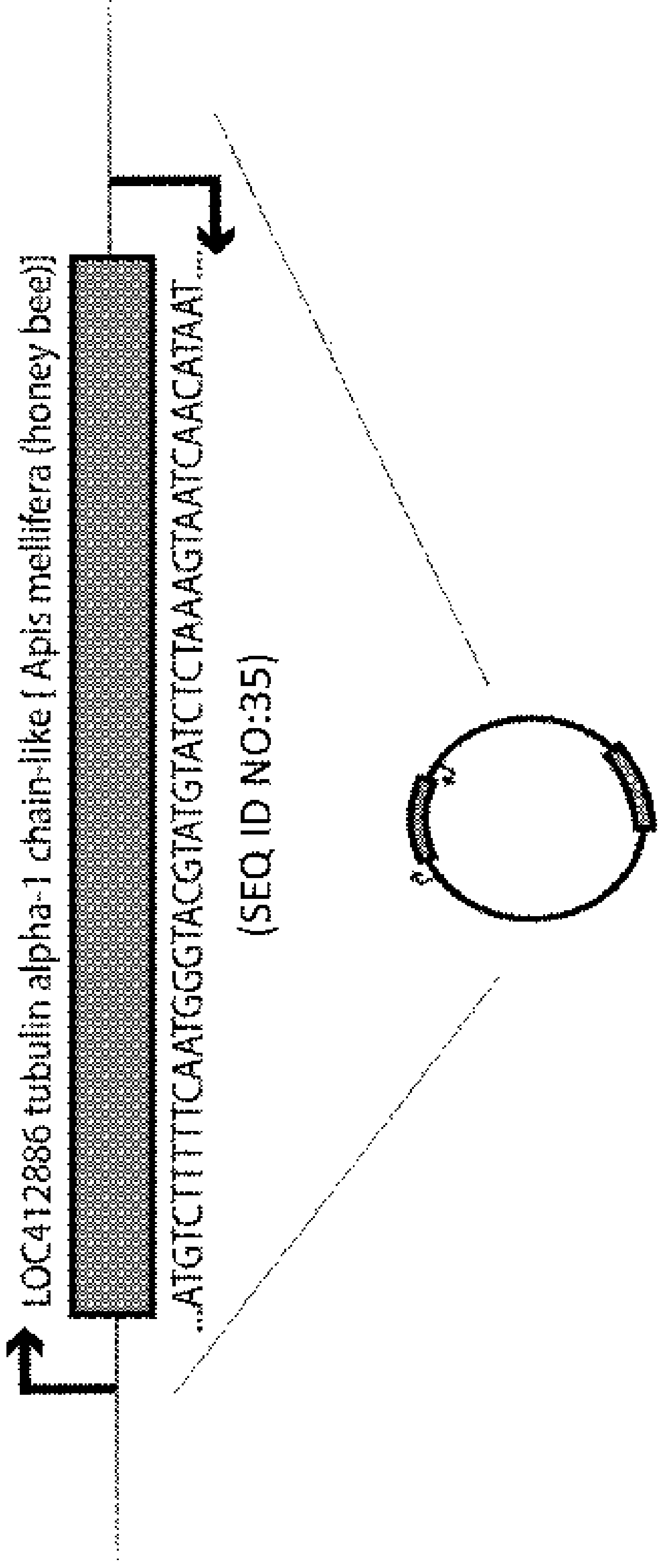



Figure 3

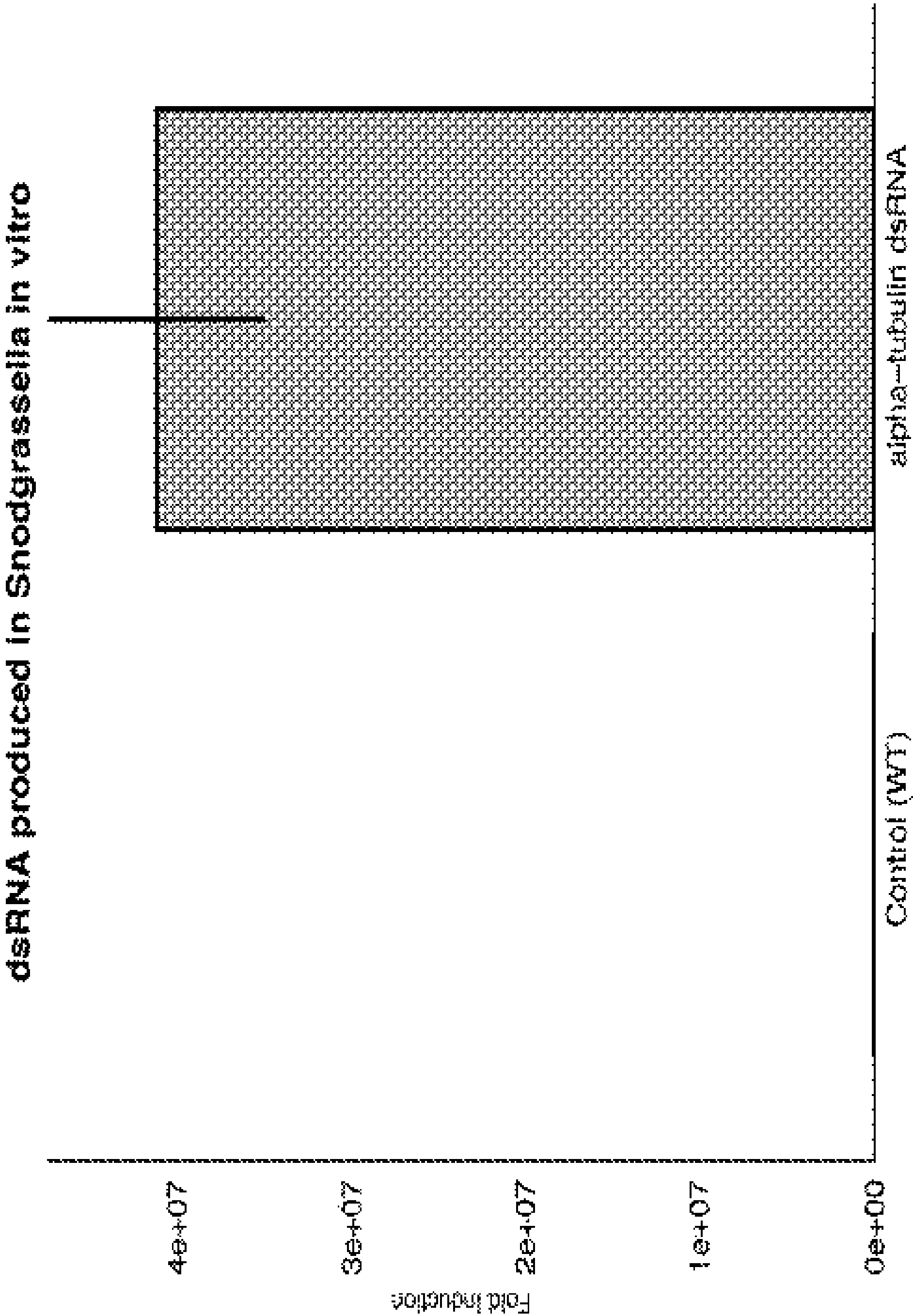



Figure 4

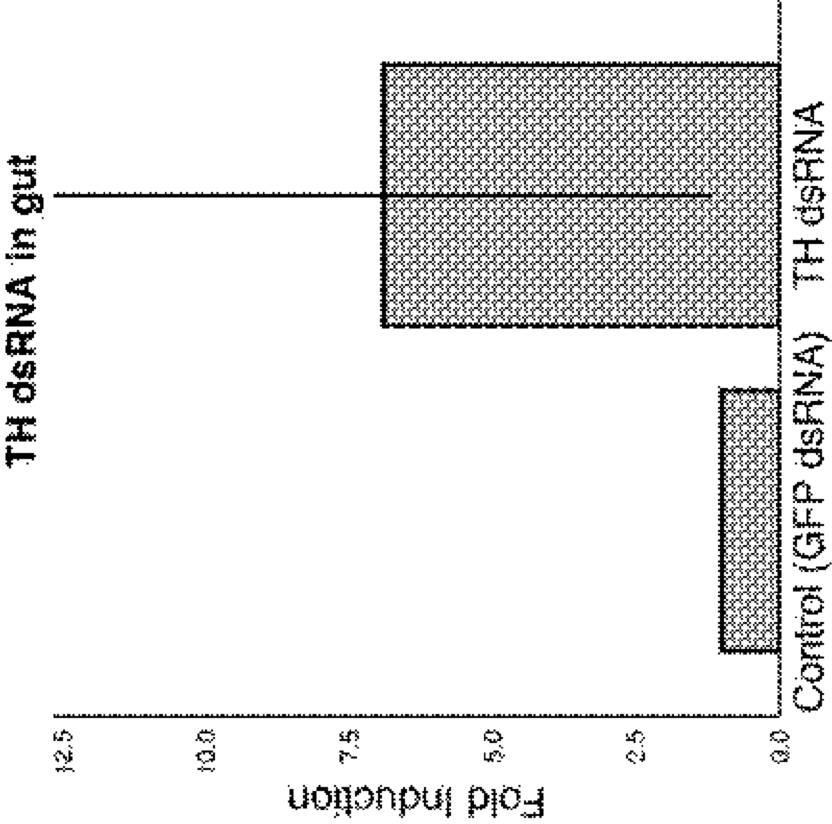



Figure 5

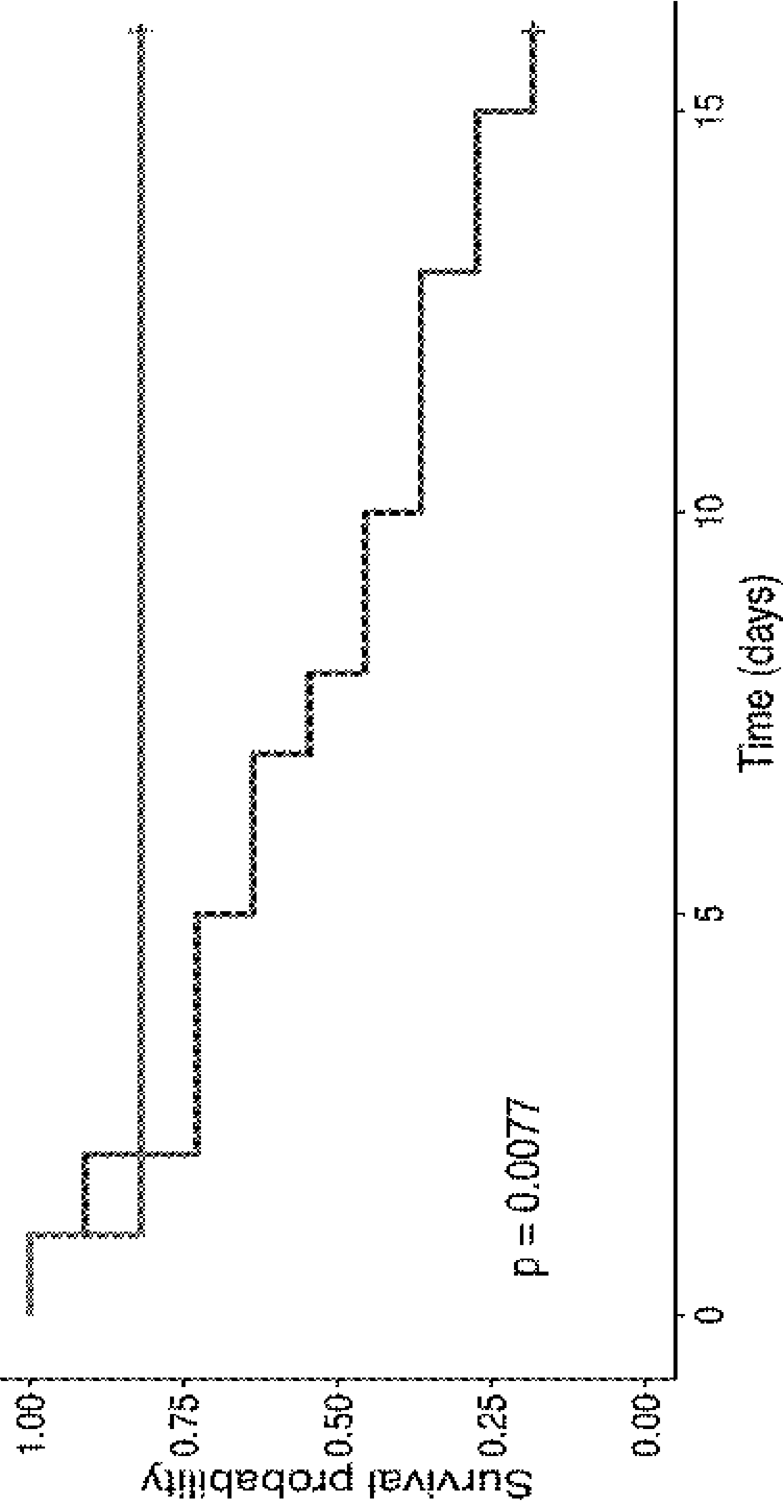
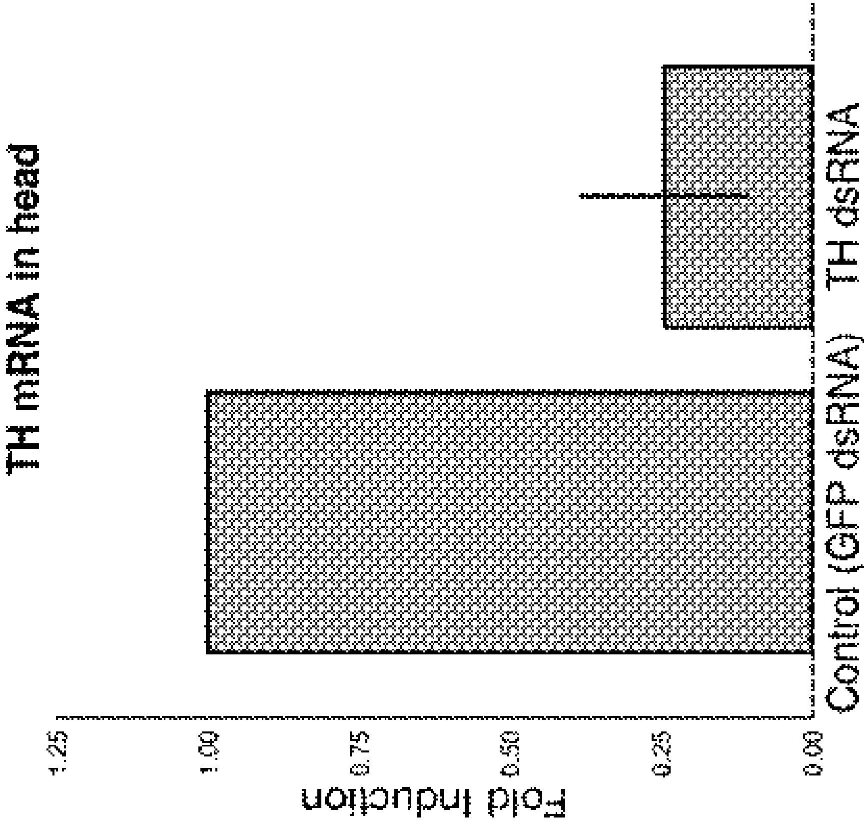



Figure 6

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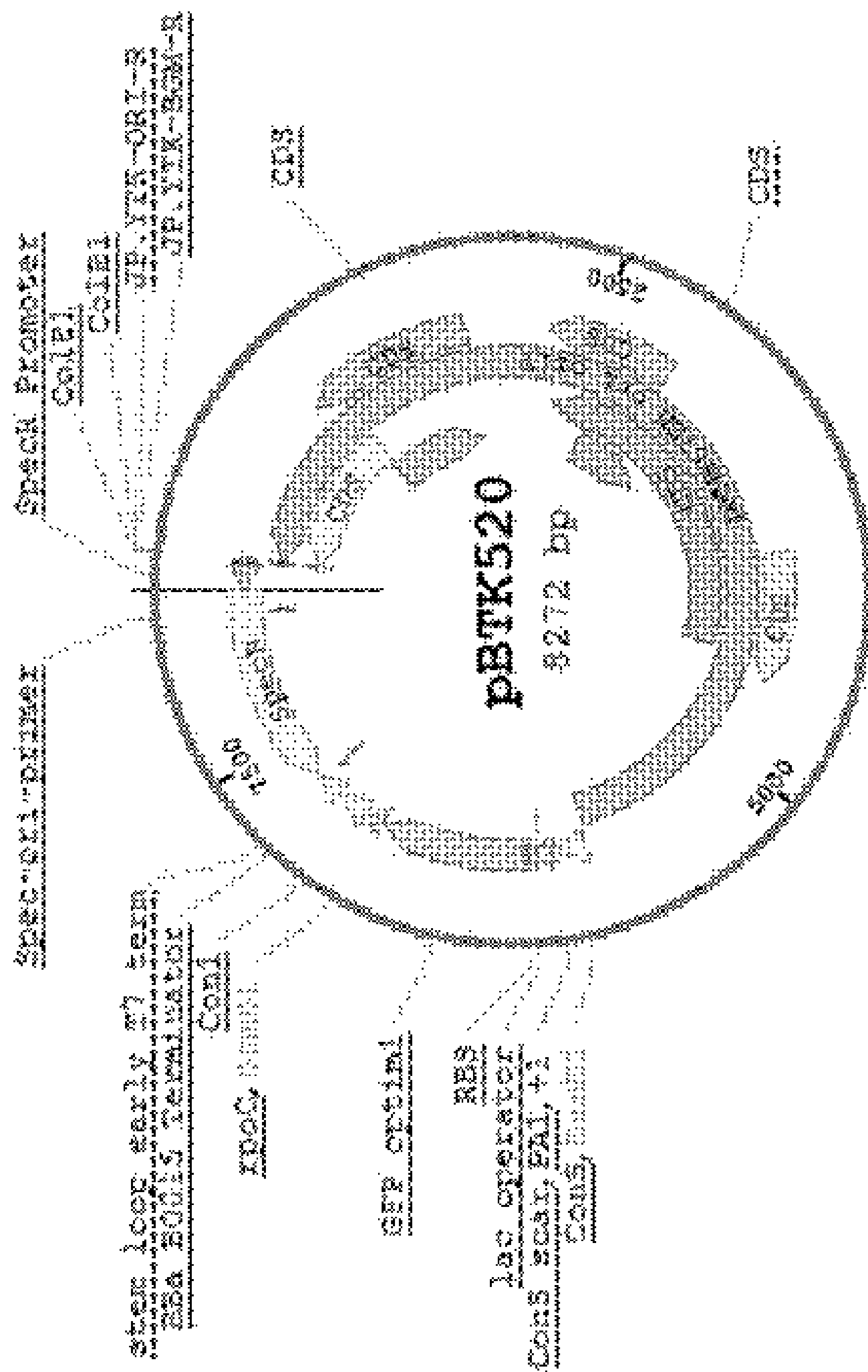


Figure 8A

Figure 8B

Figure 8C

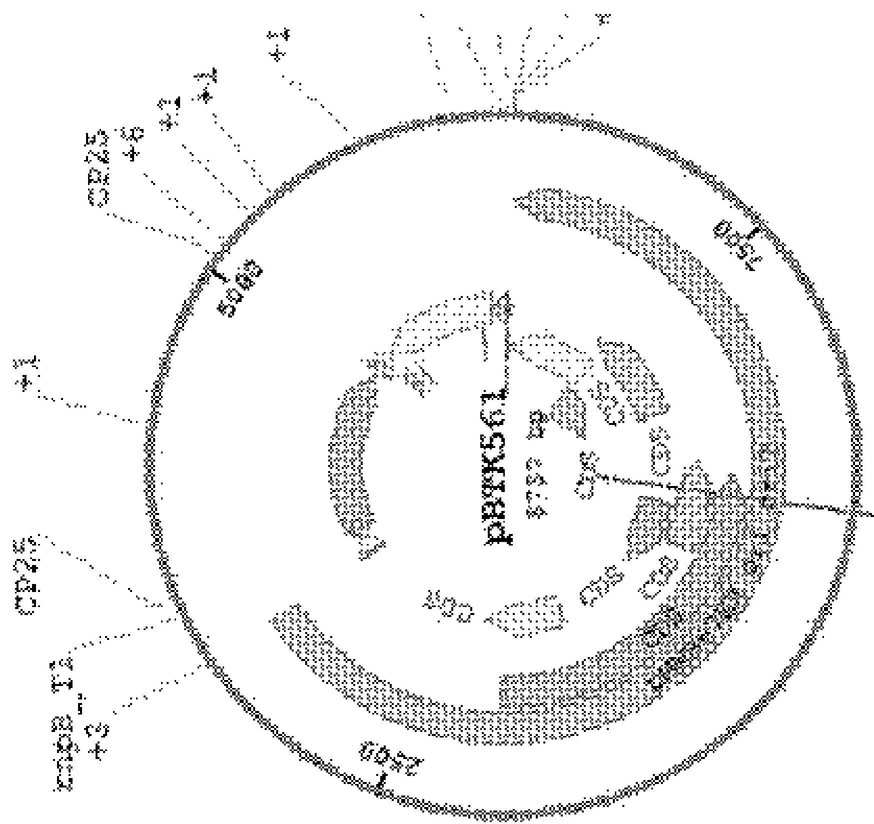

Figure 8D

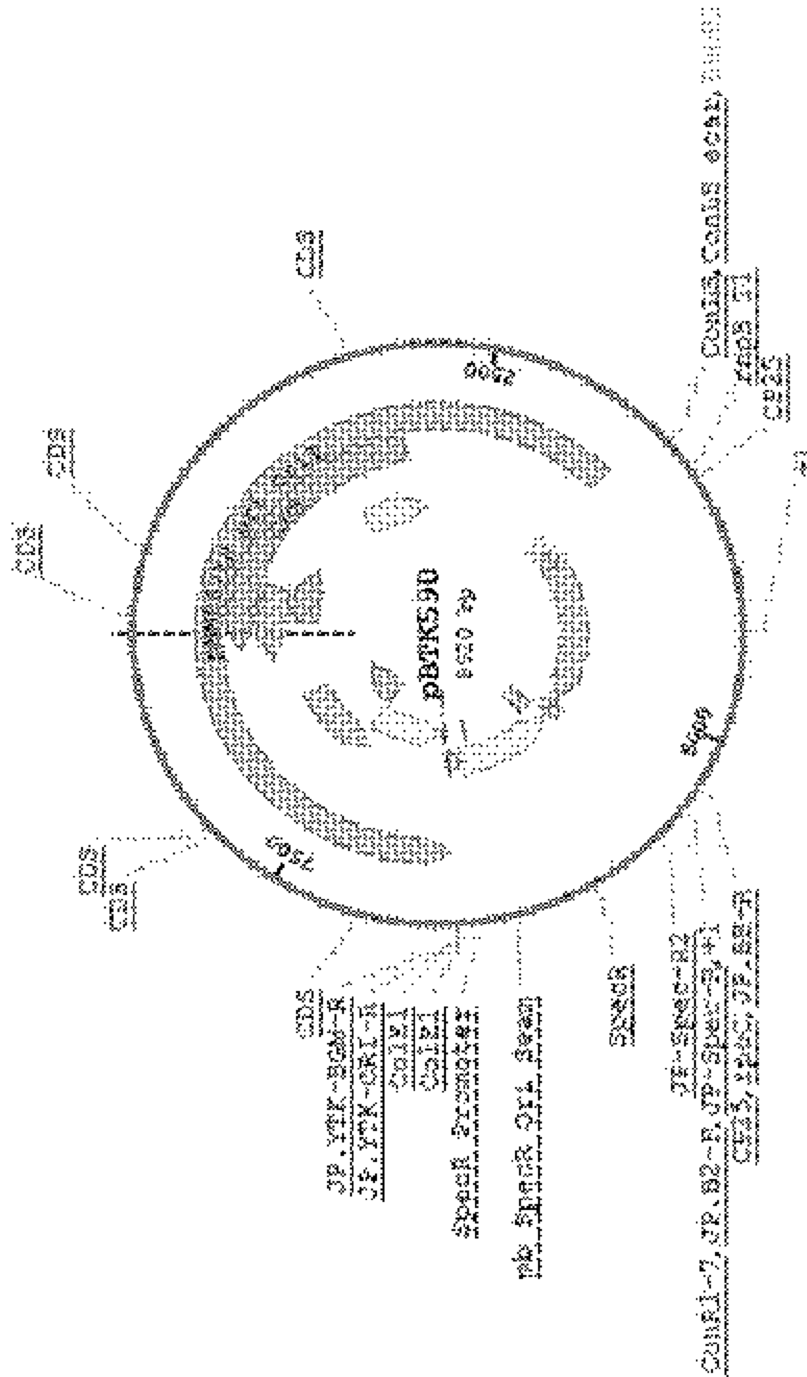


Figure 8E

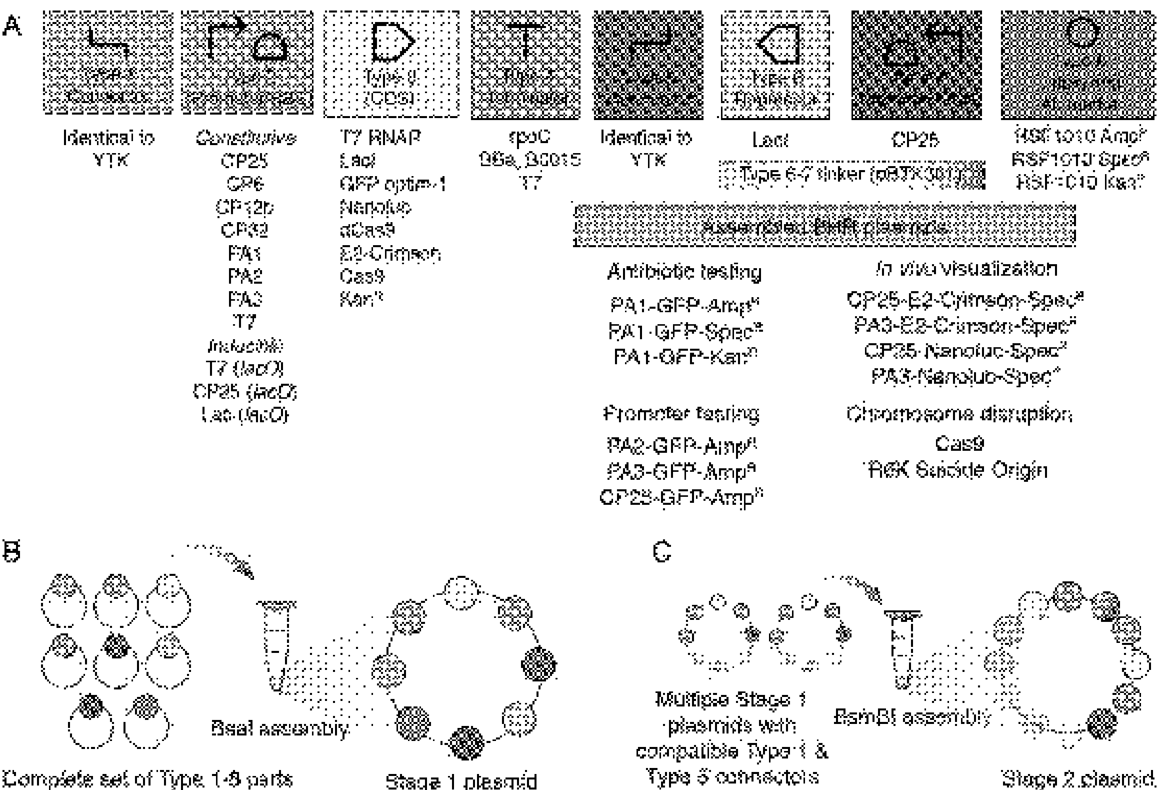


Figure 9A-Figure 9C

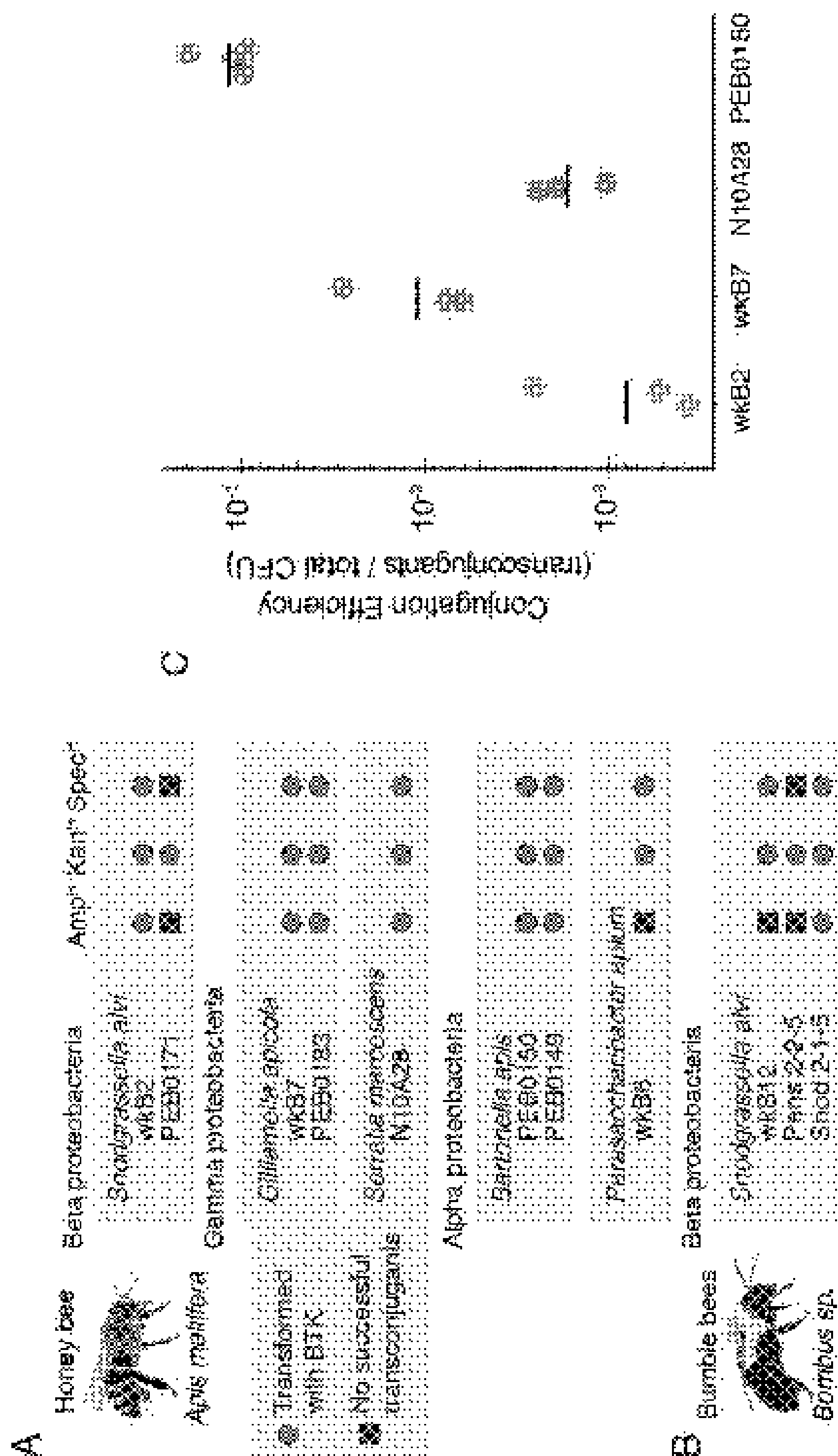


Figure 10A-Figure 10C

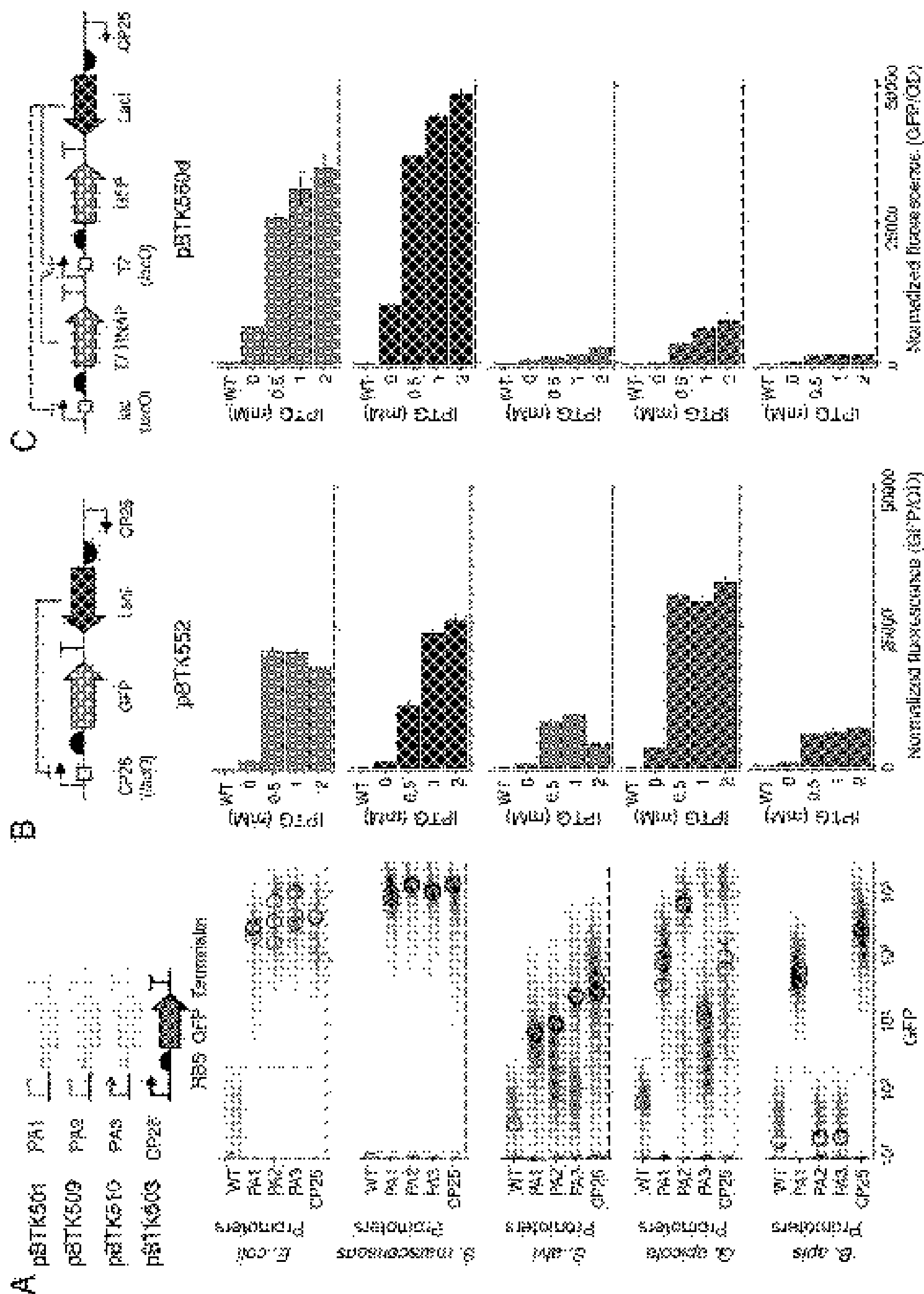


Figure 11A-Figure 11C

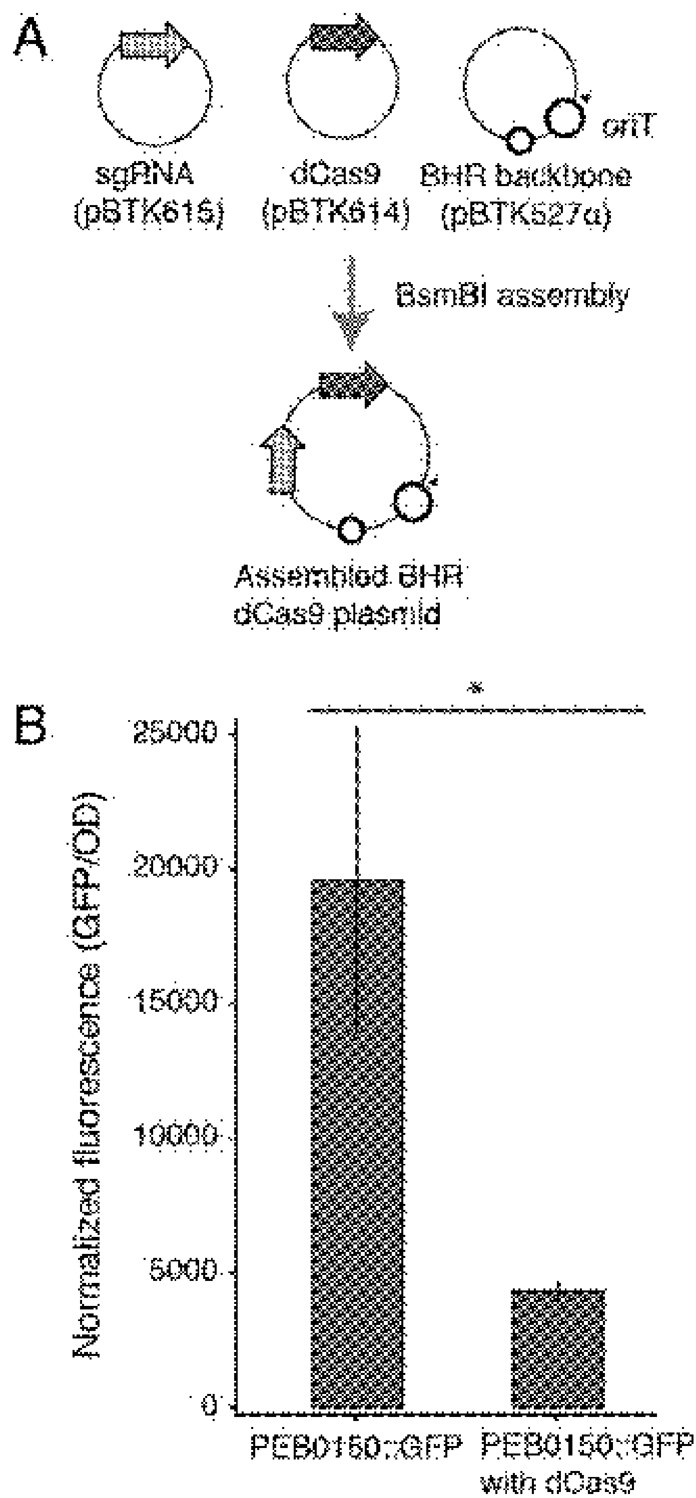


Figure 12A-Figure 12B

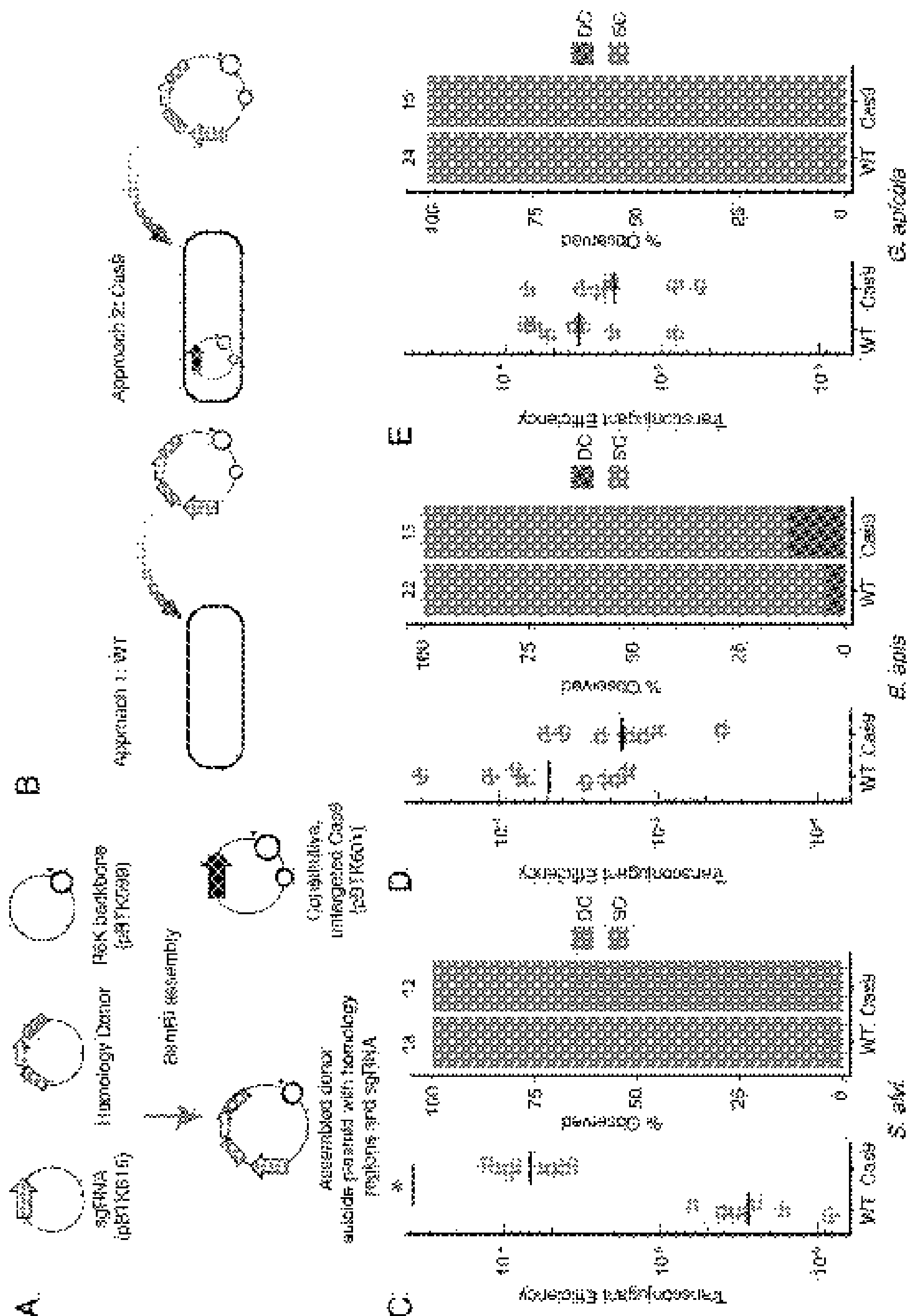


Figure 13A-Figure 13E

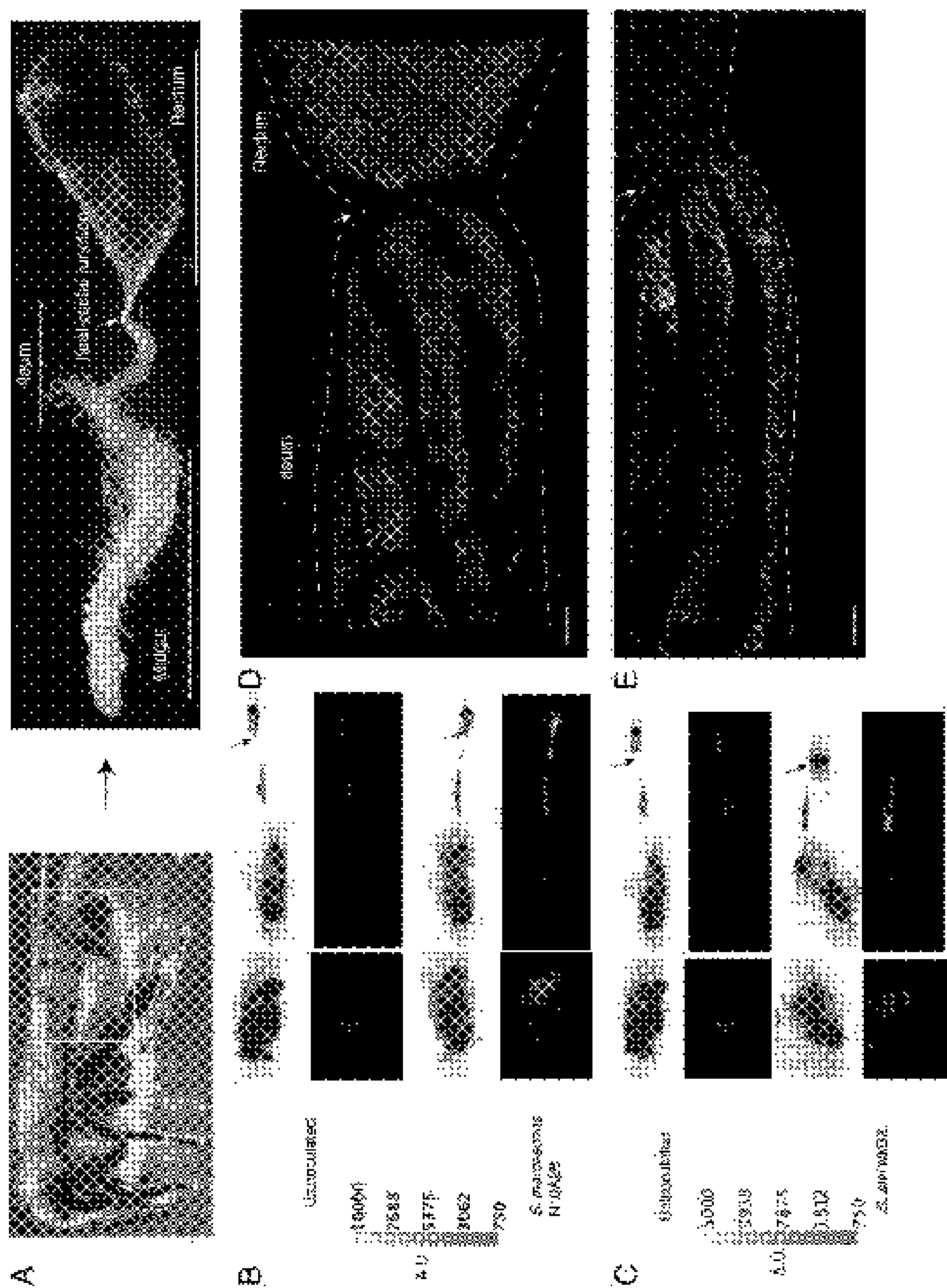

Figure 14A-Figure 14E

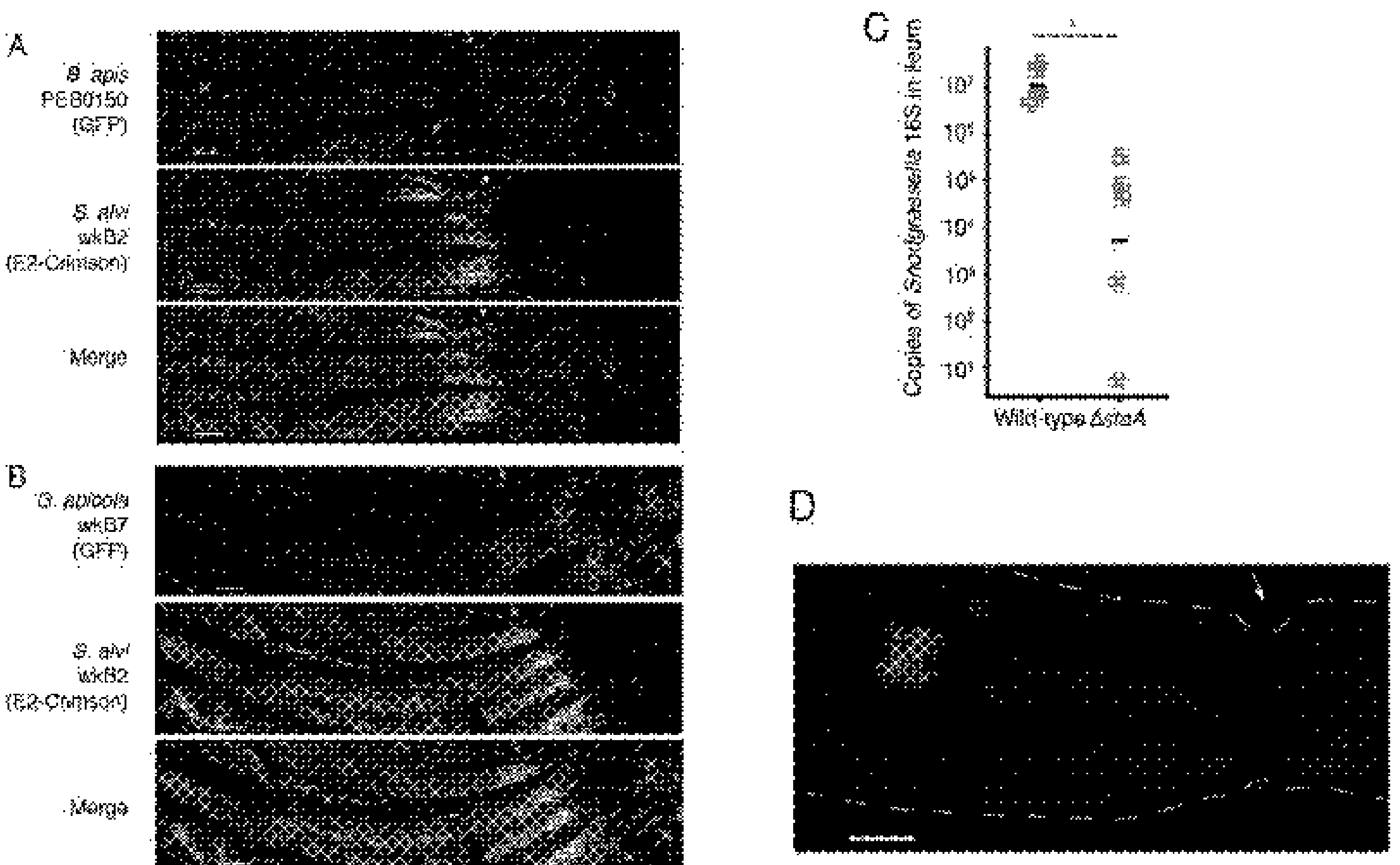


Figure 15A-Figure 15D

Broad-host-range Plasmid Screen in Bee Gut Bacteria

| **Plasmid** | RP4 | pTD-C_sfYFP | pAKgfp | pBMTBX-3 | pMMB67EH | pBMTBX-2 |
|---|---|---|---|---|---|---|
| **Origin** | RP4 | mini-rp4 | pBBR1 | pBBR1 | RSF1010 | pBBR1 |
| **Antibiotic Marker** | Amp, Kan | Strep, Spec | Amp | Cam | Amp | Kan |
| ***Snodgrassella alvi*** | - | - | + | - | + | + |
| ***Gilliamella apicola*** | - | - | - | - | + | - |

"+" indicates transconjugants were successfully passaged on selective media, and plasmid was re-isolated and able to re-transform *E. coli* DH5alpha cells.

Figure 16

Bacterial Strains

| Species and strain | Source | ID |
|---|---|---|
| *E. coli* MFDpir | [1] | N/A |
| *E. coli* DH5alpha | Thermo-Fisher | CAT# 11319-019 |
| *E. coli* EC100D | Lucigen | CAT# ECP09500 |
| *Snodgrassella alvi* wkB2 | [2] | ATCC BAA-2449 |
| *Snodgrassella alvi* PEB0171 | This study | N/A |
| *Snodgrassella alvi* wkB12 | [2] | N/A |
| *Snodgrassella alvi* Snod 2-1-5 | This study | N/A |
| *Snodgrassella alvi* PENS 2-2-5 | This study | N/A |
| *Gilliamella apicola* wkB7 | [3] | N/A |
| *Gilliamella apicola* PEB0183 | This study | N/A |
| *Bartonella apis* PEB0150 | [4] | N/A |
| *Bartonella apis* PEB0149 | [4] | N/A |
| *Parasaccharibacter apium* wkB8 | This study | N/A |
| *Serratia marcescens* N10A28 | This study | N/A |

Figure 17

| part | type | 5'-site | 3'-site | description | marker | origin | Part Source |
|---|---|---|---|---|---|---|---|
| | | | | **Entry Vector** | | | |
| pBTK001 | entry vector | | | entry vector for generating new parts | CamR | p15A | 1 |
| | | | | **pYTK001 from Yeast Toolkit is a suitable entry vector** | | | |
| | | | | **Type 1 - Connectors** | | | |
| | | | | **Use Connector sequences from Yeast Toolkit** | | | |
| | | | | **Type 2 - Promoters** | | | |
| | *Constitutive* | | | | | | |
| pBTK102 | promoter | 2 | 2 | T7 + RBS | CamR | ColE1 | 2 |
| pBTK107 | promoter | 2 | 2 | CP25 + RBS | CamR | ColE1 | 3 |
| pBTK110 | promoter | 2 | 2 | CP6 + RBS | CamR | ColE1 | 3 |
| pBTK112 | promoter | 2 | 2 | CP12b + RBS | CamR | ColE1 | 2 |
| pBTK113 | promoter | 2 | 2 | CP22 + RBS | CamR | ColE1 | 2 |
| pBTK119 | promoter | 2 | 2 | PA1 + RBS | CamR | p15A | 4 |
| pBTK120 | promoter | 2 | 2 | PA2 + RBS | CamR | p15A | 4 |
| pBTK121 | promoter | 2 | 2 | PA3 + RBS | CamR | p15A | 4 |
| | *Inducible* | | | | | | |
| pBTK103 | promoter | 2 | 2 | Lac lacO + RBS | CamR | ColE1 | 5 |
| pBTK124 | promoter | 2 | 2 | CP25 (lacO) | CamR | ColE1 | |
| pBTK130 | promoter | 2 | 2 | T7 (lacO) | CamR | ColE1 | |
| | | | | **Type 3 - Coding Sequences** | | | |
| pBTK200 | coding_sequence | 3 | 3 | T7 RNA Polymerase | CamR | ColE1 | 2 |
| pBTK203 | coding_sequence | 3 | 3 | LacI repressor | CamR | ColE1 | 6 |
| pBTK205 | coding_sequence | 3 | 3 | GFP optim-1 | CamR | ColE1 | 7 |
| pBTK206 | coding_sequence | 3 | 3 | [illegible] | CamR | ColE1 | 8 |
| pBTK209 | coding_sequence | 3 | 3 | dCas9 | CamR | ColE1 | 9 |
| pBTK224 | coding_sequence | 3 | 3 | E2-Crimson | CamR | ColE1 | 10 |
| pBTK229 | For homologous recombination | 3 | 3 | Kanamycin Resistance | CamR | ColE1 | 2 |
| | | | | **Type 4 - Terminators** | | | |
| pBTK300 | terminator | 4 | 4 | [illegible] | CamR | ColE1 | 11 |
| pBTK301 | terminator | 6 | 7 | BBa_B0015 Terminator | CamR | ColE1 | 12 |
| pBTK305 | terminator | 4 | 4 | T7 | CamR | ColE1 | 2 |
| | | | | **Type 5 - Connectors** | | | |
| | | | | **Use Connector sequences from Yeast Toolkit** | | | |
| | | | | **Type 6 - Repressors (reverse CDS)** | | | |
| pBTK211 | | 6 | 6 | LacI Reverse | CamR | ColE1 | 13 |
| | | | | **Type VII - Reverse promoters** | | | |
| pBTK136 | promoter | 7 | 7 | CP25 + RBS Reverse | CamR | ColE1 | 3 |
| | | | | **Type 8 - Origins and Antibiotics** | | | |
| pBTK401 | origin_marker | 8 | 8 | mRFP1 dropout | AmpR | RSF1010 | 14 |
| pBTK402 | origin_marker | 8 | 8 | mRFP1 dropout | KanR | RSF1010 | 14 |
| pBTK403 | origin_marker | 8 | 8 | mRFP1 dropout | SpecR | RSF1010 | 14 |

Figure 18

| Vectors for Stage 2 Assembly | | | | | | | |
|---|---|---|---|---|---|---|---|
| pBTK527 | Stage 1 | ConLS' | ConRE' | SPACE | KanR | RSF1010 | |
| pBTK527s | Stage 1 | ConLS' | ConRE' | SPACE | SpecR | RSF1010 | |
| pBTK599 | for homologous recombination | 6 | 8 | R6K-sfGFP | AmpR | R6k | 15 |
| pBTK599s | for homologous recombination | 6 | 8 | R6K-sfGFP | SpecR | R6k | 15 |

| Assembled Plasmids | | | | | | |
|---|---|---|---|---|---|---|
| pBTK501 | Stage 1 | ConLS' | ConRE | PA1 GFP optim1 | AmpR | RSF1010 |
| pBTK503 | Stage 1 | ConLS' | ConRE | CP25 GFP optim1 | AmpR | RSF1010 |
| pBTK509 | Stage 1 | ConLS' | ConRE | PA2 GFP optim1 | AmpR | RSF1010 |
| pBTK510 | Stage 1 | ConLS' | ConRE | PA3 GFP optim1 | AmpR | RSF1010 |
| pBTK519 | Stage 1 | ConLS | ConR1 | PA1 GFP optim1 | KanR | RSF1010 |
| pBTK520 | Stage 1 | ConLS | ConR1 | PA1 GFP optim1 | SpecR | RSF1010 |
| pBTK549 | Stage 1 | ConLS' | ConRE | T7 RNAP + CP25 LacI reverse | SpecR | RSF1010 |
| pBTK541 | Stage 1 | ConLS | ConRE | T7 lacO GFP optim1 | AmpR | RSF1010 |
| pBTK550d | Stage 2 | NA | NA | pBTK549 + pBTK541 | SpecR | RSF1010 |
| pBTK552 | Stage 1 | ConLS | ConR1 | CP25(lacO) inducible GFP | SpecR | RSF1010 |
| pBTK553 | Stage 1 | ConLS | ConR1 | CP25 NanoLuc luciferase | SpecR | RSF1010 |
| pBTK554 | Stage 1 | ConLS | ConR1 | PA3 NanoLuc luciferase | SpecR | RSF1010 |
| pBTK569 | Stage 2 | NA | NA | CP25 E2-crimson | SpecR | RSF1010 |
| pBTK570 | Stage 2 | NA | NA | PA3 E2-crimson | SpecR | RSF1010 |
| pBTK601 | Stage 2 | NA | NA | Cas9 (no sgRNA) | SpecR | RSF1010 |
| pBTK614 | Stage 1 | ConL1 | ConRE | dCas9 (no sgRNA) | AmpR | ColE1 |
| pBTK615 | Stage 1 | ConLS | ConR2 | sgRNA (gfp) | AmpR | ColE1 |
| pBTK619 | Stage 1 | ConLS | ConRE | CP25b GFP optim1 | KanR | RSF1010 |
| pBTK620 | Stage 1 | ConLS | ConRE | CP32 GFP optim1 | KanR | RSF1010 |
| pBTK621 | Stage 1 | ConLS | ConRE | CP6 GFP optim1 | KanR | RSF1010 |

Figure 18 (Continued)

# Oligonucleotides Used in the Study

| ID | Use | Source | Sequence (5' to 3') | |
|---|---|---|---|---|
| wkB2_KO_1 | Validate wkB2::staA mutant, upstream junction F | This Study | TAGCAACAGCGACAGAACCG | SEQ ID NO:13 |
| wkB2_KO_2 | Validate wkB2::staA mutant, upstream junction R | This Study | CTCAGGCGCAATCACAAATG | SEQ ID NO:14 |
| wkB2_KO_3 | Validate wkB2::staA mutant, downstream junction F | This Study | AATGCTGTTTTCCCGGGAT | SEQ ID NO:15 |
| wkB2_KO_4 | Validate wkB2::staA mutant, downstream junction R | This Study | CTGGAAATTCCTGCTGCCAG | SEQ ID NO:16 |
| wkB7_KO_1 | Validate wkB7::sacA mutant, upstream junction F | This Study | TCGCTTGTTCACAGCGATAGA | SEQ ID NO:17 |
| wkB7_KO_2 | Validate wkB7::sacA mutant, upstream junction R | This Study | GCTTTTGCCATTGTCACCGG | SEQ ID NO:18 |
| wkB7_KO_3 | Validate wkB7::sacA mutant, downstream junction F | This Study | ATTGGCAACGCTACCTTTGC | SEQ ID NO:19 |
| wkB7_KO_4 | Validate wkB7::sacA mutant, downstream junction R | This Study | GTCGTCGTATTTGTCAGGAGCA | SEQ ID NO:20 |
| d150_KO_1 | Validate PEB0150::carG mutant, upstream junction F | This Study | TGTTCAGGACGTGAATACACCTTAT | SEQ ID NO:21 |
| d150_KO_2 | Validate PEB0150::carG mutant, upstream junction R | This Study | AAATTGCAGTTTGATTTGATGCTGG | SEQ ID NO:22 |
| d150_KO_3 | Validate PEB0150::carG mutant, downstream junction F | This Study | GCGAGCCCATTTATACCCATATAAA | SEQ ID NO:23 |
| d150_KO_4 | Validate PEB0150::carG mutant, downstream junction R | This Study | TTCAAGGTTCCATTTGCCTTTTTCA | SEQ ID NO:24 |
| KO_5 | Amplify backbone of suicide plasmid F | This Study | ACCTGTTGATAGTACGTAGTAAGCTC | SEQ ID NO:25 |
| KO_6 | Amplify backbone of suicide plasmid R | This Study | TCAAAATTCCTTTGAGAGCCTCTAAG | SEQ ID NO:26 |
| pMMB_F | Validate replication of pMMB67EH / BTK plasmids F | This Study | TCATGTCATCCAGGTCAAACTC | SEQ ID NO:27 |
| pMMB_R | Validate replication of pMMB67EH / BTK plasmids R | This Study | TCAAGAAATCCAGAGCCATCAA | SEQ ID NO:28 |
| Beta-1009-qtF | 16S betaproteobacteria qPCR primer F, Beta-1009-qtF | * | CTTAGAGATAGGAGAGTG | SEQ ID NO:29 |
| Beta-1115-qtR | 16S betaproteobacteria qPCR primer R, Beta-1115-qtR | * | TAATGATGGCAACTAATGACAA | SEQ ID NO:30 |
| dCas9_sg | sgRNA sequence targeting gfp for dCas9 | This Study | CCCAATGCTCGTCCAATTAGACC | SEQ ID NO:31 |
| wkB2_KO_sg | Cas9 sgRNA targeting S. alvi wkB2 staA | This Study | GAATTCGAAGCATAAGAATT | SEQ ID NO:32 |
| wkB7_KO_sg | Cas9 sgRNA targeting S. apicola wkB7 sacA | This Study | TTCCACTTAATACGTGCATC | SEQ ID NO:33 |
| d150_KO_sg | Cas9 sgRNA targeting B. apis PEB0150 carG | This Study | ACACCATGTCCATGCGAAAA | SEQ ID NO:34 |

Figure 19

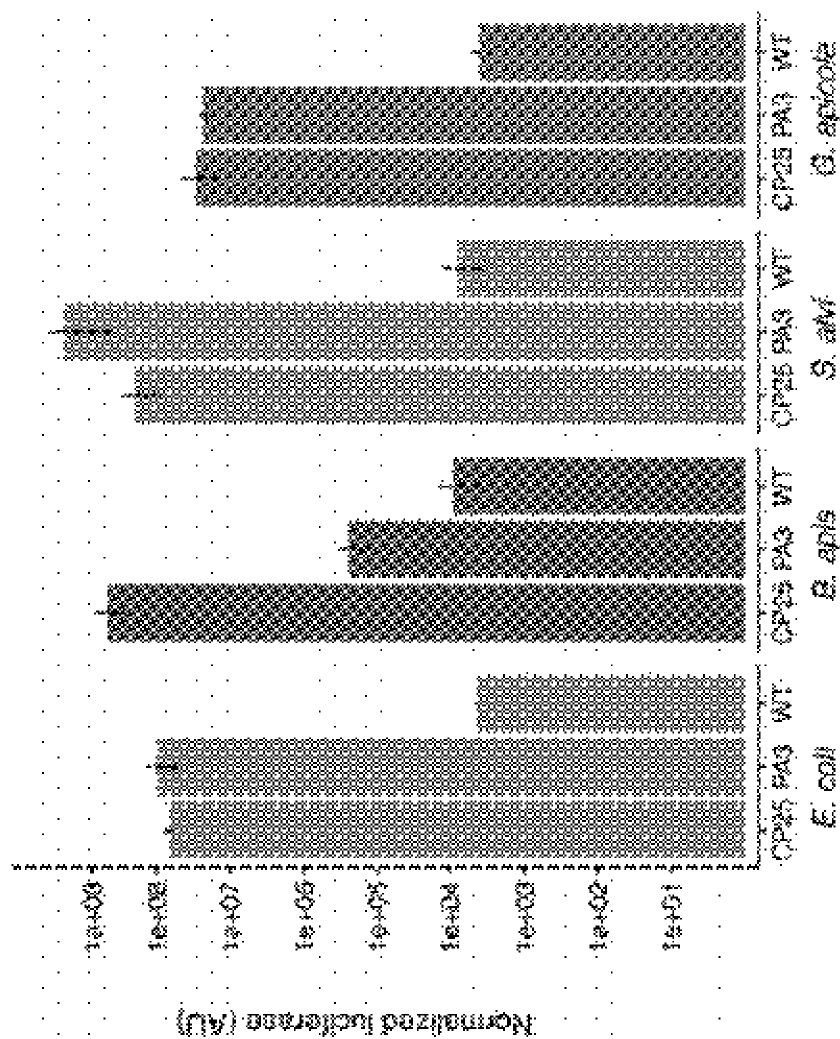


Figure 20

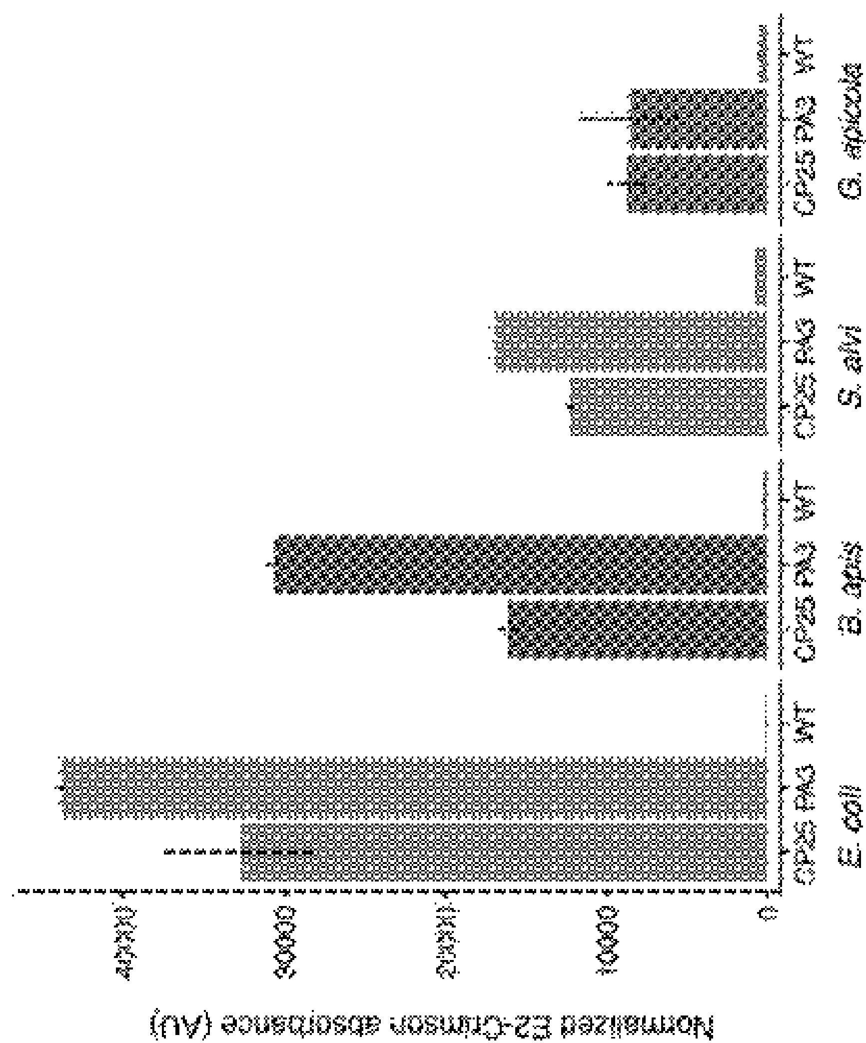


Figure 21

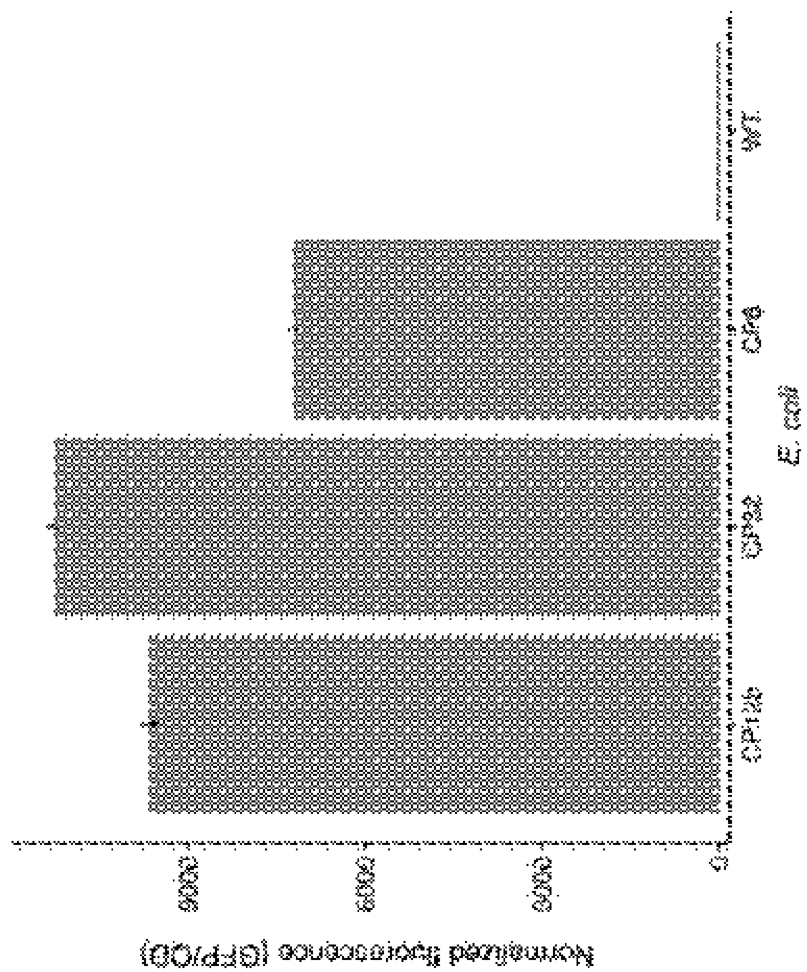


Figure 22

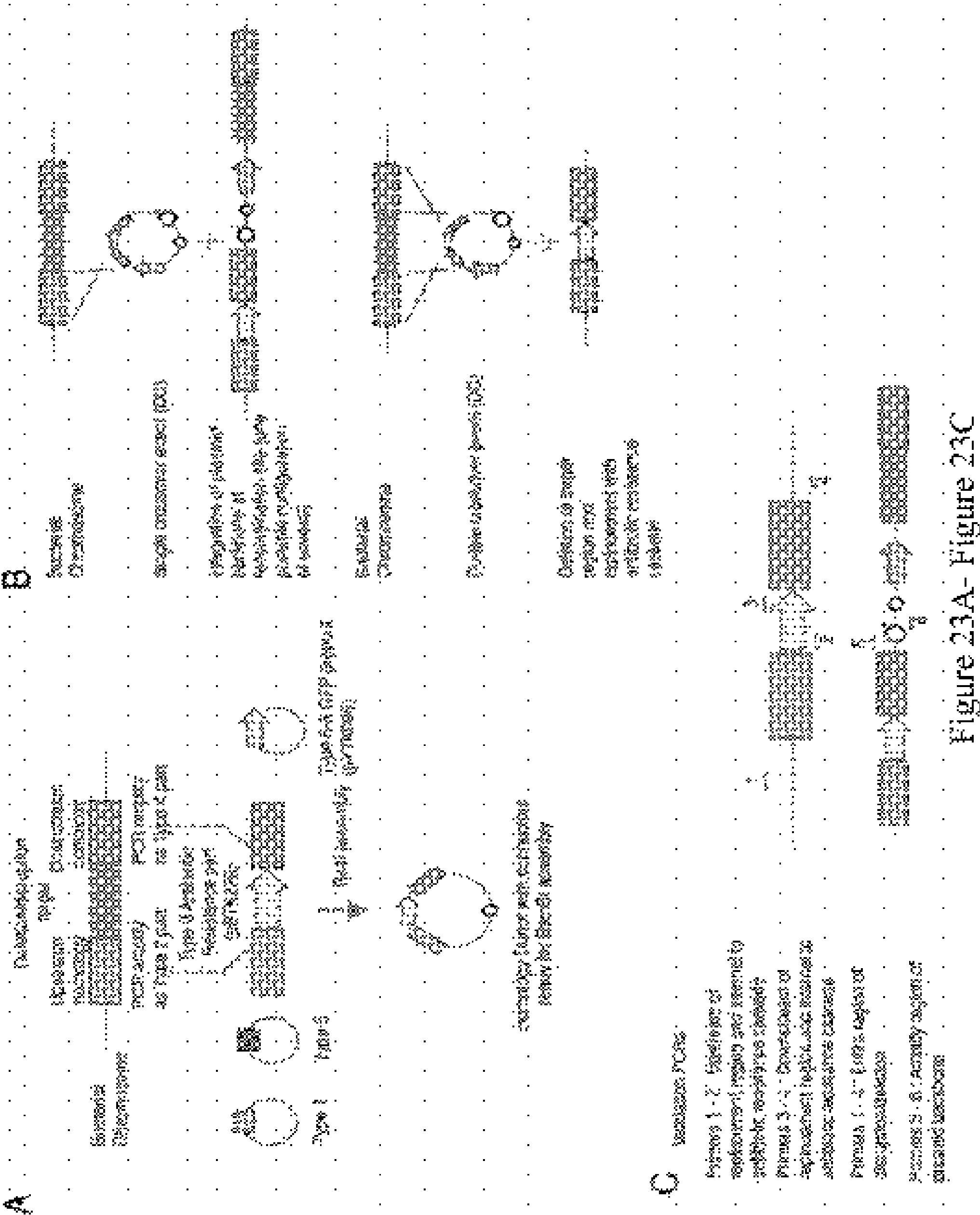

Figure 23A- Figure 23C

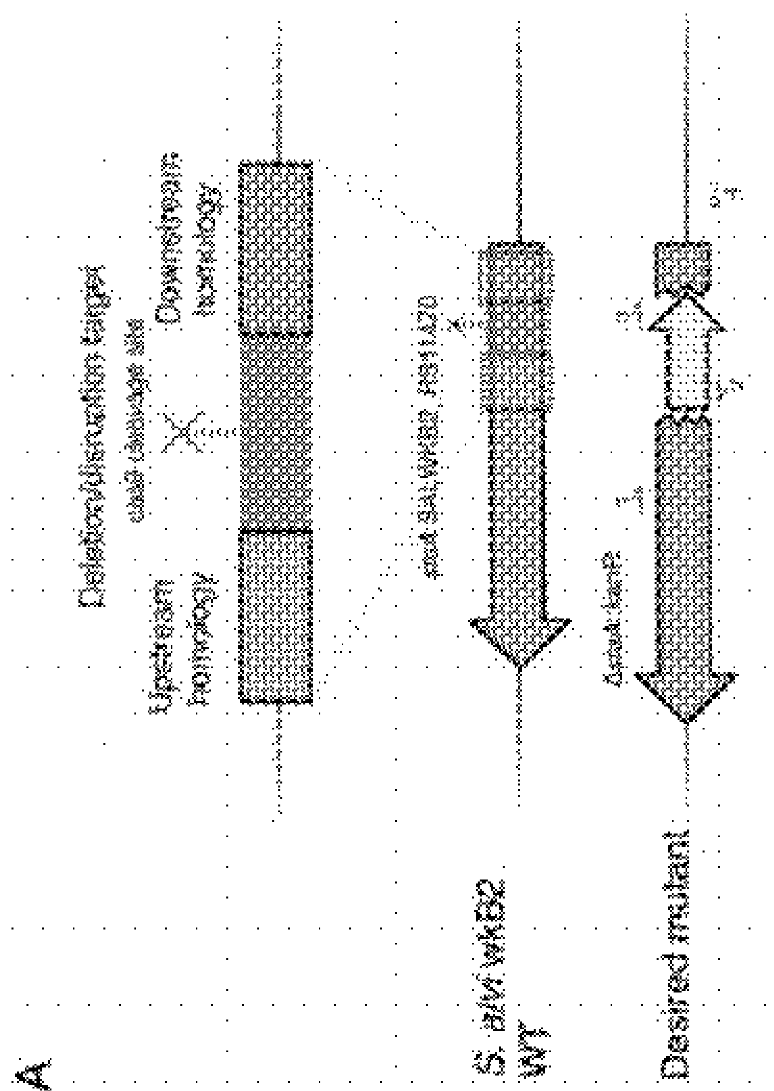


Figure 24A

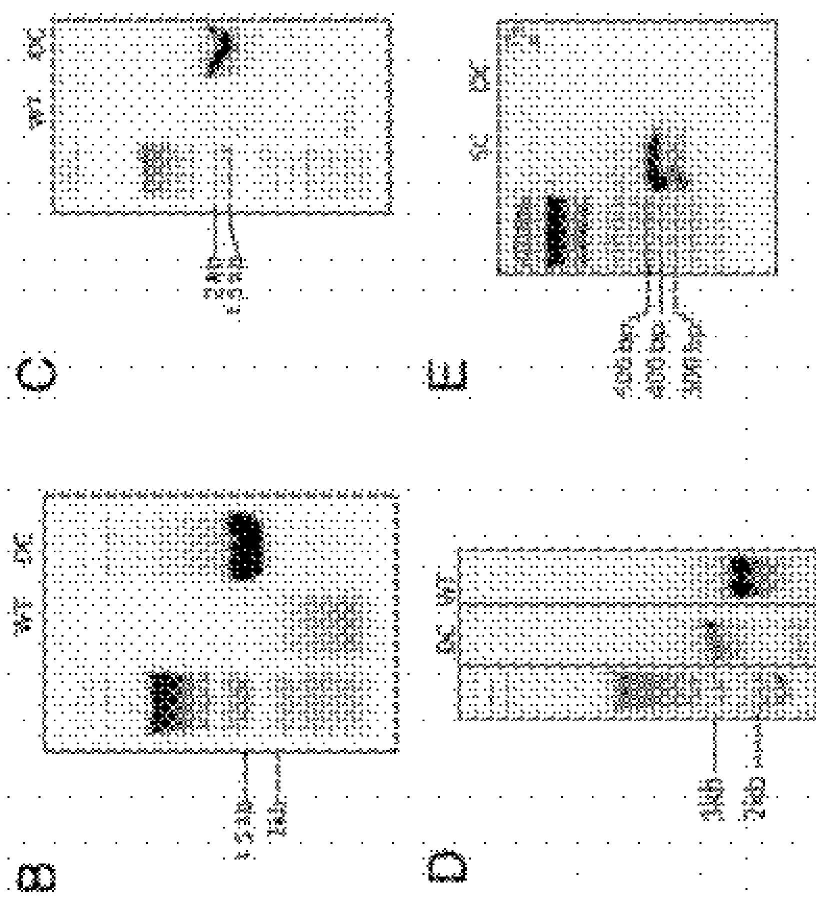


Figure 24B- Figure 24E

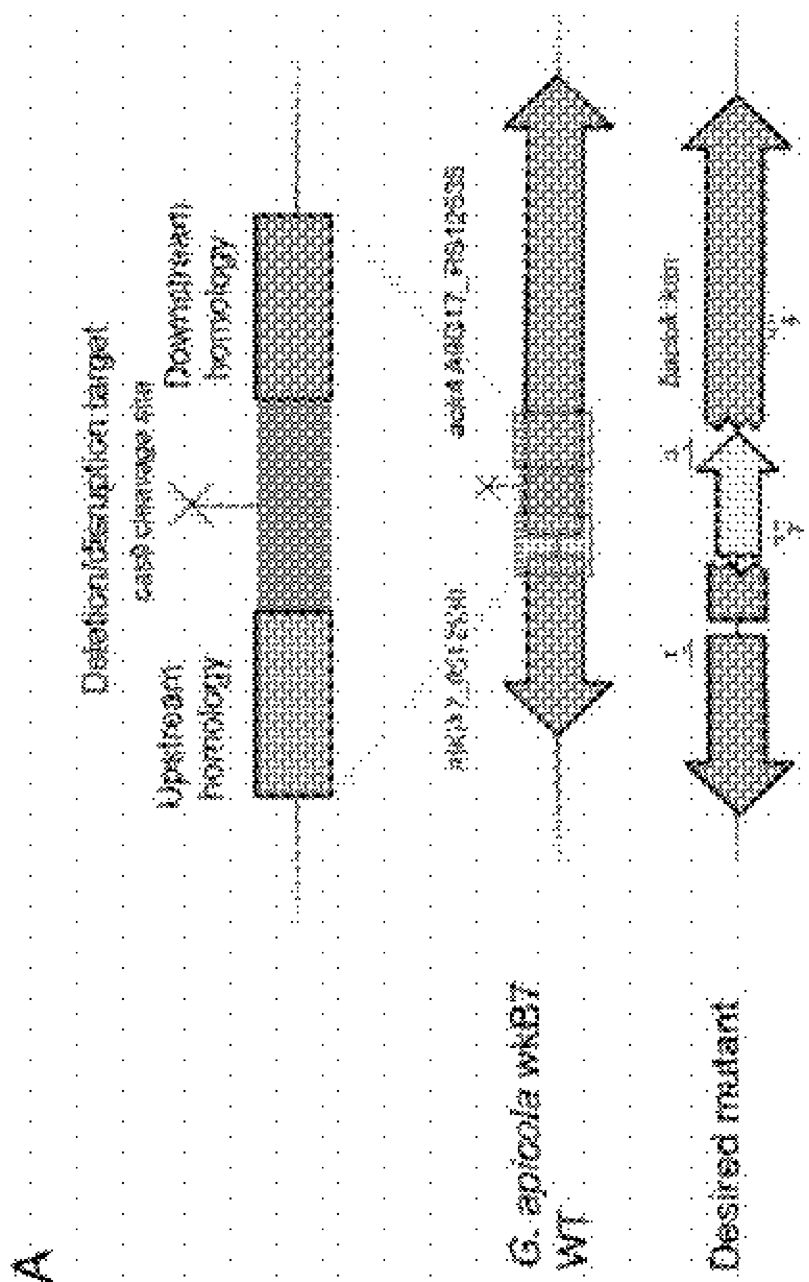


Figure 25A

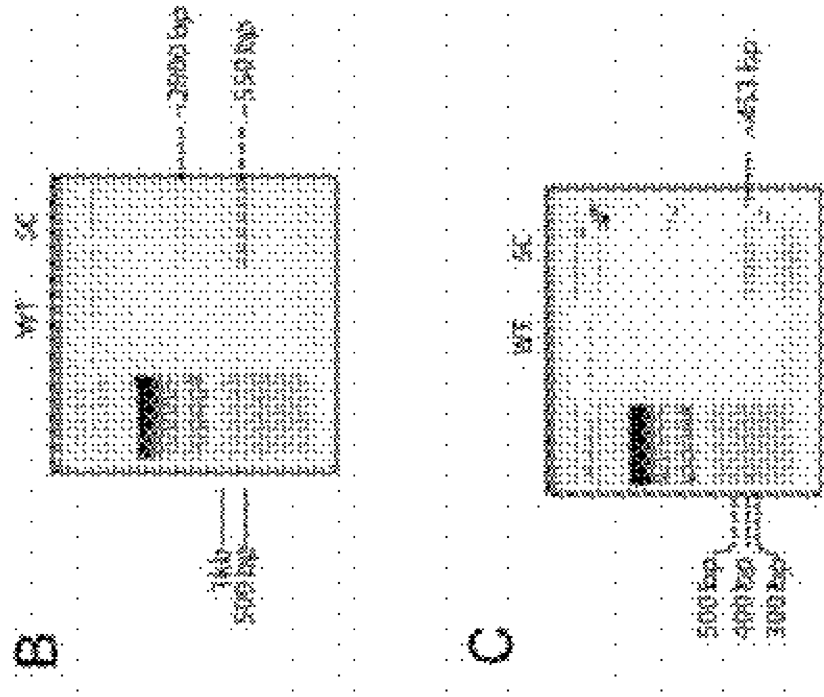


Figure 25B- Figure 25C

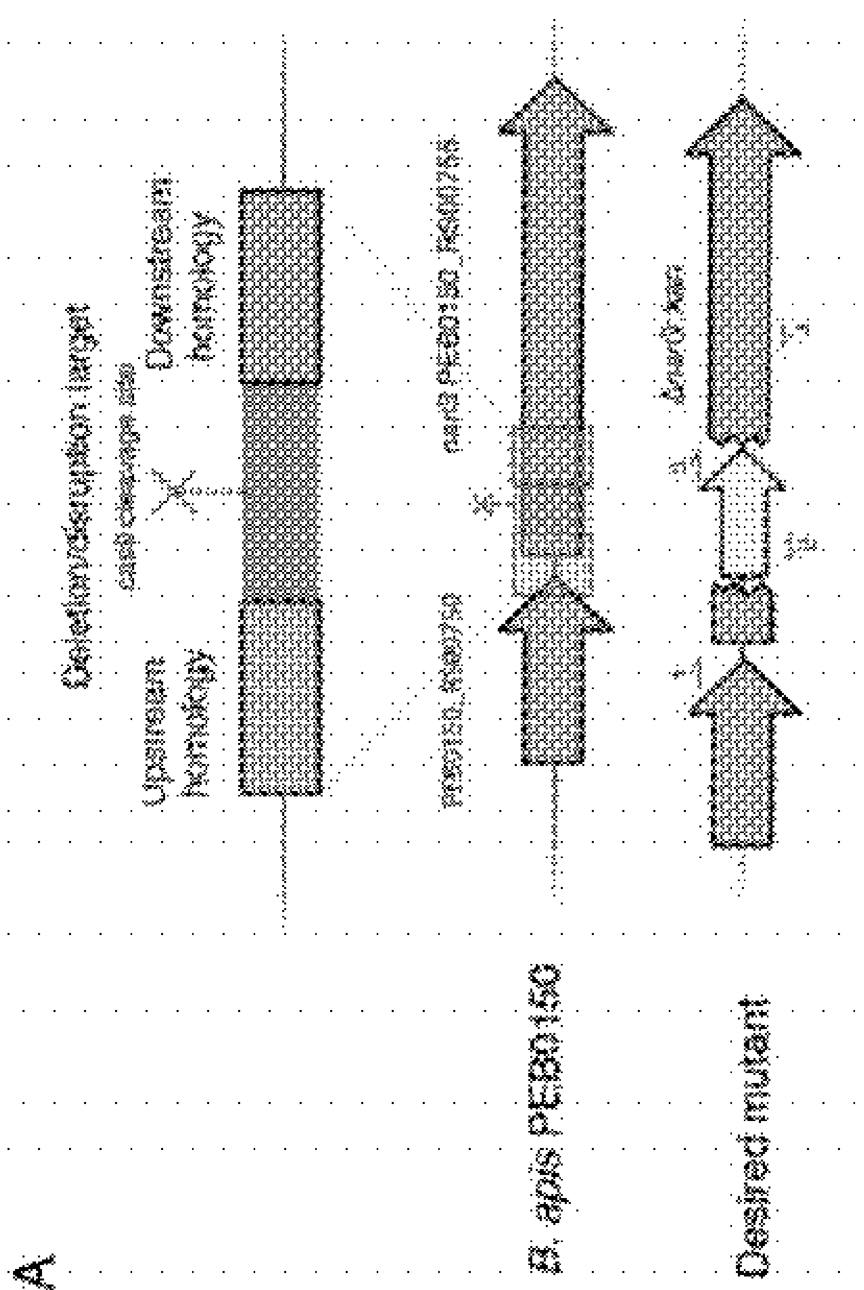


Figure 26A

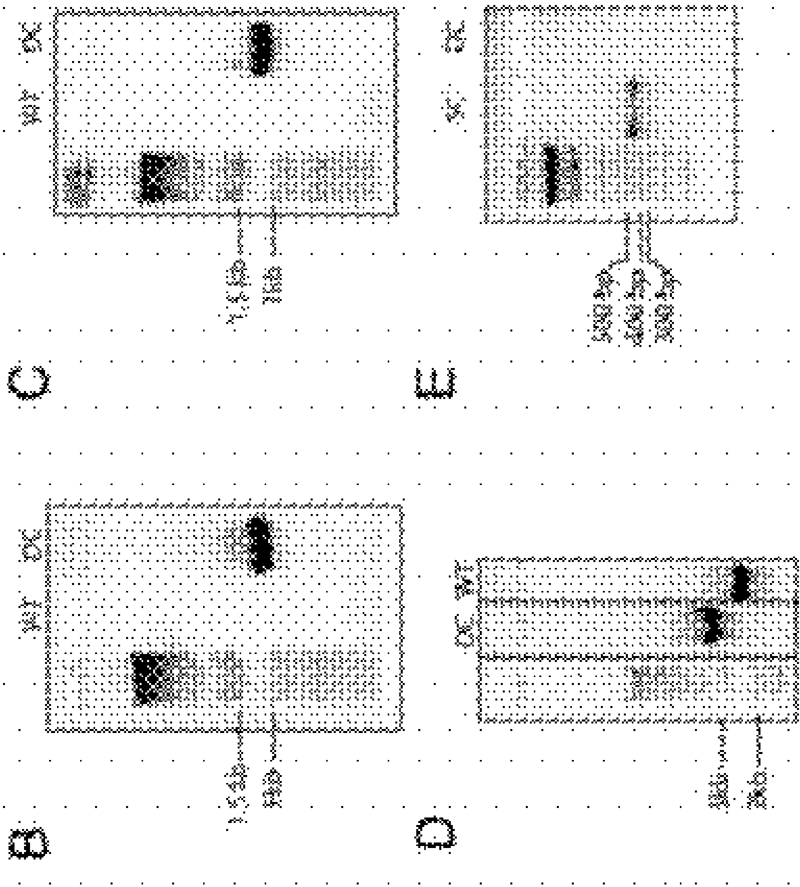

Figure 26B- Figure 26E

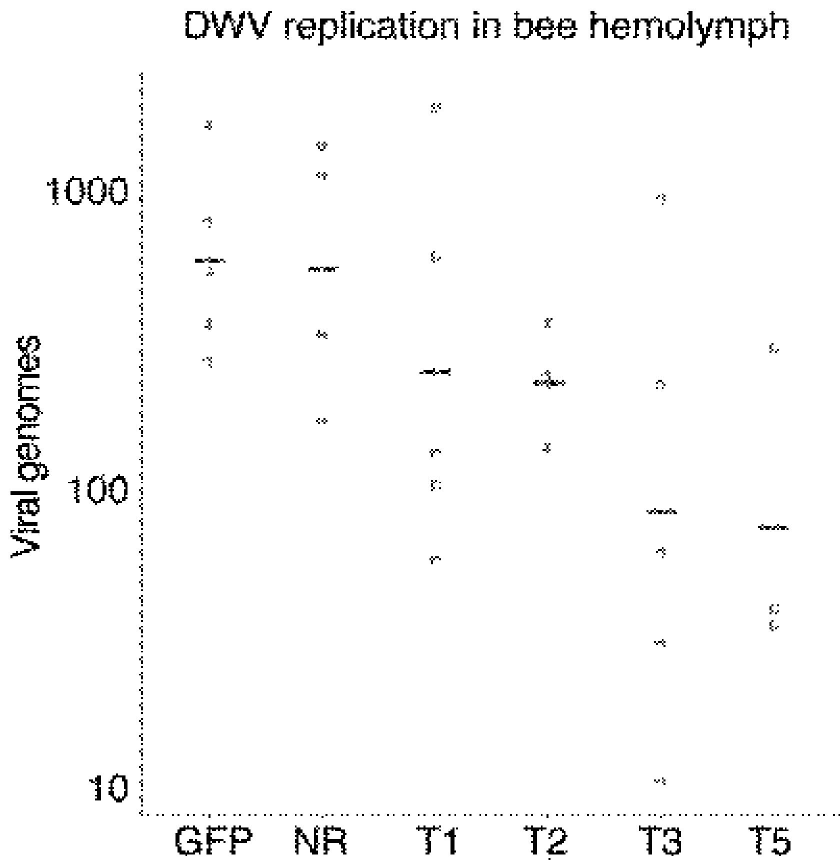


Figure 27

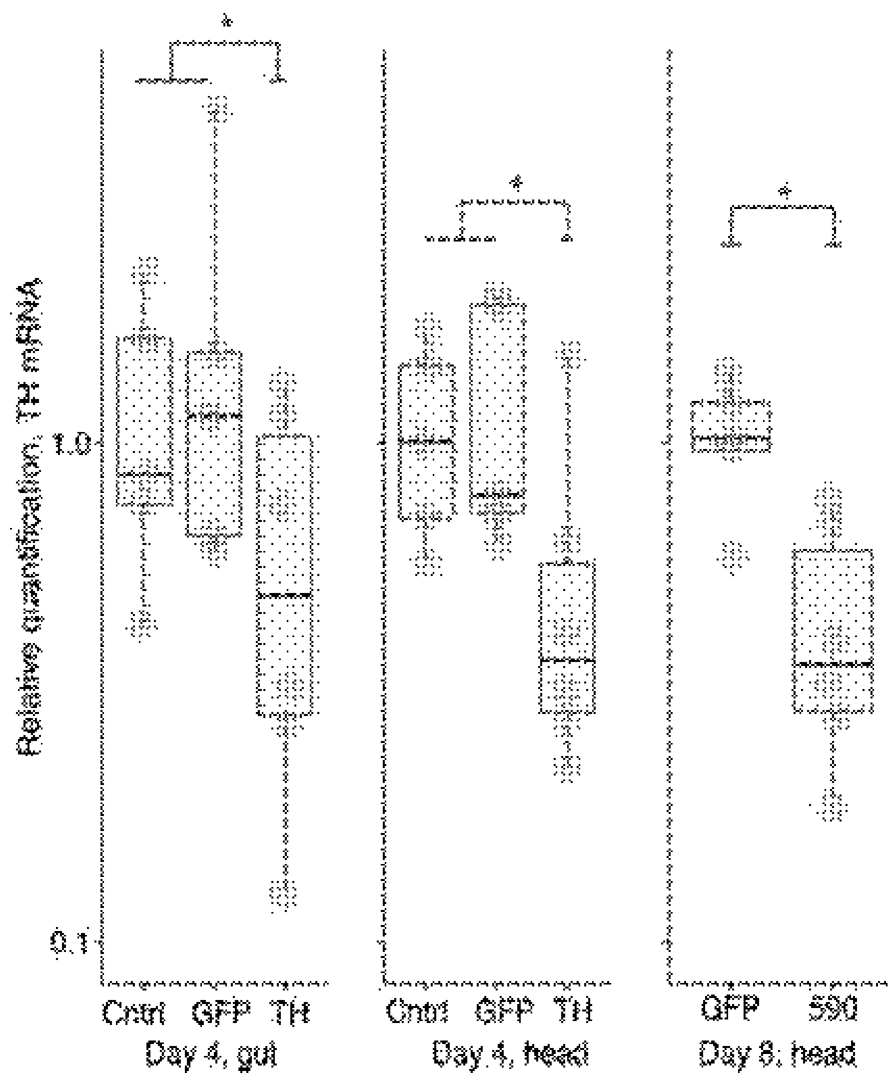


Figure 28

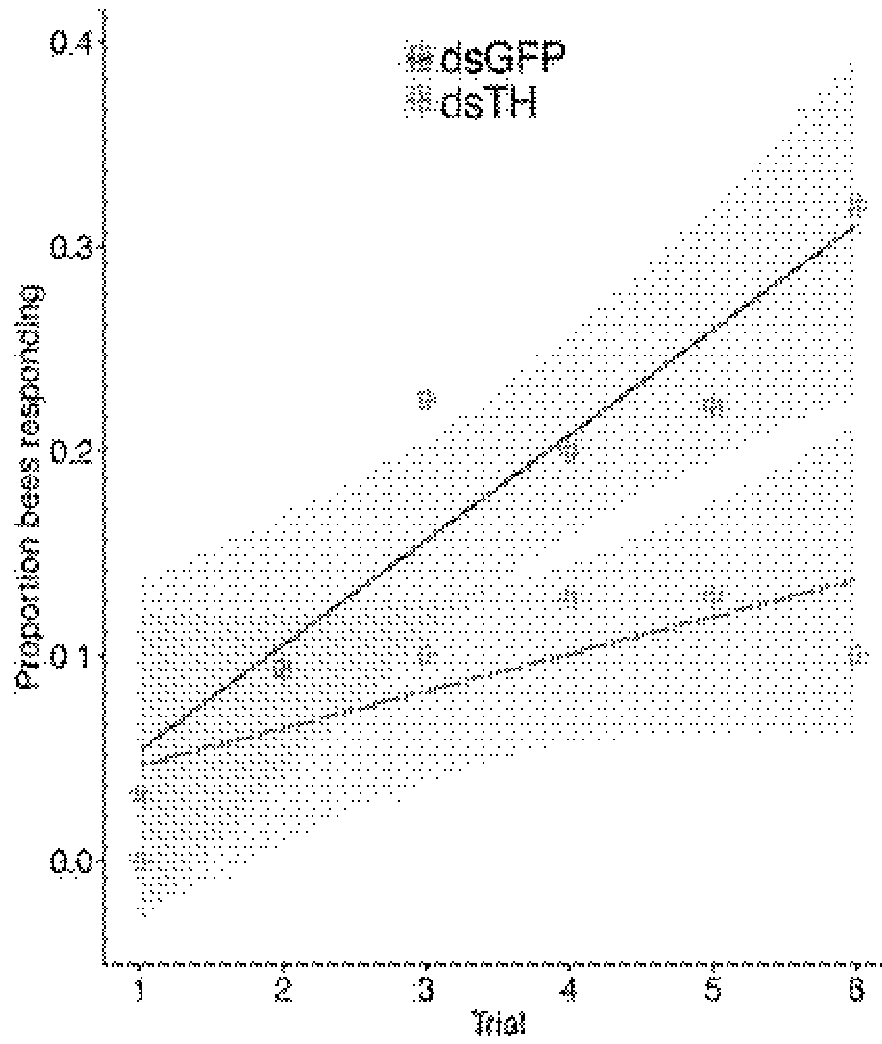


Figure 29

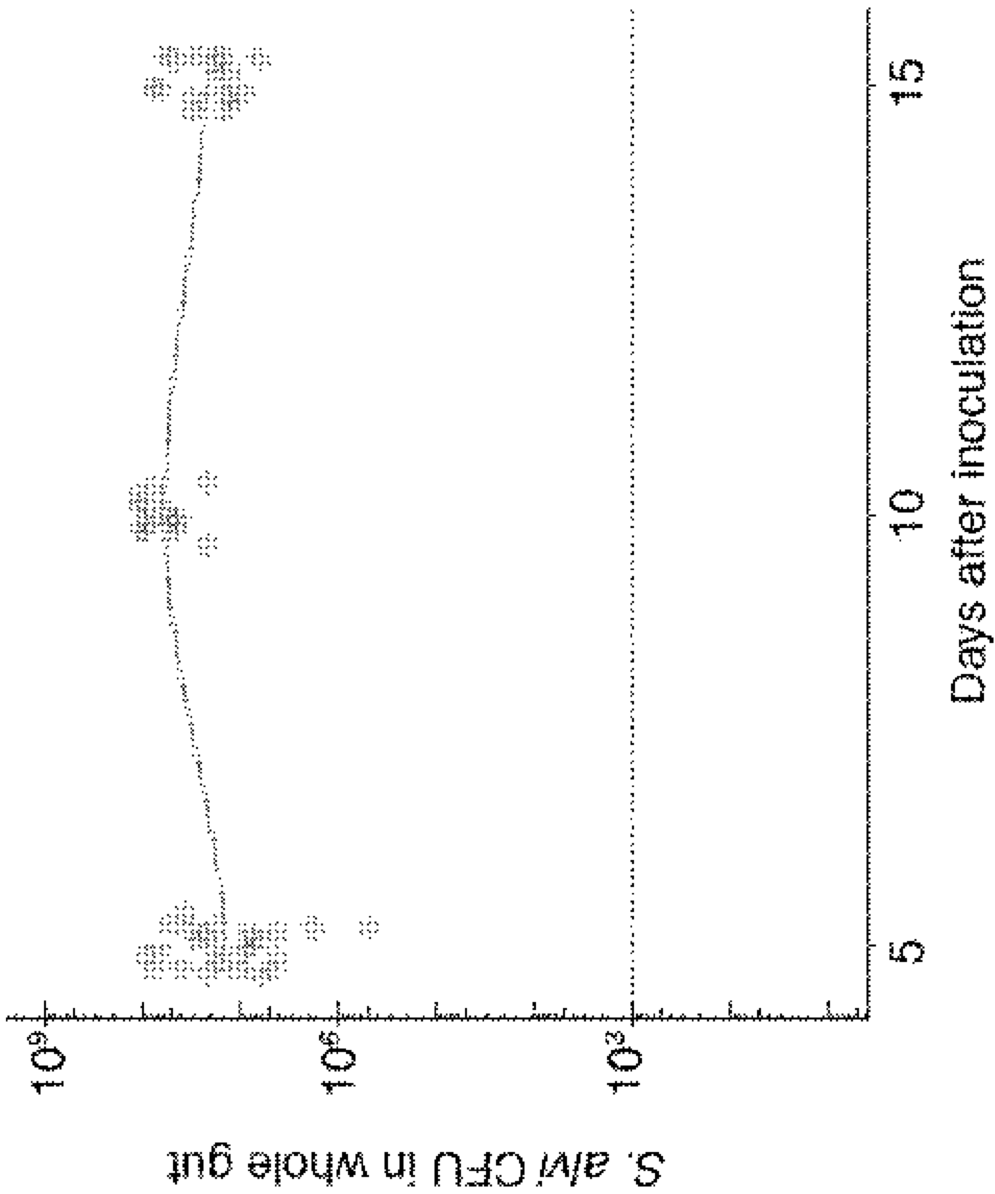


Figure 30

# ENGINEERED MICROBIAL POPULATION

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Provisional Application No. 62/529,754, filed Jul. 7, 2017 which is hereby incorporated by reference herein in its entirety.

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

**[0002]** This invention was made with government support under Grant No. HR0011-15-C-0095 awarded by the Defense Advanced Research Projects Agency. The government has certain rights in the invention.

## FIELD OF THE INVENTION

**[0003]** The present invention relates generally to the field of molecular biology. More particularly, it concerns microbiome engineering.

## BACKGROUND OF THE INVENTION

**[0004]** Most animals have symbiotic microorganisms living in their bodies. Most often these are bacteria that are specialized to live in particular animal species. Honey bees (*Apis mellifera*) are important agricultural pollinators. Unfortunately, recent years have seen substantial bee colony losses (e.g., Colony Collapse Disorder), due to a myriad of complex causes. Some of the most significant causes are bee viral pathogens and *Varroa* mite infestations.

**[0005]** RNA interference (RNAi) is a powerful technique to specifically downregulate gene expression in many eukaryotes by providing dsRNA with sequence identity to eukaryotic genes. RNAi has been shown to function in honey bees previously, and has been used to knock down bee genes to investigate their function and also improve bee health by lowering pathogen burden (e.g., viral and *varroa* mite). Injection or feeding of double stranded RNA (dsRNA) has been shown to trigger RNAi in honey bees, leading to molecular cascades that can degrade invading viral RNA and kill pests (e.g., *Varroa* mites). However, production of large quantities of dsRNA in the laboratory is expensive and the dsRNA itself is unstable and rapidly degrades in the environment. Additionally, injecting dsRNA into bees is traumatic and feeding them dsRNA is unreliable. Thus, there is an unmet need for improved methods of inducing RNAi in bees.

## SUMMARY OF THE INVENTION

**[0006]** In one embodiment, the invention relates to a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect.

**[0007]** In one embodiment, the host insect is selected from the group consisting of a honey bee and a bumble bee.

**[0008]** In one embodiment, the one or more bacteria is *Snodgrassella alvi, Bartonella apis, Gilliamella apicola, Serratia marcescens, Parasaccharibacter apium*, or *Lactobacillus* sp.

**[0009]** In one embodiment, the composition comprises 2, 3, 4, or 5 bacterial species.

**[0010]** In one embodiment, the one or more bacteria express at least two heterologous nucleic acids.

**[0011]** In one embodiment, the heterologous nucleic acid encodes a polypeptide that improves the health of a host insect.

**[0012]** In one embodiment, the heterologous nucleic acid encodes a pesticide degrading polypeptide or a cytochrome.

**[0013]** In one embodiment, the heterologous nucleic acid is an inhibitory nucleic acid. In one embodiment, the inhibitory nucleic acid is selected from the group consisting of an antisense DNA, dsRNA, siRNA, shRNA, sgRNA and a miRNA.

**[0014]** In one embodiment, the heterologous nucleic acid is incorporated into a broad host range plasmid.

**[0015]** In one embodiment, the broad host range plasmid comprises at least one regulatory sequence selected from the group consisting of an RSF1010 origin of replication, a PA1 promoter sequence, a PA2 promoter sequence, a PA3 promoter sequence, a cp25 promoter sequence, and a detectable marker.

**[0016]** In one embodiment, the composition is a bee-ingestible composition.

**[0017]** In one embodiment, the bacteria are present as a live suspension. In one embodiment, the bacteria are present as a lyophilized powder. In one embodiment, the composition is in solid form. In one embodiment, the composition is in liquid form. In one embodiment, the composition comprises protein. In one embodiment, the composition comprises pollen. In one embodiment, the composition is a sucrose solution. In one embodiment, the composition is a corn syrup solution. In one embodiment, the composition comprises a carbohydrate or sugar supplement.

**[0018]** In one embodiment, the invention relates to an insect comprising a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect.

**[0019]** In one embodiment, the insect is a bee, a honey bee, a forager, a hive bee, a pupae, an adult bee, and a bee colony parasite.

**[0020]** In one embodiment, the invention relates to a method for producing a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect, comprising transfecting said bacterial species with an expression cassette comprising at least one heterologous nucleic acid.

**[0021]** In one embodiment, the invention relates to a method for downregulating expression of a target gene product, comprising administering an effective amount of a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect to the host insect, wherein said bacteria express an inhibitor of said target gene product.

**[0022]** In one embodiment, the target gene product is a gene from an organism selected from the group consisting of a pathogen, a parasite, a virus, a mite, Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, Deformed Wing Virus, and *Varroa destructor* mite.

**[0023]** In one embodiment, the insect is selected from the group consisting of a bee, a honey bee, a forager, a hive bee, a pupae, an adult bee, and a bee colony parasite.

**[0024]** In one embodiment, the target gene is selected from the group consisting of TOM70, TIM22, TOM40, Imp2, mitochondrial Hsp70, ATM1-ABC transporter proteins, Frataxin, Ferredoxin, ERV1, ferredoxin, NADPH oxidoreductase [FNR], pyruvate dehydrogenase α subunit, pyruvate dehydrogenase β subunit, mitochondrial glycerol-3-phosphate dehydrogenase (mtG3PDH), manganese-containing superoxide dismutase (MnSOD), DNAJ (Hsp70 interacting), Iron Sulfur cluster ISU1, Cystein desulfurase Nsf1, NAR1, RLI1, ATPase subunit A, RNA polymerase I, RNA polymerase III, Inhibitor of apoptosis (IAP), and FAS apoptotic.

**[0025]** In one embodiment, the invention relates to a method for modulating expression of a target gene product in an insect, comprising administering an effective amount of a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid to said insect

**[0026]** In one embodiment, the insect is selected from the group consisting of a bee, a honey bee, a forager, a hive bee, a pupae, an adult bee, and a bee colony parasite.

**[0027]** In one embodiment, the invention relates to a method for reducing the susceptibility of a bee to a disease or disorder selected from the group consisting of Colony Collapse Disorder (CCD) and infection, comprising administering an effective amount of a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect, to said bee, wherein said bacteria express an inhibitor of a pathogen or parasite specific gene product.

**[0028]** In one embodiment, the pathogen or parasite is selected from the group consisting of Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, *Nosema ceranu*, *Nosema apis*, Deformed Wing Virus, and *Varroa destructor* mite.

**[0029]** In one embodiment, the bacteria express at least two non-contiguous dsRNAs downregulating expression of a pathogen or parasite specific gene product.

**[0030]** In one embodiment, the invention relates to a method for reducing the susceptibility of a bee colony to infestation by the Small Hive Beetle, comprising administering an effective amount of a microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid to hive components, wherein said bacteria express an inhibitor of a Small Hive Beetle specific gene product.

**[0031]** In one embodiment, the bacteria express at least two non-contiguous dsRNAs downregulating expression of a Small Hive Beetle specific gene product.

**[0032]** In one embodiment, the invention relates to a method for expression of a heterologous nucleic acid sequence in a bee, the method comprising administering to the bee at least one modified *Snodgrassella alvi* bacterium comprising an expression plasmid for expression of the heterologous nucleic acid sequence

**[0033]** In one embodiment, the heterologous nucleic acid sequence encodes a molecule selected from the group consisting of a protein, a peptide, an inhibitory RNA, a dsRNA, a siRNA, a shRNA, a sgRNA and a miRNA.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0034]** The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

**[0035]** FIG. **1**: In vitro fluorescent protein expression in bee gut microbiome bacteria.

**[0036]** FIGS. **2A-2C**: Fluorescent imaging of engineered bee gut bacteria colonizing the bee gut microbiome.

**[0037]** FIG. **3**: Schematic of dsRNA-expressing broad-host-range construct.

**[0038]** FIG. **4**: In vitro production of dsRNA by engineered *S. alvi*.

**[0039]** FIG. **5**: In vivo production of dsRNA in the bee gut.

**[0040]** FIG. **6**. dsRNA against essential honey bee gene alpha-tubulin increases mortality.

**[0041]** FIG. **7**: Quantification of tyrosine hydrolase mRNA in the head of bees.

**[0042]** FIGS. **8A-8D**: Schematics depicting various plasmids including pBTK520, pBTK570, pBTK562, and pBTK561

**[0043]** FIGS. **9A-9C**. Depicts design of the bee microbiome toolkit (BTK) and schematic assembly. FIG. **9A** depicts the BTK designed for Golden Gate assembly according to a scheme with eight-part types compatible with the yeast toolkit (YTK) (Lee M E et al., 2015, ACS Synth Biol., 4:975-986). Parts of each type generated in this study are shown in the top panel. Type 1-5 and Type 8 parts are defined as in the YTK except that Type 3 open reading frames include the stop codon. Type 6 and 7 parts are either replaced with a linker part or used to incorporate a reverse reading frame encoding a transcriptional regulator for inducible expression of the main Type 3 open-reading frame and its promoter, respectively, during Stage 1 assembly, so that costly or toxic genes can be repressed while they are assembled into transcriptional units. FIG. **9B** Schematic of Stage 1 (BsaI) assembly. Plasmid parts are shown, but PCR products with appropriate overhangs can be substituted. FIG. **9c** Schematic Stage 2 (BsmBI) assembly. Compatible Stage 2 connectors are described in the YTK documentation.

**[0044]** FIGS. **10A-10B**: Depicts the bee microbiome toolkit (BTK) functions in diverse bee-associated bacteria. FIG. **10A** depicts replication of the BTK backbone and the function of three antibiotic resistance cassettes were tested in eight honey bee-associated bacterial strains as described in the Methods. At least one antibiotic resistance cassette functioned in each strain, and the kanamycin cassette functioned in all eight strains. FIG. **10B** depicts replication of the BTK backbone and the function of three antibiotic resistance cassettes were tested in three bumble bee-associated bacterial strains. Again, the plasmid with kanamycin resistance was maintained in all three bacteria. FIG. **10C** depicts conjugation frequency in four bee gut-associated strains. Black bars are the geometric mean and each point is an independent conjugation. Conjugation in *B. apis* is the most efficient, with conjugation efficiency approximately 10%

**[0045]** FIGS. **11A-11C**: Depicts constitutive and inducible control of in vitro gene expression in bee gut bacteria. FIG. **11A** depicts flow cytometry results of GFP fluorescence from four broad-host-range promoters in each of four honey bee-associated bacterial strains and an *E. coli* control. One representative fluorescence distribution for each promoter is

shown, with the medians from three biological replicates plotted as open circles. Spotted grey line indicates maximum detected fluorescence in wildtype cells. Median fluorescent values were calculated from cells more fluorescent than wildtype. FIG. **11B** depicts GFP fluorescence from a designed CP25 (lacO) promoter at different levels of IPTG-induction, measured in four BGM strains and an *E. coli* control. All tested species are responsive to IPTG induction, and *G. apicola* shows the highest expression across all strains. FIG. 11C depicts GFP fluorescence from a T7 (lacO) promoter at different levels of IPTG-induction of T7 RNAP expression in the same four BGM strains. Schematics in FIG. **11A** through FIG. **11C** show the design of tested constructs using Synthetic Biology Open Language (SBOL) standard glyphs (Galdzicki M et al., 2014. Nat Biotechnol., 32:545-550). Error bars are standard deviations (n=3).

**[0046]** FIGS. **12A-12B**: Depicts dCas9 gene silencing in *Bartonella apis*. FIG. **12A** depicts schematic assembly of dCas9 plasmids for gene suppression. FIG. **12B** depicts fluorescence from chromosomally integrated GFP in PEB0150 in the presence and absence of dCas9 and sgRNA targeting GFP. Background fluorescence of wild-type PEB0150 was subtracted. GFP fluorescence decreased in presence of dCas9 targeting GFP (p=0.004, Kruskal-Wallis rank sum test). Error bars are 95% confidence intervals (n=4).

**[0047]** FIGS. **13A-13E**: Depicts Cas9 assisted gene disruption in species from the bee gut microbiota. FIG. **13A** depicts schematic assembly of R6K-based suicide plasmids. Assembly strategy and validation primers are described in FIG. **23**. FIG. **13B** depicts the two tested approaches for gene disruption. The suicide plasmids were introduced into either wild-type bacteria or bacteria possessing the constitutively active Cas9 (pBTK601). FIG. 13C depicts transconjugation frequency and percent of desired mutants in *B. apis*, in the presence and absence of Cas9. The Cas9 plasmid did not increase the efficiency of genome modification. Numbers above each bar indicate the number of clones evaluated. FIG. **13D** depicts transconjugation frequency and proportion of desired mutants in *S. alvi*. *S. alvi* wkB2 showed increased efficiency of genome modification in the presence of the Cas9 plasmid (p=0.0007, Kruskal-Wallis rank sum test). FIG. **13E** depicts transconjugation frequency and proportion of desired mutants in *G. apicola*. Each point in FIG. **13C** and FIG. **13E** is from an independent conjugation experiment. Bars in FIG. **13C** and FIG. **13E** represent the geometric mean of estimated transconjugation efficiencies.

**[0048]** FIGS. 14A-**14E**: Depicts visualization of engineered bacteria in the honey bee gut. FIG. **14A** depicts intact honey bee worker and dissection of honey bee gut showing brightfield microscopy of midgut, ileum, and rectum. FIG. **14B** depicts fluorescent imaging of whole bee (left) and dissected bee (right) 5 days after inoculation with *S. marcescens* N10A28 expressing E2-Crimson (plasmid pBTK570). Control bee is uninoculated. Color corresponds to pixel fluorescence intensity. Engineered *S. marcescens* N10A28 is present in the midgut, ileum, and rectum. FIG. **14C** Similar to FIG. **14B**, with *S. alvi* wkB2 expressing E2-Crimson as inoculum. Control bee is identical to FIG. **14B**, but different fluorescent intensity scales are used for comparison between bees inoculated with *S. alvi* and *S. marcescens*. Engineered *S. alvi* wkB2 is visibly fluorescent in the midgut and ileum. FIG. 14D depicts confocal imaging of partial ileum and rectum in bees inoculated with *S. marcescens* N10A28 expressing E2-Crimson (red). As in FIG. **14B**, *S. marcescens* can be seen robustly colonizing throughout the ileum and rectum. FIG. 14E Similar to FIG. 14D, with *S. alvi* wkB2 expressing E2-Crimson (green). *Snodgrassella alvi* wkB2 colonizes the ileum, but not the rectum. Scale bars in FIG. **14D** and FIG. **14E** are 100 m. Images are representative of multiple bees inspected (n=3-5 per condition) for (FIG. **14B** through FIG. **14E**). White and black arrows correspond to the ileum-rectum junction across images (FIG. 14A through FIG. **14E**).

**[0049]** FIGS. **15A-15D**: Depicts visible co-inoculation of the bee gut with species from the bee gut microbiota and the role of staA in colonization. FIG. **15A** depicts the ileum-rectum junction imaged by confocal fluorescence microscopy 5 days after co-inoculating *B. apis* PEB0150 and *S. alvi* wkB2. When co-inoculated, *B. apis* and *S. alvi* are co-located in the ileum, but only *B. apis* colonizes the rectum. FIG. **15B**, similar to FIG. 15A, depicts images taken 5 days after co-inoculation of *G. apicola* wkB7 and *S. alvi* wkB2. As in FIG. **15A**, *S. alvi* remains restricted to the ileum, while *G. apicola* is present in both ileum and rectum. Scale bars are 100 m. Images are representative of multiple bees inspected (n=3 per condition). FIG. **15C** depicts the number of *S. alvi* 16S ribosomal DNA copies 5 days after inoculating newly emerged worker bees with the *S. alvi* WT or ΔstaA mutant, based on quantitative PCR. Horizontal bars represent means per condition (n=5). The ΔstaA has a significant colonization defect compared to WT (p=2.7×10-6, Kruskall-Wallis rank sum test). FIG. **15D** depicts the ileums of bees inoculated with *S. alvi* wkB2ΔstaA expressing E2-Crimson (pBTK570) were imaged 5 days after colonization. Mutants achieved lower colonization levels than did *S. alvi* WT (see FIG. **6E**). Localized colonization was typical of multiple ileums inspected (n=3). Scale bar is 100 μm.

**[0050]** FIG. **16** depicts broad-host-range plasmid screen in bee gut bacteria.

**[0051]** FIG. 17 depicts the bacterial strains used in this study.

**[0052]** FIG. **18** depicts BTK plasmids.

**[0053]** FIG. **19** depicts oligonucleotides used in the study.

**[0054]** FIG. **20** depicts expression of nanoluc in BGM strains. Bee gut microbiota strains were conjugated with pBTK563 (CP25-Nanoluc) or pBTK564 (PA3-Nanoluc) and luciferase activity measured per manufacturer's instructions. Luciferase is plotted on a log 10 scale. Bars are the mean from three biological replicates and error bars are standard deviation.

**[0055]** FIG. **21** depicts expression of E2-Crimson in BGM strains. Bee gut microbiota strains with pBTK569 (CP25-E2-Crimson) or pBTK570 (PA3-E2-Crimson) were measured for expression of E2-Crimson. Bars are the mean from three biological replicates and error bars are standard deviation. E2-Crimson fluorescence expression was measured as GFP except using excitation/emission wavelengths of 611/646 nm.

**[0056]** FIG. **22** depicts validation of additional BTK promoters in *E. coli*. Promoter parts CP12b, CP32, and CP6 were used to build GFP expression plasmids (pBTK619, pBTK620, pBTK621) and tested in *E. coli* MFDpir. Bars are the mean from three biological replicates and error bars are standard deviation.

**[0057]** FIGS. **23A-23C**: Depicts construction of replacement cassette plasmids. FIG. **23A** depicts schematic assem-

bly of homology donor plasmids using BTK Golden Gate assembly. Type 2, 3, and 4 overhangs are repurposed for the upstream homology, antibiotic resistance, and downstream homology respectively. Combined with parts Type 1, 5, and pYTK095 (Type 6-8), the donor plasmid is then ready for further BsmBI assembly as shown in FIG. **12**. FIG. **23B** depicts possible outcomes from homologous recombination crossing-over events. Single-crossover mutants are more common and occur with integration of the suicide plasmid backbone. Double-crossover mutants are the desired mutant, where only the antibiotic resistance cassette is retained in the chromosome of the target strain. FIG. **23C** depicts sets of PCR primers used to verify mutants.

**[0058]** FIGS. **24A-24E**: Depicts schematic and validation of staA disruption in *S. alvi*. FIG. **24A** depicts schematic of staA disruption in *S. alvi*. FIG. **24B** depicts DNA gel with products from the PCR of upstream junctions using primers 1-2. The double-crossover mutant (DC) shows a band at the expected size of 1583 bp, wild type (WT) shows no amplification. FIG. **24C** depicts DNA gel with products from the PCR of downstream junctions using primers 3-4. DC shows a band at the expected size of 1587 bp, WT shows no amplification. FIG. **24D** depicts DNA gel with products from the PCR of the entire region using primers 1-4. DC shows an increase in size of approximately 880 bp compared to WT. Lanes rearranged from original gel for clarity. FIG. **24E** depicts DNA gel with products from the PCR of plasmid backbone. A single crossover mutant (SC) shows expected amplification at 453 bp, DC shows no amplification. Black bars indicate image cropping for clarity.

**[0059]** FIGS. **25A-25C**: Depicts schematic and validation of ackA disruption in *G. apicola*. FIG. **25A** depicts schematic of planned ackA disruption in *G. apicola*. FIG. **25B** depicts DNA gel showing products from the PCR of upstream junctions using primers 1-2. Forty clones were tested, and two distinct single cross-over events (SC) were observed: a smaller than expected band at ~550 bp and a second, larger band at ~2800 bp (often in the same clone). Neither of these is the expected size of 1501 bp. This may represent a duplication or other complex recombination event. No downstream junctions were effectively amplified using primers 3-4 (data not shown). PCR using primers 1-4 showed no change in size between wild-type (WT) and SC mutants, indicating the SC event likely did not disrupt ackA function (data not shown). FIG. **25C** depicts DNA gel showing product from the PCR using primers KO_5 and KO_6. Expected product at 453 bp shows retention of the suicide backbone in the SC mutants.

**[0060]** FIGS. **26A-26E**: Depicts schematic and validation of narG disruption in *B. apis*. FIG. **26A** depicts schematic of planned narG disruption in *B. apis*. FIG. **26B** depicts DNA gel with products from the PCR of upstream junctions using primers 1-2. The double-crossover mutant (DC) shows a band at the expected size of 1169 bp, wild type (WT) shows no amplification. FIG. **26C** depicts DNA gel with products from the PCR of downstream junctions using primers 3-4. DC shows a band at the expected size of 1309 bp, WT shows no amplification. FIG. **26D** depicts DNA gel with products from the PCR of the entire region using primers 1-4. DC shows an increase in size of approximately 757 bp compared to WT. Lanes rearranged from original gel for clarity. FIG. **26E** depicts DNA gel with products from the PCR of plasmid backbone. A single crossover mutant (SC) shows expected amplification at 453 bp. DC shows no amplification. Black bars indicate image cropping for clarity.

**[0061]** FIG. **27**: Depicts exemplary experimental results of DWV replication in bee hemolymph.

**[0062]** FIG. **28**: Depicts exemplary experimental results demonstrating the relative quantification of TH mRNA.

**[0063]** FIG. **29**: Depicts exemplary experimental results demonstrating the proportion of bees responding to dsTH or dsGFP.

**[0064]** FIG. **30**: Depicts exemplary experimental results demonstrating the proportion of *S. alvi* CFU persisting in the gut of inoculated bees at different times.

## DETAILED DESCRIPTION

**[0065]** In some embodiments, the present disclosure provides methods and compositions concerning microbiome engineering, such as in the gut microbiome of arthropods. In certain embodiments, one or more species of bacteria that are naturally present in the arthropod gut are genetically engineered. These methods may be used to improve arthropod health in a variety of ways. For example, these engineered bacterial species may then be introduced to an insect population, such as a bee population, to directly produce one or more compounds in the insect gut. In some instances, the engineered bacterial species are used to directly express double-stranded RNA (dsRNA) in an insect. In some embodiments, the microbe-produced dsRNA induces RNA interference (RNAi) against a host insect gene product. In some embodiments, the microbe-produced dsRNA induces RNA interference (RNAi) against a gene product of a pathogen or parasite of a host insect.

**[0066]** A broad host range plasmid (e.g., comprising a RSF 1010 origin of replication, such as from the pMMB67EH plasmid) may be used to introduce genes into one or more arthropod gut microbiome strains including, but not limited to, *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, *Serratia* sp., *Parasaccharibacter apium*, and *Lactobacillus* sp.

**[0067]** In one embodiment, the invention relates to the use of paired, convergent transcriptional promoters on a plasmid to generate dsRNA constructs against any target gene product or series of targets. In this embodiment, no purification of the dsRNA is required, as the genetically engineered bacteria continually produce the desired dsRNA and the dsRNA is directly taken up through the gut of the arthropod. Because these are modified natural arthropod gut microbiome species, they can be maintained over the arthropod's lifetime. In one embodiment, they may be naturally transferred to newly emerged arthropod (e.g., newly emerged bees in a hive) from adults. Thus, the present methods may reduce the need for frequent and costly reapplication.

**[0068]** The present studies showed the production of dsRNA directly in the bee gut by engineering natural members of their microbiota. By producing dsRNA directly in the honey bee gut, the present methods can provide a continual and cost-effective supply of dsRNA to silence bee or beepest genes. In one example, the efficacy of the present methods was demonstrated by using *Snodgrassella alvi* to produce a dsRNA that targets an essential honey bee cytoskeletal gene. Application of this engineered bacterium to bees resulted in increased bee mortality compared to one encoding an off-target dsRNA control. Further aspects may comprise additional methods to increase dsRNA expression,

such as knock out of bacterial RNaseII or RNase III or using T7 RNA polymerase to produce dsRNA.

**[0069]** Thus, in one embodiment, the present methods may be used to produce and administer dsRNA by genetically engineering bacteria that are native to the bee gut microbiome. The methods may be useful in reducing bee mortality from RNA viruses (e.g., Israeli acute paralysis virus, Deformed wing virus) and for *Varroa* mite and Small Hive Beetle control as well as other microbial and insect pathogens. As bacterial production can be inexpensive, the present methods be useful to small and large scale apiaries. Further embodiments may concern bumble bee production, an industry that is important in providing pollination for many fruit and vegetable crops.

**[0070]** In some cases, Colony Collapse Disorder (CCD) of honeybees can be due to *Varroa* mite infections. *Varroa* mites are suspected of acting as vectors for a number of honey bee pathogens, including Deformed Wing Virus (DWV), Kashmir Bee Virus (KBV), Acute Bee Paralysis Virus (ABPV) and Black Queen Cell Virus (BQCV), and may weaken the immune systems of their hosts, leaving them vulnerable to infections. Accordingly, certain embodiments of the present disclosure provide methods of reducing the susceptibility of honeybees to Colony Collapse Disorder (CCD). Thus, in some aspects, the dsRNA of the present methods and compositions may target a gene product of picorna-like viruses (e.g., Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), and Israeli Acute Paralysis Virus (IAPV)), *Nosema* parasite, Deformed Wing Virus, and/or a *Varroa destructor* mite, or Small Hive Beetle. The inhibitory nucleic acid molecules (e.g., dsRNA) may be complementary to the mRNA of the target gene product. For example, the inhibitory nucleic acid molecule can be complementary to region of a mRNA comprising at least 10, 15, 20, 21, 22, 23, 24, or 25 contiguous nucleotides. In some aspects, the inhibitory nucleic acid molecule can be complementary to region of a mRNA comprising at least 50, 100, 150, 200, 300 400 or 500 contiguous nucleotides or essentially the entire mRNA. In some aspects a dsRNA comprise at least 10, 15, 20, 21, 22, 23, 24, or 25 complementary nucleotides. For example, the dsRNA produced by the engineered bacteria may comprise a sequence complementary to *Varroa destructor* mite mRNA of and capable of inducing degradation of the *Varroa destructor*-specific mRNA. The target mRNA sequences for use in the present methods include those described in, but are not limited to, U.S. Patent Publication No. 20140371298 or 20150133532; both incorporated herein by reference in their entirety.

**[0071]** In some embodiments, there is provided an expression cassette encoding a dsRNA under the control of one or more broad host range promoters, wherein the dsRNA is complementary to a target gene product of Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema* parasite, Deformed Wing Virus, *Varroa destructor* mite, or Small Hive Beetle. The expression cassette may encode for 2, 3, 4, 5, 6, 7, 8, 9, 10 or more inhibitory nucleic acids, such as dsRNAs. In some aspects, the inhibitory nucleic acids may target the same virus, parasite or mite. In other aspects, the inhibitory nucleic acids target mRNAs encoding different gene products, such as a dsRNA to a gene product of the *Varroa destructor* mite.

**[0072]** In further embodiments, there are provided microbial compositions comprising one or more insect microbiome bacteria engineered to express one or more heterologous nucleic acids, such as inhibitory nucleic acids. The inhibitory nucleic acid may be dsRNA, siRNA, shRNA, and/or miRNA. The dsRNAs may also be precursor miRNAs. In some cases, the inhibitory nucleic acids may be at least 15 base pairs in length, such as at 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 base pairs in length. In further aspects, the inhibitory nucleic acids may be complementary to 50, 100 or more based pairs of a target mRNA. Exemplary insect microbiome species include, but are not limited to, *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, *Serratia marcescens*, *Parasaccharibacter apium* and *Lactobacillus* sp. The microbial composition may comprise 2, 3, 4, or 5 bacterial species. Each engineered bacterium may express 1, 2, 3, 4, 5, or more heterologous nucleic acids. The nucleic acids may be pathogen, pest or parasite-specific, such as parasites which may infect insects, particularly bees. Exemplary pathogens, pests and parasites include, but are not limited to, viruses, microbial pathogens, Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), Deformed Wing Virus, parasites such as *Nosema ceranae*, mites such as the *Varroa destructor* mite and pests such as the Small Hive Beetle (*Aethina tumida*).

**[0073]** The microbial composition may be formulated for insect ingestion, particularly as an ingestible composition (e.g., oral formulations). The composition may be solid or liquid (e.g. a sucrose solution or corn syrup solution). The composition may comprise additives or excipients, such as a carbohydrate or sugar supplement.

**[0074]** The microbial composition may be formulated for application to an insect pest food source, for example bee hive components.

**[0075]** The engineered bacteria or microbial compositions provided herein may be used to reduce insect susceptibility to infections, such as viral infections. They may also be used to down-regulated expression of a target gene product, such as by inducing RNAi in the insect.

**[0076]** In addition, the same bacterial species including *S. alvi* and *G. apicola* live in both honey bees (species in the genus *Apis*) and bumble bees (species in the genus *Bombus*), and the broad host range plasmid replicated in diverse bacterial hosts. Thus, the present methods may be applied to other bees or other species of insects, such as to induce similar RNAi effects. Additionally, the present methods allow for easy targeting of bee-specific genes to silence, and thus may be used for research.

Definitions

**[0077]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used.

**[0078]** 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.

**[0079]** As used herein the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used

in conjunction with the word "comprising," the words "a" or "an" may mean one or more than one.

**[0080]** The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." As used herein "another" may mean at least a second or more.

**[0081]** Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

**[0082]** As used herein, "essentially free," in terms of a specified component, is used herein to mean that none of the specified component has been purposefully formulated into a composition and/or is present only as a contaminant or in trace amounts. The total amount of the specified component resulting from any unintended contamination of a composition is therefore well below 0.01%. Most preferred is a composition in which no amount of the specified component can be detected with standard analytical methods. "Genetically engineered bacteria" refers to bacterial cells that replicate a heterologous nucleic acid, or express a polypeptide encoded by a heterologous nucleic acid.

**[0083]** "Heterologous nucleic acid" is one that originates from a source foreign to the particular host cell, or, if from the same source, is modified from its original form.

**[0084]** As used herein, an "instructional material" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of a compound, composition, vector, or system of the invention in the kit. Optionally, or alternately, the instructional material can describe one or more methods of modulating expression of a gene product using a compound, composition, vector, or system of the invention in the kit. The instructional material of the kit of the invention can, for example, be affixed to a container which contains the identified compound, composition, vector, or delivery system of the invention or be shipped together with a container which contains the identified compound, composition, vector, or system. Alternatively, the instructional material can be shipped separately from the container with the intention that the instructional material and the kit be used cooperatively by the recipient.

**[0085]** "Promoter" is a nucleic acid sequence that acts as a signal sequence necessary to initiate transcription of a gene.

**[0086]** As used herein, the term "bee" is defined as any of several winged, hairy-bodied, usually stinging insects of the superfamily Apoidea in the order Hymenoptera, including both solitary and social species and characterized by sucking and chewing mouthparts for gathering nectar and pollen. Exemplary bee species include, but are not limited to species in the genera *Apis*, *Bombus*, *Trigona*, *Osmia* and the like. In one embodiment, bees include, but are not limited to bumblebees (*Bombus terrestris*, *Bombus impatiens*, or other *Bombus* species) and honeybees (*Apis mellifera* or *Apis cerana*).

**[0087]** As used herein, the term "colony" is defined as a population of dozens to typically several tens of thousand honeybees that cooperate in nest building, food collection, and brood rearing. A colony normally has a single queen, the remainder of the bees being either "workers" (females) or "drones" (males). The social structure of the colony is maintained by the queen and workers and depends on an effective system of communication. Division of labor within the worker caste primarily depends on the age of the bee but varies with the needs of the colony. Reproduction and colony strength depend on the queen, the quantity of food stores, and the size of the worker force. Honeybees can also be subdivided into the categories of "hive bees", usually for the first part of a workers lifetime, during which the "hive bee" performs tasks within the hive, and "forager bee", during the latter part of the bee's lifetime, during which the "forager" locates and collects pollen and nectar from outside the hive, and brings the nectar or pollen into the hive for consumption and storage.

**[0088]** As used herein, the term "susceptibility" is defined as the ability of a bee or bee colony to become infested or infected by and/or support proliferation of a pathogen, including, but not limited to, degree of infection, severity of symptoms, infectivity to other individuals (contagion), and the like. Susceptibility can be assessed, for example, by monitoring infectivity, presence of symptoms, such as, but not limited to, hunger, vitality, flight range, etc, presence of pathogenic organisms, mortality or time course of a disease in an individual bee or bee population following a challenge with the pathogen.

**[0089]** As used herein, the terms "bee disease" or "bee colony disease" are defined as undesirable changes in the behavior, physiology, morphology, reproductive fitness, economic value, viability, honey production, pollination capability, resistance to infection and/or infestation of a bee, a population of bees and/or a bee colony, directly or indirectly resulting from contact with a parasite or a parasite-infected bee or other organism.

**[0090]** As used herein, the term "downregulating expression" is defined as causing, directly or indirectly, reduction in the transcription of a desired gene, reduction in the amount, stability or translatability of transcription products (e.g. RNA) of said gene, reduction in translation of the polypeptide(s) encoded by the desired gene and/or reduction in the amount, stability, or alteration of biochemical function of the polypeptides encoded by the desired gene, so as to reduce the amount or function of the gene products. Downregulating expression of a gene RNA can be monitored, for example, by direct detection of gene transcripts (for example, by PCR), by detection of polypeptide(s) encoded by the gene or bee RNA (for example, by Western blot or immunoprecipitation), by detection of biological activity of polypeptides encode by the gene (for example, catalytic activity, ligand binding, and the like), or by monitoring changes in a cell or organism resulting from reduction in expression of a desired gene or RNA.

**[0091]** "Measuring" or "measurement," or alternatively "detecting" or "detection," means assessing the presence, absence, quantity or amount (which can be an effective amount) of either a given substance within a clinical or subject-derived sample, including the derivation of qualitative or quantitative concentration levels of such substances, or otherwise evaluating the values or categorization of a subject's clinical parameters.

**[0092]** The term "operably linked", as used in reference to a regulatory sequence and a structural nucleotide sequence, means that the regulatory sequence causes regulated expression of the linked structural nucleotide sequence. "Regulatory sequences" or "control elements" refer to nucleotide

sequences located upstream, within, or downstream of a structural nucleotide sequence, and which influence the timing and level or amount of transcription, RNA processing or stability, or translation of the associated structural nucleotide sequence. Regulatory sequences may include promoters, translation leader sequences, introns, enhancers, stem-loop structures, repressor binding sequences, termination sequences, pausing sequences, polyadenylation recognition sequences, and the like.

**[0093]** As used herein, the term "RNA silencing agent" refers to an RNA which is capable of inhibiting or "silencing" the expression of a target gene. In certain embodiments, the RNA silencing agent is capable of preventing complete processing (e.g, the full translation and/or expression) of an mRNA molecule through a post-transcriptional silencing mechanism.

**[0094]** RNA silencing agents include noncoding RNA molecules, for example RNA duplexes comprising paired strands, as well as precursor RNAs from which such small non-coding RNAs can be generated. Exemplary RNA silencing agents include dsRNAs such as siRNAs, miRNAs and shRNAs. In one embodiment, the RNA silencing agent is capable of inducing RNA interference. In another embodiment, the RNA silencing agent is capable of mediating translational repression.

**[0095]** RNA interference commonly refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes and is commonly shared by diverse eukaryotic species, including plants and animals. Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA.

**[0096]** The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes. The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex.

**[0097]** The term "siRNA" refers to small inhibitory RNA duplexes (generally between 18-30 basepairs, between 19 and 25 basepairs) that induce the RNA interference (RNAi) pathway. Typically, siRNAs are chemically synthesized as 21mers with a central 19 bp duplex region and symmetric 2-base 3'-overhangs on the termini, although it has been recently described that chemically synthesized RNA duplexes of 25-30 base length can have as much as a 100-fold increase in potency compared with 21mers at the same location. The observed increased potency obtained using longer RNAs in triggering RNAi is theorized to result from providing Dicer with a substrate (27mer) instead of a product (21mer) and that this improves the rate or efficiency of entry of the siRNA duplex into RISC.

**[0098]** The term "shRNA", as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region. The number of nucleotides in the loop is a number between and including 3 to 23, or 5 to 15, or 7 to 13, or 4 to 9, or 9 to 11. Some of the nucleotides in the loop can be involved in base-pair interactions with other nucleotides in the loop.

**[0099]** The terms "subject," "individual," and the like are used interchangeably herein, and refer to any animal, or cells thereof whether in vitro or in situ, amenable to the methods described herein. In certain non-limiting embodiments, subject or individual is a bee.

**[0100]** "Sample" or "biological sample" as used herein means a biological material isolated from a subject. The biological sample may comprise cellular and/or non-cellular material obtained from the subject. One example of a biological sample is a tissue sample.

**[0101]** According to one embodiment of the present disclosure, the nucleic acid in the expression cassette is capable of causing cleavage and/or degradation of a target polynucleotide sequence. As used herein, the phrases "target" or "target polynucleotide sequence" refer to any sequence present in a target cell (e.g., viral or microbial pathogen), whether naturally occurring sequence or a heterologous sequence present due to an intracellular or extracellular pathogenic infection or a disease, which polynucleotide sequence has a function that is desired to be reduced or inhibited. The target sequence may be a coding sequence, that is, it is translated to express a protein or a functional fragment thereof. Alternatively, the target sequence may be non-coding, but may have a regulatory function, or it may be without any known function.

**[0102]** As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

**[0103]** The term "gene" is intended to include any target sequence intended to be "silenced", whether or not transcribed and/or translated, including regulatory sequences, such as promoters, enhancers and other non-coding sequences.

**[0104]** Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from

2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

## DESCRIPTION

**[0105]** In one embodiment, the present invention relates to a method for the production of an encoded molecule in an arthropod in vivo, comprising administering a genetically engineered bacterium to the arthropod, wherein the genetically engineered bacterium comprises a nucleic acid for expression of the gene encoded molecule. Therefore, in various embodiments the invention relates to nucleic acid molecules for expression of an encoded molecule, engineered bacteria comprising the nucleic acid molecules, arthropods comprising the engineered bacteria, and methods of use of the nucleic acid molecules and engineered bacteria to treat or prevent a disease or disorder of the arthropod. In one embodiment, the invention provides compositions and methods of using engineered bacteria to deliver nucleic acid molecules to insects for therapeutic purposes. In one embodiment, the invention provides compositions and methods of using engineered bacteria to deliver nucleic acid molecules to insects for purposes of modulating at least one of the level or activity of a gene, the level or activity of a protein or a behavior of the insect. Exemplary behaviors that can be modified according to the invention include, but are not limited to, foraging behavior and aggression. In one embodiment, the invention provides compositions and methods of using engineered bacteria to deliver nucleic acid molecules to insects for purposes of killing or otherwise impairing the insect. In one embodiment, the invention provides compositions and methods of using engineered bacteria to deliver nucleic acid molecules to insects to harm or to kill a pathogen or parasite of the insect through expression of a nucleic acid molecule that is harmful for the pathogen or parasite of the insect.

**[0106]** In some embodiments, the invention relates to methods of use of the engineered bacteria to treat or prevent a disease or disorder of a bee or colony of bees. In one embodiment, the disease or disorder is associated with a bee or bee colony parasite or pathogen

### Compositions

**[0107]** In one embodiment, the invention provides nucleic acid molecules for expression of a heterologous protein or polypeptide. In certain aspects, the heterologous polypeptide is a polypeptide that improves the health of a host insect. In one embodiment, the heterologous polypeptide is a pesticide-degrading polypeptide or a cytochrome.

**[0108]** In one embodiment, the invention provides nucleic acid molecules for expression of a modulator of a gene or protein of interest. Consequently, in the context of the present invention, the term "nucleic acid molecule" refers to a DNA or RNA molecule. DNA is understood as double-stranded deoxyribonucleic acid molecules. These may be linear or circular. Exemplary RNA molecules that can be encoded by the nucleic acid molecules of the invention, include, but are not limited to RNAi, dsRNA, siRNA, shRNA, miRNA and short guide RNA (sgRNA). In one embodiment, the encoded RNA molecule functions as an inhibitor of a target RNA. In one embodiment, the target RNA is an RNA of a pathogen or other organism that may harm the host insect. In one embodiment, the target RNA is an RNA of the host insect.

**[0109]** In specific aspects, the modulator is an inhibitory nucleic acid. In particular aspects, the inhibitory nucleic acid comprises an antisense DNA. In some aspects, the inhibitory nucleic acid is a dsRNA, siRNA, shRNA, sgRNA, or miRNA. The nucleic acid may be at least 15 base pairs in length, such as 19 to 25 base pairs in length. In other aspects, the nucleic acid is longer in length, such as at least 30 base pairs.

**[0110]** An RNAi construct is understood as a double-stranded RNA that works in accordance with the principle of an interfering RNA. It is known in the state of the art how RNAi constructs have to be designed that degrade target RNA (Voorhoeve et al. (2003). "Knockdown stands up". Trends Biotechnol. 21 (1): 2-4; Henschel A, Buchholz F, Habermann B (2004) "DEQOR: a web-based tool for the design and quality control of siRNAs". Nucleic Acids Res 32 (Web Sever issue): W113-20). In this context, it relates to genes that encode for double-stranded RNA. In particular, the RNAi construct may encode for a dsRNA (double-stranded RNA) against an organism that harms the insect. In certain cases, the inhibitory nucleic acid can be targeted to an insect gene, such a bee gene. For example, insect genes can be targeted to improve the health or alter the development of a host insect. For example, vitellogenin can be targeted to alter foraging behavior, and thus modulate pollinator effectiveness.

**[0111]** The nucleic acid may be (i) plasmid DNA, (ii) linear DNA, (iii) circular DNA, (iv) single stranded DNA, (v) RNA, (vi) non natural DNA like molecules or (vii) a hybrid formed out of any of these molecules. These molecules are known in the art (see Sambrook and Russel, 2001). In one embodiment, the nucleic acid molecule is a broad-host-range vector. In one embodiment, the nucleic acid molecule is integrated into the bacterial genomic DNA.

### Broad Host Vector

**[0112]** In one embodiment, at least one nucleic acid molecule to be expressed is cloned into a broad-host-range vector backbone. Therefore, in one embodiment, the invention provides broad host vectors for use in the generation of genetically modified bacteria for expression of a gene product. The broad host vectors of the invention may comprise at least one of: a broad-host-range promoter, an antibiotic resistance cassette, an oriT sequence for delivery into recipient cells via conjugation, a ribosome binding site, an origin of replication, a bacterial terminator, at least one nucleic acid sequence for expression, and a sequence that encodes for a detectable marker.

**[0113]** Promoters are operably linked with those encoding sequences of which they initiate transcription. The encoding sequences may encode for RNA constructs, peptides or proteins. Exemplary promoters are promoters that are active in a broad range of cells including, but not limited to, CMV promoter, TK promoter, PA1, PA2, and PA3 from bacteriophage T7, cp12b, cp18, cp32, cp6, and cp25 promoters, and SV40. In one embodiment, the promoter is inducible. An exemplary inducible promoter includes a modified CP25 promoter with lacO sites (cp25 (lacO); SEQ ID NO: 12).

**[0114]** Generally, a promoter of the invention is understood to enable the transcription of DNA sequences in genetically engineered bacteria. The particular promoter

sequence will depend on the bacteria in which the gene product is to be expressed. In this context, a number of DNAs or vectors could be cloned that present a combination of different promoters having the gene sequence encoding for the desired gene product or a reporter such as GFP.

**[0115]** In exemplary embodiments, the broad host range vector comprises the RSF 1010 origin of replication and further comprises at least one heterologous nucleic acid sequence under the control of one or more (e.g., 2 or 3) broad host range promoters, such as PA1, PA2, PA3, cp12b, cp18, cp32, cp6, cp25 and cp25 (lacO). In one embodiment, the nucleic acid molecule of the invention comprises paired, convergent transcriptional promoters on a broad range vector. Exemplary pairs of transcriptional promoters that can be included on a nucleic acid molecule (e.g., for the generation of dsRNA molecules) include, but are not limited to at least two of PA1, PA2, PA3, cp12b, cp18, cp32, cp6, cp25 and cp25 (lacO). Exemplary, paired convergent transcriptional promoters include, but are not limited to, paired convergent cp25 promoters, paired convergent cp6 promoters, paired convergent cp18 promoters and paired convergent cp25 (lacO) promoters.

**[0116]** In one embodiment, the origin of replication is selected based on the bacterial species to be engineered to express the broad range vector. Origins of replication that can be included in the broad-range-vector of the invention include, but are not limited to, the RSF1010 plasmid origin of replication, the pBBR1 plasmid origin of replication, the RK2 plasmid origin of replication, the RP4 plasmid origin of replication and the pAMß1 plasmid origin of replication.

**[0117]** Furthermore, the nucleic acid molecules of the invention may also comprise enhancers. Enhancers may enhance the transcription initiation of a promoter, while they are not directly attached to the sequence of the promoter or the encoding sequence. Enhancers may be located far away or even on another DNA. Preferably, they are located on the same DNA as the promoter and the encoding sequence.

Toolkit for Modular Assembly of Broad-Host-Range Plasmids

**[0118]** In one embodiment, the invention provides one or more plasmids comprising genetic parts for the modular construction of vectors of the invention. In one embodiment, one or more plasmids comprises at least one of a broad-host-range promoter, an antibiotic resistance cassette, an oriT sequence for delivery into recipient cells via conjugation, a ribosome binding site, an origin of replication, a bacterial terminator, at least one nucleic acid sequence for expression, and a sequence that encodes for a detectable marker.

**[0119]** In one embodiment, the toolkit comprises a plasmid containing a promoter sequence for use in generating a vector of the invention. In one embodiment, the plasmid further comprises a ribosome binding site (RBS). Promoter sequences that may be included in a toolkit plasmid of the invention include, but are not limited to, SEQ ID NO: 12, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO: 41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, and SEQ ID NO:45. Exemplary plasmids comprising a promoter sequence for use in generating a vector of the invention include, but are not limited to, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58 and SEQ ID NO:59.

**[0120]** In one embodiment, the toolkit comprises a plasmid containing a reverse promoter sequence for use in generating a vector of the invention. In one embodiment, the plasmid further comprises a ribosome binding site (RBS). An exemplary reverse promoter sequence that may be included in a toolkit plasmid of the invention is set forth in SEQ ID NO:46. An exemplary plasmid comprising a reverse promoter sequence for use in generating a vector of the invention is SEQ ID NO:60.

**[0121]** In one embodiment, the toolkit comprises a plasmid containing a coding sequence for use in generating a vector of the invention. Coding sequences that may be included in a toolkit plasmid of the invention include, but are not limited to, a coding sequence encoding a sgRNA, dsRNA, siRNA, shRNA, miRNA, protein, or peptide. In one embodiment, the coding sequence encodes dCas9. An exemplary dCas9 coding sequence that may be included in a toolkit plasmid of the invention is set forth in SEQ ID NO:47. An exemplary plasmid comprising a coding sequence encoding dCas9 for use in generating a vector of the invention is SEQ ID NO:65. Exemplary plasmids comprising coding sequences for T7 RNA Polymerase, LacI repressor, GFP optim-1, Nanoluc, E2-Crimson and Kanamycin Resistance are provided as SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:67 and SEQ ID NO:68 respectively.

**[0122]** In one embodiment, the toolkit comprises a plasmid containing a terminator sequence for use in generating a vector of the invention. Terminator sequences that may be included in a toolkit plasmid of the invention include, but are not limited to, rpoC, BBa_B0015 and T7 terminators. Exemplary terminator coding sequences that may be included in a toolkit plasmid of the invention are set forth in SEQ ID NO:48, SEQ ID NO:49 and SEQ ID NO:50. Exemplary plasmids comprising a terminator sequence for use in generating a vector of the invention include, but are not limited to, SEQ ID NO:69, SEQ ID NO:70 and SEQ ID NO:71.

**[0123]** In one embodiment, the toolkit comprises a plasmid containing a repressor sequence for use in generating a vector of the invention. An exemplary plasmid comprising a repressor sequence for use in generating a vector of the invention is SEQ ID NO:66.

**[0124]** In one embodiment, the toolkit comprises a plasmid containing an origin of replication sequence for use in generating a vector of the invention. Origin of replication sequences that may be included in a toolkit plasmid of the invention include, but are not limited to, RSF1010 and R6k. Exemplary plasmids comprising an origin of replication sequence for use in generating a vector of the invention include, but are not limited to, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403 and SEQ ID NO: 11.

Inducible System

**[0125]** In one embodiment, the invention provides an inducible system for inducible expression of a gene product in bacteria. In one embodiment, the inducible system of the invention comprises lacI driven by the CP25 promoter, and a cp25 (lacO) promoter (SEQ ID NO: 12) operably linked to a nucleic acid sequence to be expressed. In one embodiment, the inducible system comprises lacI driven by the CP25 promoter, T7 RNAP under control of the inducible lac promoter, and a T7 promoter with lacO sites operably linked to a nucleic acid sequence to be expressed. In one embodi-

ment, the inducible system is on a single plasmid or vector. Alternatively, the inducible plasmid system may be on two or more plasmids or vectors.

Vectors for Integration into the Bacterial Genome

**[0126]** In one embodiment, the vector of the invention is capable of integrating into the genome of a target bacterial species. In one embodiment, the vector may comprise homology arms flanking at least one of a broad-host-range promoter, an antibiotic resistance cassette, a ribosome binding site, a bacterial terminator, a nucleic acid sequence for expression, and a sequence that encodes for a detectable marker. In one embodiment, a homology arm comprises at least 100 bp, at least 200 bp, at least 300 bp, at least 400 bp, at least 500 bp, at least 600 bp, at least 700 bp, at least 800 bp, at least 900 bp, at least 1000 bp, at least 1100 bp, at least 1200 bp, at least 1300 bp, at least 1400 bp, or at least 1500 bp having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% sequence identity to a target genomic DNA sequence. Alternatively the vector that is capable of integrating into the genome of a target bacterial species may be integrated using any method that is known in the art, including, but not limited to, lambda/red recombination, and may therefore comprises one or more elements allowing for the integration of the vector or selection or counter selection of bacteria comprising the integrated vector.

**[0127]** In one embodiment, the vector for integration comprises an origin of replication of a suicide plasmid that prevents plasmid replication in the target bacterial species. An exemplary suicide plasmid origin that can be used on a vector for integration includes, but is not limited to, the R6K plasmid origin of replication.

Nucleic Acid Sequences for Expression

**[0128]** In one embodiment, the broad-host-range vector of the invention comprises at least one nucleic acid sequence to be expressed. In one embodiment, the nucleic acid sequence expresses a RNA, protein or peptide. In one embodiment the nucleic acid sequence encodes a therapeutic molecule. For example, in various embodiments, the nucleic acid sequence encodes a pesticide degrading polypeptide or a cytochrome, or encodes an enzyme in a biosynthetic pathway producing neuro-active molecules that affect behaviors such as those determining aggression or pollinator effectiveness.

**[0129]** In one embodiment, the nucleic acid sequence to be expressed is a modulator of (e.g., an inhibitor or activator) of a target gene or gene product. In various embodiments, the present invention includes compositions for modulating the level or activity of a target gene or gene product in a subject, a cell, a tissue, or an organ in need thereof. In various embodiments, the compositions of the invention modulate the amount or activity of a target polypeptide, the amount or activity of a target protein, the amount or activity of a target mRNA. In one embodiment, the compositions of the invention modulate the amount or activity of a target polypeptide, the amount or activity of a target protein, the amount or activity of a target mRNA in an insect. In one embodiment, the compositions of the invention modulate the amount or activity of a target polypeptide, the amount or activity of a target protein, the amount or activity of a target mRNA in a pathogen, or parasite of an insect.

Activators

**[0130]** In one embodiment, the nucleic acid molecules and engineered bacteria of the invention can be used to activate or increase the levels of expression or activity of a target gene or protein in a subject. Therefore, in one embodiment, the invention relates to nucleic acid molecules encoding a protein, a recombinant polypeptide, an active polypeptide fragment, or combinations thereof, which function to increase, or activate, the expression or activity of a target gene or protein. It will be understood by one skilled in the art, based upon the disclosure provided herein, that an increase in the level of a target gene or protein encompasses the increase in gene expression, including transcription, translation, or both. The skilled artisan will also appreciate, once armed with the teachings of the present invention, that an increase in the level of a protein includes an increase in protein activity (e.g., enzymatic activity, receptor binding activity, etc.). Thus, increasing the level or activity of a target gene or protein includes, but is not limited to, increasing the amount of polypeptide, increasing transcription, translation, or both, of a nucleic acid encoding a target polypeptide; and it also includes increasing any activity of a target polypeptide as well.

**[0131]** Examples of host proteins for which it would be beneficial to have increased expression using the methods of the invention include, but are not limited to, immune system proteins (e.g., Dorsal, argonaut (ago2), relish, and proteins in the toll and imd pathways) conferring greater disease resistance or enzymes in pathways producing neuro-active molecules that affect behaviors such as those determining aggression or pollinator effectiveness.

Inhibitors

**[0132]** In various embodiments, the modulator of the invention comprises an inhibitor of a target gene or protein. In one embodiment, the inhibitor of the invention decreases the amount of polypeptide, the amount of mRNA, the amount of activity, or a combination thereof, of the target gene or protein. Exemplary target genes that can be inhibited according to the methods of the invention include, but are not limited to, TOM70, TIM22, TOM40, Imp2, mitochondrial Hsp70, ATM1-ABC transporter proteins, Frataxin, Ferredoxin, ERV1, ferredoxin, NADPH oxido-reductase [FNR], pyruvate dehydrogenase α subunit, pyruvate dehydrogenase β subunit, mitochondrial glycerol-3-phosphate dehydrogenase (mtG3PDH), manganese-containing superoxide dismutase (MnSOD), DNAJ (Hsp70 interacting), Iron Sulfur cluster ISU1, Cystein desulfurase Nsf1, NAR1, RLI1, ATPase subunit A, RNA polymerase I, RNA polymerase III, Inhibitor of apoptosis (IAP), and FAS apoptotic.

**[0133]** It will be understood by one skilled in the art, based upon the disclosure provided herein, that a decrease in the level of a target gene or protein encompasses the decrease in the expression, including transcription, translation, or both. The skilled artisan will also appreciate, once armed with the teachings of the present invention, that a decrease in the level of a target protein includes a decrease in the activity of the target protein. Thus, decrease in the level or activity of a target protein includes, but is not limited to, decreasing the amount of polypeptide, and decreasing transcription, translation, or both, of a nucleic acid encoding a target protein, and it also includes decreasing any activity of the target protein as well.

**[0134]** In one embodiment, the invention provides a generic concept for inhibiting an essential gene of a virus or parasite of a bee. In one embodiment, the inhibitor is selected from the group consisting of a small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, and a ribozyme.

**[0135]** One skilled in the art will appreciate, based on the disclosure provided herein, that one way to decrease the mRNA and/or protein levels of a target protein in a cell is by reducing or inhibiting expression of the nucleic acid encoding the target protein. Thus, the protein level can be decreased using a molecule or compound that inhibits or reduces gene expression such as, for example, dsRNA, siRNA, an antisense molecule or a ribozyme. However, the invention should not be limited to these examples.

**[0136]** In one embodiment, siRNA is used to decrease the level of a target gene or protein. RNA interference (RNAi) is a phenomenon in which the introduction of double-stranded RNA (dsRNA) into a diverse range of organisms and cell types causes degradation of the complementary mRNA. In the cell, long dsRNAs are cleaved into short 21-25 nucleotide small interfering RNAs, or siRNAs, by a ribonuclease known as Dicer. The siRNAs subsequently assemble with protein components into an RNA-induced silencing complex (RISC), unwinding in the process. Activated RISC then binds to complementary transcript by base pairing interactions between the siRNA antisense strand and the mRNA. The bound mRNA is cleaved and sequence specific degradation of mRNA results in gene silencing. See, for example, U.S. Pat. No. 6,506,559; Fire et al., 1998, Nature 391(19):306-311; Timmons et al., 1998, Nature 395:854; Montgomery et al., 1998, TIG 14 (7):255-258; David R. Engelke, Ed., RNA Interference (RNAi) Nuts & Bolts of RNAi Technology, DNA Press, Eagleville, PA (2003); and Gregory J. Hannon, Ed., RNAi A Guide to Gene Silencing, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2003). Soutschek et al. (2004, Nature 432:173-178) describe a chemical modification to siRNAs that aids in intravenous systemic delivery. Optimizing siRNAs involves consideration of overall G/C content, C/T content at the termini, Tm and the nucleotide content of the 3' overhang. See, for instance, Schwartz et al., 2003, Cell, 115:199-208 and Khvorova et al., 2003, Cell 115:209-216. Therefore, the present invention also includes methods of decreasing protein levels using RNAi technology.

**[0137]** In other related aspects, the invention includes a nucleic acid encoding an inhibitor, wherein an inhibitor such as a dsRNA, siRNA or antisense molecule, inhibits a target gene, operably linked to a nucleic acid comprising a promoter/regulatory sequence such that the nucleic acid is preferably capable of directing expression of the dsRNA, siRNA or antisense molecule encoded by the nucleic acid. Thus, the invention encompasses expression vectors and methods for the introduction of exogenous DNA into cells with concomitant expression of the exogenous DNA in the cells such as those described, for example, in Sambrook et al. (2012, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York) and as described elsewhere herein.

**[0138]** In another aspect, the invention includes a vector comprising an siRNA or antisense polynucleotide. The dsRNA, siRNA or antisense polynucleotide can be cloned into a number of types of vectors as described elsewhere herein. For expression of the dsRNA, siRNA or antisense polynucleotide, at least one module in each promoter functions to position the start site for RNA synthesis.

**[0139]** In order to assess the expression of the dsRNA, siRNA or antisense polynucleotide, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other embodiments, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers are known in the art and include, for example, antibiotic-resistance genes, such as neomycin resistance and the like.

**[0140]** In one embodiment of the invention, an antisense nucleic acid sequence which is expressed by a plasmid vector is used to inhibit a target gene or protein. The antisense expressing vector is used to transfect a bacterial cell to generate a genetically engineered bacteria of the invention.

**[0141]** Antisense molecules and their use for inhibiting gene expression are well known in the art (see, e.g., Cohen, 1989, In: Oligodeoxyribonucleotides, Antisense Inhibitors of Gene Expression, CRC Press). Antisense nucleic acids are DNA or RNA molecules that are complementary, as that term is defined elsewhere herein, to at least a portion of a specific mRNA molecule (Weintraub, 1990, Scientific American 262:40). In the cell, antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule thereby inhibiting the translation of genes.

**[0142]** The use of antisense methods to inhibit the translation of genes is known in the art, and is described, for example, in Marcus-Sakura (1988, Anal. Biochem. 172: 289). Such antisense molecules may be provided to the cell via genetic expression using DNA encoding the antisense molecule as taught by Inoue, 1993, U.S. Pat. No. 5,190,931.

**[0143]** Alternatively, antisense molecules of the invention may be made synthetically and then provided to the cell. Antisense oligomers of between about 10 to about 30, and more preferably about 15 nucleotides, are preferred, since they are easily synthesized and introduced into a target cell. Synthetic antisense molecules contemplated by the invention include oligonucleotide derivatives known in the art which have improved biological activity compared to unmodified oligonucleotides (see U.S. Pat. No. 5,023,243).

**[0144]** Compositions and methods for the synthesis and expression of antisense nucleic acids are as described elsewhere herein.

**[0145]** Ribozymes and their use for inhibiting gene expression are also well known in the art (see, e.g., Cech et al., 1992, J. Biol. Chem. 267:17479-17482; Hampel et al., 1989, Biochemistry 28:4929-4933; Eckstein et al., International Publication No. WO 92/07065; Altman et al., U.S. Pat. No. 5,168,053). Ribozymes are RNA molecules possessing the ability to specifically cleave other single-stranded RNA in a manner analogous to DNA restriction endonucleases. Through the modification of nucleotide sequences encoding these RNAs, molecules can be engineered to recognize specific nucleotide sequences in an RNA molecule and

cleave it (Cech, 1988, J. Amer. Med. Assn. 260:3030). A major advantage of this approach is the fact that ribozymes are sequence-specific.

**[0146]** There are two basic types of ribozymes, namely, tetrahymena-type (Hasselhoff, 1988, Nature 334:585) and hammerhead-type. Tetrahymena-type ribozymes recognize sequences which are four bases in length, while hammerhead-type ribozymes recognize base sequences 11-18 bases in length. The longer the sequence, the greater the likelihood that the sequence will occur exclusively in the target mRNA species. Consequently, hammerhead-type ribozymes are preferable to tetrahymena-type ribozymes for inactivating specific mRNA species, and 18-base recognition sequences are preferable to shorter recognition sequences which may occur randomly within various unrelated mRNA molecules.

Modified Cas9 System

**[0147]** In one embodiment, the invention provides a modified CRISPR system for expression of a sgRNA in bacteria, wherein one or more components of the CRISPR system is encoded on a broad-host-range vector of the invention. In one embodiment, the CRISPR system of the invention comprises an endonuclease enzyme (e.g., Cas9) which binds to a target nucleic acid sequence via a sgRNA, to modulate the target sequence. In one embodiment, the CRISPR system of the invention can be used to modulate a target sequence in an insect. In one embodiment, the CRISPR system of the invention can be used to modulate a target sequence in a parasite or pathogen of an insect.

**[0148]** In some embodiments, the Cas9 enzyme comprises catalytically dead Cas9 (dCas9) or a homolog, an ortholog or mimic thereof. Orthologs of Cas9 may be from a genus which includes but is not limited to *Corynebacter, Sutterella, Legionella, Treponema, Filifactor, Eubacterium, Streptococcus, Lactobacillus, Mycoplasma, Bacteroides, Flavivola, Flavobacterium, Sphaerochaeta, Azospirillum, Gluconacetobacter, Neisseria, Roseburia, Parvibaculum, Staphylococcus, Nitratifractor, Mycoplasma* and *Campylobacter*. Catalytically dead Cas9 mimics include, but are not limited to, proteins or peptides which are capable of interaction with an sgRNA to target the CRISPR fusion construct to a site of interest. Catalytically dead or inactive Cas9, and homologs, orthologs or mimics thereof are referred to herein collectively as "dCas9."

**[0149]** In one embodiment, dCas9 lacks cleavage or nickase activity. In one embodiment dCas9, or an ortholog thereof, has a diminished nuclease activity of at least 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96, 97%, 98%, 99% or 100% as compared with a wild-type Cas9 enzyme or ortholog. In one embodiment, the CRISPR fusion constructs comprising dCas9 serve as DNA-binding proteins with very little or no catalytic activity. In one embodiment, a dCas9 comprises one or more mutations in its catalytic domain which disrupt or inactivate the nuclease activity of the Cas9 enzyme.

**[0150]** Guide RNAs

**[0151]** The present system may be used with any short guide RNA (sgRNA.) In embodiments of the invention the terms guide sequence and guide RNA are used interchangeably. In general, a guide sequence is any polynucleotide sequence having sufficient complementarity with a target polynucleotide sequence to hybridize with the target sequence and direct sequence-specific binding of a CRISPR complex to the target sequence, in some embodiments, the degree of complementarity between a guide sequence and its corresponding target sequence, when optimally aligned using a suitable alignment algorithm, is about or more than about 50%, 60%, 75%, 80%, 85%, 90%, 95%, 97.5%, 99%, or more. Optimal alignment may be determined with the use of any suitable algorithm for aligning sequences, non-limiting example of which include the Smith-Waterman algorithm, the Needleman-Wunsch algorithm, algorithms based on the Burrows-Wheeler Transform (e.g. the Burrows Wheeler Aligner), ClustalW, Clustal X, BLAT, Novoalign, ELAND (Illumina, San Diego, Calif.), SOAP, and Maq. In some embodiments, a guide sequence is about or more than about 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 75, or more nucleotides in length. In some embodiments, a guide sequence is less than about 75, 50, 45, 40, 35, 30, 25, 20, 15, 12, or fewer nucleotides in length. In some embodiments, the guide sequence is 10-30 nucleotides long. The ability of a guide sequence to direct sequence-specific binding of a CRISPR complex to a target sequence may be assessed by any suitable assay. For example, cleavage of a target polynucleotide sequence may be evaluated in a test tube by providing the target sequence, components of a CRISPR complex, including the guide sequence to be tested and a control guide sequence different from the test guide sequence, and comparing binding or rate of cleavage at the target sequence between the test and control guide sequence reactions. Other assays are possible, and will occur to those skilled in the art. A guide sequence may be selected to target any target sequence. In one embodiment, the sgRNAs for use in the system of the invention hybridize to a target sequence in an insect administered the genetically engineered bacteria. In one embodiment, the sgRNAs for use in the system of the invention hybridize to a target sequence in a pathogen or a pest of an insect administered the genetically engineered bacteria.

Constructs Encoding Multiple Gene Products

**[0152]** In one embodiment, the compositions of the invention encode at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 gene products. In one embodiments, multiple gene products may be encoded on a single nucleic acid molecule. In an alternative embodiment, multiple gene products may be encoded on multiple nucleic acid molecules, for example, at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 gene products may be encoded on at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 nucleic acid molecules. In one embodiment, a single bacterial cell comprises multiple nucleic acid molecules encoding multiple gene products of the invention.

**[0153]** In one embodiment, the compositions of the invention comprise multiple genetically modified bacteria or populations thereof wherein each genetically modified bacteria or populations comprises at least one nucleic acid molecule encoding at least one inhibitor of the invention. Therefore, in various embodiments, the invention provides a composition comprising at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 genetically modified bacteria or populations comprising nucleic acid molecules encoding for at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 gene products of the invention. In one embodiment, multiple genetically modified bacterial popu-

lations are of the same bacterial species. In one embodiment, multiple genetically modified bacterial populations are of different bacterial species.

**[0154]** In one embodiment, multiple nucleic acid molecules encode multiple gene products of the same target gene or protein. In an alternative embodiment, multiple nucleic acid molecules encode gene products of the multiple target genes or proteins. Multiple target genes or proteins may be multiple targets in a single pathogen or parasite, or multiple targets in multiple pathogens or parasite. Therefore, in one embodiment, the invention provides a composition comprising multiple genetically encoded bacteria comprising multiple nucleic acid constructs for inhibiting at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 target genes or proteins. In one embodiment, the invention provides a composition comprising multiple genetically encoded bacteria comprising multiple nucleic acid constructs for inhibiting or modulating at least 1, at least 2, at least 3, at least 4, at least 5 or more than 5 target pathogens or parasites.

Genetically Modified Bacteria

**[0155]** In one embodiment, the invention provides genetically modified bacteria comprising a nucleic acid molecule for expression of a heterologous nucleic acid sequence. In one embodiment the present disclosure provides microbial compositions comprising one or more bacteria genetically engineered to express a heterologous nucleic acid. In one embodiment, the one or more bacteria are native to the microbiome of an arthropod. In one embodiment, the one or more bacteria are native to the microbiome of a bee. In some aspects, the one or more bacteria are *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, *Serratia marcescens* or *Parasaccharibacter apium*. In one embodiment, the one or more bacteria are bacterial species that can live in bee hive materials. In one embodiment, *Parasaccharibacter apium* or *Lactobacillus* sp. In some aspects, the composition comprises 2, 3, 4, or 5 genetically engineered bacterial species.

**[0156]** In one embodiment, one or more nucleic acid molecule for expression of a heterologous nucleic acid sequence is contained in the bacterial cell. In one embodiment, one or more nucleic acid molecule for expression of a heterologous nucleic acid sequence is integrated into the genome of said one or more bacteria. In certain aspects, the one or more bacteria express at least two heterologous nucleic acids.

Host Organisms

**[0157]** The methods of the present invention can be applied to all arthropods. The compositions and methods of the invention can be used for all purposes where the production of a gene encoded molecule in an arthropod is suitable and/or desirable. This includes the use of the method of the invention to generate a host arthropod, where at least one genetically modified bacteria for production of a gene encoded molecule has been administered to the host arthropod.

**[0158]** In one embodiment of the present invention, the arthropod may be, but is not limited, to an insect, an arachnid, a crustacean and a myriapodum. In one embodiment, the arthropod is an insect. Insects that can serve as hosts according to the methods of the invention include, but are not limited to, a holometabolic insect, a hemimetabolic insect, and an insect from the order Hymenoptera, Coleoptera or Orthoptera. Exemplary insects include, but are not limited to, a honey bee (*Apis mellifera*) and a small hive beetle (*Aethina tumida*). In another embodiment of the present invention, the arthropod is an arachnid, for example, a mite.

**[0159]** In some embodiments, the insect is a bee. As used herein, the term "bee" refers to both an adult bee and pupal cells thereof. According to one embodiment, the bee is in a hive. An adult bee is defined as any of several winged, hairy-bodied, usually stinging insects of the superfamily Apoidea in the order Hymenoptera, including both solitary and social species and characterized by sucking and chewing mouthparts for gathering nectar and pollen. Exemplary bee species include, but are not limited to, *Apis, Bombus, Trigona, Osmia* and the like. In one embodiment, bees include, but are not limited to bumblebees (*Bombus terrestris*), honeybees (*Apis mellifera*) (including foragers and hive bees) and *Apis* cerana.

**[0160]** According to one embodiment, the bee is part of a colony. The term "colony" refers to a population of bees comprising dozens to typically several tens of thousand bees that cooperate in nest building, food collection, and brood rearing. A colony normally has a single queen, the remainder of the bees being either "workers" (females) or "drones" (males). The social structure of the colony is maintained by the queen and workers and depends on an effective system of communication. Division of labor within the worker caste primarily depends on the age of the bee but varies with the needs of the colony. Reproduction and colony strength depend on the queen, the quantity of food stores, and the size of the worker force. Honeybees can also be subdivided into the categories of "hive bees", usually for the first part of a workers lifetime, during which the "hive bee" performs tasks within the hive, and "forager bee", during the latter part of the bee's lifetime, during which the "forager" locates and collects pollen and nectar from outside the hive, and brings the nectar or pollen into the hive for consumption and storage.

Formulations

**[0161]** In some embodiments, the composition is a bee-ingestible composition. In certain aspects, the bacteria are present as a live suspension or a lyophilized powder. The composition may be in solid form or liquid form, such as a sucrose solution or a corn syrup solution. In some aspects, the composition comprises protein and/or pollen. In additional aspects, the composition further comprises a carbohydrate or sugar supplement or other additive or excipient as described elsewhere herein.

Methods

**[0162]** The present invention also relates to the use of a genetically engineered bacteria comprising a nucleic acid encoding a molecule for use in a method for protecting an arthropod against pest influences, parasites or ectoparasites or for use in a method for treating an arthropod disease in an arthropod, wherein the genetically engineered bacteria is fed to the arthropod or is administered orally. All embodiments described above with respect to the method of the invention also apply to said use of the invention.

**[0163]** In one embodiment, there is provided a method for producing a genetically engineered bacterial species accord-

ing to the composition of the embodiments (e.g., engineered bacteria) comprising transfecting said bacterial species with an expression cassette comprising at least one heterologous nucleic acid.

**[0164]** In one embodiment, there is provided a method for downregulating expression of a target gene product in an insect pathogen or parasite comprising administering an effective amount of one or more genetically engineered bacteria to a host insect, wherein said bacteria express an inhibitor of the target gene product. In some aspects, the target gene product is a pathogen or parasite-specific gene product, such as a virus- or mite-specific gene product. Parasites and pathogens that can be targeted using the methods of the invention include, but are not limited to, Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, deformed wing virus, or *Varroa destructor* mite and other parasites or pathogens which infect insects.

**[0165]** In one embodiment, there is provided a method for downregulating expression of a target gene product in a target insect. In one embodiment, the method comprises administering an effective amount of one or more genetically engineered bacteria to a food source of a target insect, wherein said bacteria express a dsRNA complementary to a gene product of the target insect. In one embodiment, the target insect is a pest insect. In one embodiment, the target insect is a Small Hive Beetle, and a food source of the target insect is a bee hive.

**[0166]** In some aspects, the one or more genetically engineered bacteria are comprised in a composition of the embodiments described herein. In particular aspects, the one or more genetically engineered bacteria are selected from the group consisting of *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, *Serratia marcescens*, *Parasaccharibacter apium*, and *Lactobacillus* sp.

**[0167]** In one embodiment, there is provided a method for expression of a heterologous nucleic acid sequence in an arthropod. In one embodiment, the method comprises administering to the arthropod a composition comprising one or more genetically modified bacteria, wherein the one or more genetically modified bacteria comprise a vector for expression of a heterologous nucleic acid sequence. In one embodiment, one or more bacteria is native to the host arthropod microbiome and as such is able to persist in the gut of the arthropod for at least one day, at least two days, at least three days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, at least 15 days, or for more than 15 days. In one embodiment, the one or more bacteria persists in the gut of the arthropod for the duration of the arthropod's lifespan.

**[0168]** In a further embodiment, there is provided a method for reducing the susceptibility of a bee to a disease or disorder associated with a pathogen or parasite. In one embodiment, the disease or disorder is Colony Collapse Disorder (CCD). Therefore, in one embodiment, the invention provides a method of treating or preventing CCD comprising administering an effective amount of one or more genetically engineered bacteria to a bee, or bee hive component, wherein said bacteria express a dsRNA complementary to a pathogen or parasite-specific gene product.

**[0169]** In another embodiment, there is provided method for reducing the susceptibility of a bee to an infection comprising feeding the bee an effective amount of one or more genetically engineered bacteria to said bee, wherein said bacteria express a dsRNA complementary to a pathogen or parasite-specific gene product.

**[0170]** In some aspects of the above embodiments, the pathogen or parasite is Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, deformed wing virus, *Varroa destructor* mite, or Small Hive Beetle. In certain aspects, the *Nosema ceranae* is *N. ceranae* or *N. apis*. In specific aspects, the pathogen or parasite-specific gene product is an mRNA encoding a *Nosema* mitosomal protein. In some aspects, the *Nosema* mitosomal protein is selected from the group consisting of TOM70, TIM22, TOM40, Imp2, mitochondrial Hsp70, ATM1-ABC transporter proteins, Frataxin, Ferredoxin, ERV1, ferredoxin, NADPH oxido-reductase [FNR], pyruvate dehydrogenase a subunit, pyruvate dehydrogenase 3 subunit, mitochondrial glycerol-3-phosphate dehydrogenase (mtG3PDH), manganese-containing superoxide dismutase (MnSOD), DNAJ (Hsp70 interacting), Iron Sulfur cluster ISU1, Cystein desulfurase Nfs1, NAR1 and RLI1. In other aspects, the parasite-specific gene product is ATPase subunit A, RNA polymerase I, RNA polymerase III, Inhibitor of apoptosis (IAP), or FAS apoptotic. In certain aspects, the bacteria express at least two non-contiguous dsRNAs targeting a gene product of at least one of Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, deformed wing virus, *Varroa destructor* mite, and/or Small Hive Beetle. In certain aspects, the bacteria express at least two non-contiguous dsRNAs targeting a gene product of at least two of Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, deformed wing virus, *Varroa destructor* mite, and/or Small Hive Beetle.

**[0171]** In one embodiment, the agents of the present invention are used to prevent the *Varroa destructor* mite from living as a parasite on the bee, or larvae thereof. In one embodiment, the agents of the present invention are used to prevent the Small Hive Beetle from living as a parasite on the bee colony. Therefore, in one embodiment, the agents of the present invention are capable of down-regulating expression of a gene product of a *Varroa destructor* mite or Small Hive Beetle.

**[0172]** In one embodiment, the agents of the present invention are used to prevent a viral infection of the bee, or larvae thereof. Therefore, in one embodiment, the agents of the present invention are capable of down-regulating expression of a gene product of a viral gene.

**[0173]** As used herein, the phrase "gene product" refers to an RNA molecule or a protein. According to one embodiment, the targeted gene product is one which is essential for parasite viability, parasite reproduction, viral replication or viral pathogenicity. Down-regulation of such a gene product would typically result in killing of a parasite, extermination of the parasite population or reduced viral pathogenicity.

**[0174]** It will be appreciated that whilst the agents of the present invention are capable of downregulating expression of a gene product of a parasite or pathogen, it is preferable that they downregulate to a lesser extent expression of the gene product in other animals, such as the bee. Accordingly, the agents of the present invention must be able to distinguish between the target gene and the bee gene, down-regulating the former to a greater extent than the latter.

According to another embodiment the agents of the present invention do not down-regulate the bee gene whatsoever. This may be effected by targeting a gene that is present or expressed in the target pathogen or parasite and not in the bee. Alternatively, the agents of the present invention may be targeted to parasite-specific sequences of a gene that is expressed both in the target parasite and in the bee.

**[0175]** According to one embodiment the agents of the present invention target segments of genes that are at least 100 bases long and do not carry any sequence longer than 19 bases that is entirely homologous to any bee-genome sequence or human-genome sequence.

**[0176]** Downregulating expression of a gene product can be monitored, for example, by direct detection of gene transcripts (for example, by PCR), by detection of polypeptide(s) encoded by the gene or bee pathogen RNA (for example, by Western blot or immunoprecipitation), by detection of biological activity of polypeptides encode by the gene (for example, catalytic activity, ligand binding, and the like), or by monitoring changes in the parasite or pathogen (for example, reduced proliferation, reduced virulence, reduced motility etc) and by testing bee infectivity/pathogenicity.

**[0177]** Downregulation of a target gene product can be effected on the genomic and/or the transcript level using a variety of agents which interfere with transcription and/or translation (e.g., RNA silencing agents, Ribozyme, DNAzyme and antisense).

**[0178]** According to one embodiment, the agent which down-regulates expression of a target gene product is a polynucleotide agent, such as an RNA silencing agent. According to this embodiment, the polynucleotide agent is greater than 15 base pairs in length.

**[0179]** As used herein, the phrase "RNA silencing" refers to a group of regulatory mechanisms (e.g. RNA interference (RNAi), transcriptional gene silencing (TGS), post-transcriptional gene silencing (PTGS), quelling, co-suppression, and translational repression) mediated by RNA molecules which result in the inhibition or "silencing" of the expression of a corresponding protein-coding gene or bee pathogen RNA sequence. RNA silencing has been observed in many types of organisms, including plants, animals, and fungi.

**[0180]** In one embodiment of the present disclosure, synthesis of RNA silencing agents suitable for use with the present invention can be effected as follows. First, the pathogen polypeptide mRNA or other target sequence is scanned downstream of the AUG start codon for AA dinucleotide sequences. Occurrence of each AA and the 3' adjacent 19 nucleotides is recorded as potential siRNA target sites. Preferably, siRNA target sites are selected from the open reading frame, as untranslated regions (UTRs) are richer in regulatory protein binding sites. UTR-binding proteins and/or translation initiation complexes may interfere with binding of the siRNA endonuclease complex. It will be appreciated though, that siRNAs directed at untranslated regions may also be effective, as demonstrated for GAPDH wherein siRNA directed at the 5' UTR mediated about 90% decrease in cellular GAPDH mRNA and completely abolished protein level (see Ambion® technical library 91/912 at the Ambion® website).

**[0181]** Second, potential target sites are compared to an appropriate genomic database (e.g., human, mouse, rat, insect, etc.) using any sequence alignment software, such as the BLAST software available from the NCBI server of the NIH. Putative target sites which exhibit significant homology to other coding sequences are filtered out. For example, host (e.g. bee) target sites can be filtered out in this manner.

**[0182]** Qualifying target sequences are selected as template for siRNA synthesis. Preferred sequences are those including low G/C content as these have proven to be more effective in mediating gene silencing as compared to those with G/C content higher than 55%. Several target sites are preferably selected along the length of the target gene or sequence for evaluation. For better evaluation of the selected siRNAs, a negative control is preferably used in conjunction. Negative control siRNA preferably include the same nucleotide composition as the siRNAs but lack significant homology to the genome. Thus, a scrambled nucleotide sequence of the siRNA is preferably used, provided it does not display any significant homology to host gene sequences, or non-relevant pathogen target sequences.

**[0183]** It will be appreciated that the dsRNA sequences target RNA transcripts complementary to DNA sequences of the targeted gene which are expressed in the parasite (transcribed into RNA), and that the actual complementation taking place in the RNAi pathways occurs following reduction of the dsRNA to smaller fragments by the RNAi enzymes.

**[0184]** It will be appreciated that since *Varroa* mites use their mouths to puncture the bee exoskeleton and feed on the bee's hemolymph, the present invention contemplates delivering the polynucleotide agents of the present invention to the bees via the genetically engineered bacteria, whereby they become presented in the bee's hemolymph thereby becoming available to the mite. Thus, according to another embodiment, the nucleic acid agents are delivered indirectly to the mites (e.g. via the bee). In this embodiment, the promoter of the nucleic acid construct is typically operational in bee gut bacterial cells

**[0185]** In one embodiment said nucleic acid encodes an siRNA or an antisense RNA. In this case, the siRNA or antisense RNA molecule is produced in the arthropod by feeding the arthropod with the genetically engineered bacteria. In this context, the nucleic acid is preferably a vector encoding the siRNA and further containing promoter sequences enabling the production of the siRNA.

**[0186]** In one embodiment, of the present invention, the genetically engineered bacteria is fed to the arthropod. In principle, every feed can be used that is accepted by the arthropod to be fed. This includes any kind material that is consumed orally by the arthropods, independent on whether it is natural feed, agricultural feed or laboratory feed and independent on whether it is consumed naturally or is administered by means of technical devices or is taken up casually. In one embodiment, the feed that is used to induce the production of the gene encoded molecules in the arthropods is either a liquid feed comprising the genetically engineered bacteria, a dry feed mixed with a solution comprising the genetically engineered bacteria or a dry feed comprising the genetically engineered bacteria in any of these formulations.

**[0187]** As detailed herein, bee feeding is common practice amongst bee-keepers, for providing both nutritional and other, for example, supplemental needs. Bees typically feed on honey and pollen, but have been known to ingest non-natural feeds as well. Bees can be fed various foodstuffs including, but not limited to Wheast (a dairy yeast grown on cottage cheese), soybean flour, yeast (e.g. brewer's yeast,

torula yeast) and yeast products products-fed singly or in combination and soybean flour fed as a dry mix or moist cake inside the hive or as a dry mix in open feeders outside the hive. Also useful is sugar, or a sugar syrup. The addition of 10 to 12 percent pollen to a supplement fed to bees improves palatability. The addition of 25 to 30 percent pollen improves the quality and quantity of essential nutrients that are required by bees for vital activity.

**[0188]** Cane or beet sugar, isomerized corn syrup, and type-50 sugar syrup are satisfactory substitutes for honey in the natural diet of honey bees. The last two can be supplied only as a liquid to bees.

**[0189]** Liquid feed can be supplied to bees inside the hive by, for example, any of the following methods: friction-top pail, combs within the brood chamber, division board feeder, boardman feeder, etc. Dry sugar may be fed by placing a pound or two on the inverted inner cover. A supply of water must be available to bees at all times. In one embodiment, pan or trays in which floating supports-such as wood chips, cork, or plastic sponge—are present are envisaged. Detailed descriptions of supplemental feeds for bees can be found in, for example, USDA publication by Standifer, et al 1977, entitled "Supplemental Feeding of Honey Bee Colonies" (USDA, Agriculture Information Bulletin No. 413).

**[0190]** All the bees in a hive are potentially susceptible to the pathogenic diseases detailed herein. Thus, according to some embodiments, the bees can be honeybees, forager bees, hive bees and the like.

**[0191]** Also provided is a method for reducing the susceptibility of a bee to a disease caused by pathogens, the method effected by feeding the bee on an effective amount of a nucleic acid or nucleic acid construct comprising a nucleic acid agent downregulating expression of a polypeptide of the bee pathogen and/or causing cleavage and/or degradation of a bee pathogen RNA. Methods for reducing the susceptibility of a bee colony or bee-hive to bee pathogens by feeding oligonucleotides and/or polynucleotides are envisaged. Thus, in some embodiments, the present invention can be used to benefit any numbers of bees, from a few in the hive, to the entire bee population within a hive and its surrounding area. It will be appreciated, that in addition to feeding of oligonucleotides and/or polynucleotides for reduction of the bee pathogen infection and infestation, enforcement of proper sanitation (for example, refraining from reuse of infested hives) can augment the effectiveness of treatment and prevention of infections.

Kits

**[0192]** The invention also includes a kit comprising a composition of the invention, for example, a kit comprising one or more plasmid comprising a genetic part for the modular construction of a vector for use in generating a genetically modified bacterium of the invention or a genetically modified bacterium comprising a nucleic acid molecule for expression of a heterologous gene product. In one embodiment, the kit may also comprise instructional material which describes, for instance, methods of generation of a vector of the invention, methods of generating a genetically engineered bacterium of the invention, or methods of administering a genetically engineered bacterium of the invention to a target arthropod.

I. EXAMPLES

**[0193]** The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1 Microbiome Engineering in Honey Bee Gut

**[0194]** Several bacterial species including *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, and *Parasaccharibacter apium* from the bee gut were engineered to express heterologous genes. A broad host range plasmid pMMB67EH was used to express the heterologous gene. It was then confirmed that these modified bacteria can reestablish and be maintained in bees.

**[0195]** A variety of broad host range promoters were tested for their ability to express GFP in vitro in the various bacterial species. The promoters that were tested included PA1, PA2, PA3, and cp25 (FIG. **1**). For *S. alvi*, all of the promoters tested resulted in similar expression of GFP. PA2, PA3, and cp25 resulted in higher GFP expression as compared to PA1 in *G. apicola*. Finally, PA1 was observed to have the highest expression of GFP in *B. apis*.

**[0196]** To determine if the modified bacteria could continue to function in the bee gut, the engineered strains *Snodgrassella alvi* and *Serratia marcescens* producing fluorescent proteins were inoculated into germ-free bees and the guts were fluorescently imaged 5 days later (FIG. **2**). The control uninoculated bees showed no fluorescent signal. On the other hand, bees inoculated with either the *S. marcescens* or *S. alvi* had expression of the fluorescent proteins. In addition, co-inoculation with both fluorescent strains resulted in expression of both fluorescent proteins.

**[0197]** In order to test the ability of the engineered bacterial species to produce dsRNA in honey bees, the broad host range backbone plasmid and the knowledge of promoter strength in bee gut species were used to produce a dsRNA-producing construct (FIG. **3**). The construct has flanking broad range promoters driving RNA transcription of the tubulin alpha-1 chain-like gene (*Apis mellifera* (honey bee)). The *Snodgrassella alvi* wkB2 strain was used to produce dsRNA using the construct and was then grown in cultures in vitro for 48 hours. RNA was extracted, transcribed to cDNA, and qPCR was performed, normalizing to bacterial 16S copies (FIG. **4**). The bacteria was found to produce dsRNA in vitro for alpha tubulin.

**[0198]** Next, it was determined whether the bacteria would produce dsRNA in vivo in bees. Bees were inoculated with *S. alvi* expressing Tyrosine Hydroxylase (TH) dsRNA or a GFP dsRNA control. After 6 days, guts were homogenized and RNA was extracted. Quantitative RT-PCR was used to assess the relative amount of TH RNA present in the gut compared to an actin control (FIG. **5**).

Example 2 Induction of RNAi in Honey Bees

**[0199]** The broad-host-range backbone was used to build two dsRNA-producing constructs to test in vivo. In one construct, a dsRNA cassette targeting alpha-tubulin, an essential bee gene, was used. Downregulation of this essen-

tial gene by induction of an RNAi response should result in increased mortality. Newly emerged workers were colonized with *S. alvi* wkB2 containing dsRNA constructs targeting alpha-tubulin or GFP-control. Survival was monitored daily (FIG. 6). The bees with dsRNA constructs targeting alpha tubulin were observed to have increased mortality. Thus, the microbe-produced dsRNA can induces RNAi in vivo in honey bees.

**[0200]** The second construct that was tested had dsRNA targeting of tyrosine hydroxylase (TH). Bees were inoculated with bacteria containing the construct targeting TH and the ability to induce a systemic RNAi response and down regulated gene transcription in other body sites was determined. FIG. 7 shows that the dsRNA construct was able to induce RNAi and downregulated expression of TH in the bee head. Therefore, the present methods can be used to engineer bacteria which are introduced to bees and induce expression of a gene or induce RNAi against a target gene. This method may be broadly useful for downregulating honey bee genes for research as well as industrial uses to improve bee health and lower the impact of bee pathogens.

Example 3—Materials and Methods

**[0201]** The plasmids used for the above experiments were all derived from the rsf1010 origin from the pMMB67EH broad host range *E. coli* plasmid. The pBTK520 plasmid was used to express GFP fluorescent protein and had spectinomycin resistance (FIG. 8A). The pBTK570 (FIG. 8B) plasmid expressing E2-Crimson fluorescent protein was used to validate gene expression in vivo. The pBTK562 plasmid (FIG. 8C) expressing dsRNA against GFP was used as control in dsRNA experiments. The pBTK561 plasmid (FIG. 8D) expressing dsRNA against bee alpha tubulin was used to show in vivo killing of bees and expression of dsRNA in vitro. Finally, the pBTK590 plasmid (FIG. 8E) expressing dsRNA against Tyrosine Hydroxlyase was used to confirm gene knock down in the head in vivo.

Example 4—Genetic Engineering of Bee Gut Microbiome Bacteria with a Toolkit for Modular Assembly of Broad-Host-Range Plasmids

**[0202]** A preliminary screen with a variety of broad-host-range plasmids was performed with different replication origins (RP4, pBBR1, RSF1010) and antibiotic resistance markers (kanamycin, ampicillin, chloramphenicol, spectinomycin) for their ability to be transferred by conjugation and stably maintained in two bacterial species, *S. alvi* and *G. apicola*, which are both abundant in the honey bee gut (FIG. 16). Plasmid pMMB67EH, a synthetic plasmid containing an RSF1010 origin (Furste J P, et al., 1986, Gene, 48:119-131), was the most versatile: it replicated in both species. Plasmids containing an RSF1010 origin are known to be extremely broad-hostrange (BHR) because they encode multiple ORFs that make them less dependent on the presence of specific proteins in a host cell for replication (Jain A et al., 2013, FEMS Microbiol Lett., 348:87-96; Meyer R. et al., 2009, Plasmid, 62:57-70). Additionally, they contain a promiscuous origin of transfer (oriT) that enables one-way transfer of the plasmid to a recipient cell from a donor cell encoding a conjugation apparatus in trans on the chromosome, such as *E. coli* MFDpir (Ferrieres L. et al., 2010, J Bacteriol., 192:6418-6427).

**[0203]** Because of these characteristics of pMMB67EH, it was decided to create a toolkit of genetic parts for hierarchical and combinatorial assembly into its RSF1010-derived backbone for testing in additional species (FIG. 9A). These BTK parts are compatible with the Golden Gate cloning scheme used by the Yeast Toolkit (YTK) (Lee M E, 2015, ACS Synth Biol., 4:975-986), and connector parts from the YTK are required for BTK assembly. BTK parts are classified into eight types defined by the specific flanking overhangs generated by type IIS restriction enzyme cleavage. Entry vectors containing any complete set of parts labeled 1-8 can be combined via one BsaI Golden Gate assembly reaction into a complete plasmid (FIG. 9B). This assembly creates a Stage 1 plasmid comprising parts 2-4 flanked by assembly connector parts 1 and 5 with vector backbone components in parts 6-8. Transcriptional units from multiple Stage 1 plasmids that have matching sets of connector parts can be further composed into one vector by Stage 2 assembly using BsmBI (FIG. 9C).

**[0204]** To create BTK vector backbone parts, the high-copy number bacterial ColE1 origin of YTK part 8 plasmids ($Amp^R$, $Kan^R$, $Spec^R$) was replaced with the RSF1010 origin from pMMB67EH. These backbones retain the oriT for delivery into recipient cells via conjugation, which is useful for genetically modifying bacterial species and strains lacking established chemical or electrical transformation techniques. In the original YTK, Type 6 and 7 parts encode a yeast marker and a yeast origin, respectively. Type 6 part overhangs was repurposed for flanking a DNA sequence encoding an optional additional CDS (such as a repressor) in the reverse orientation relative to the Type 3 part CDS, and Type 7 part overhangs for incorporating an optional reverse promoter for driving expression of the part 6 CDS. A combined Type 6-7 linker (pBTK301) can be used in lieu of these parts to create constructs lacking this extra reverse gene. These vectors were used to construct a variety of plasmids containing a single fluorescent protein driven by a broad-host-range promoter. To build more complex assemblies, such as those with T7 RNA polymerase driving inducible expression of GFP, multiple vectors from BsaI Stage 1 assembly in a Stage 2 BsmBI assembly were combined. Notable components of the BTK that expand on the set of genetic parts available in the YTK for compatible assembly include: 3 BHR plasmids with different antibiotic resistance cassettes and oriT as Type 8 origin parts for Stage 1 assembly; 2 BHR plasmids ready for Stage 2 assembly ($Spec^R$, $Kan^R$); 11 bacterial promoter/RBS combinations as Type 2 parts; 6 new CDSs including E2-Crimson (Strack R L et al., 2009, Biochemistry, 48:8279-8281) and Nanoluc (Hall M P et al., 2012, ACS Chem Biol., 7:1848-1857) for in vivo visualization as Type 3 parts; 3 bacterial terminators as Type 4 parts; 1 transcriptional repressor (LacI) as a Type 6 part; 2 R6K-origin plasmid backbones to assemble suicide plasmids for gene disruption or chromosomal modification and pre-assembled plasmids with BHR promoters for immediate testing in new bacterial strains.

**[0205]** In summary, BTK, the first Golden Gate toolkit designed specifically for the combinatorial assembly of broad-host-range plasmids was built, with the aim of expanding synthetic biology into diverse bacteria native to non-laboratory environments. In this study, BTK was applied to modify bacteria found in the honey bee gut microbiome. These species are typical of many other bacteria in natural microbial communities of interest: they have

only been cultured recently, are phylogenetically diverse, and have few or no established genetic tools. Fundamental BTK components needed for genetic modification was validated, including antibiotic selection markers, conjugation procedures, and promoters to express proteins under constitutive or inducible control. BGM strains engineered with the BTK colonize the guts of newly emerged bees, and fluorescent in vivo imaging revealed a characteristic spatial distribution of each species in the gut.

**[0206]** The species engineered are within the Proteobacteria, a diverse Gram-negative phylum that is a common component of animal- and plant-associated communities. Although it has not yet being tested more broadly, BTK components should also be useful for genetically modifying other bacteria native to other natural communities. The core of the BTK is the RSF1010 plasmid origin, which is known to replicate in diverse bacterial lineages including Cyanobacteria, *Agrobacterium*, and others (Jain A et el., 2013, FEMS Microbiol Lett., 348:87-96; Meyer R et al., 2009, Plasmid, 62:57-71; Taton A et al., 2014, Nucleic Acids Res., 42:gku673-e136; Clewell D B et al., 1974, J Bacteriol., 117:283-289). The BTK also includes promoters that have previously been shown to function in both Gram-negative and Gram-positive bacteria (Jensen P R et al., 1998, Appl Environ Microbiol., 64:82-87). The E2-Crimson reporter gene fluoresces at far-red excitation wavelengths, which is ideal for in vivo imaging of bacteria through tissue in host-associated systems (Strack R L et al., 2009, Biochemistry, 48:8279-8281). While broadhost-range plasmids have already been extensively used to study newly isolated bacteria in the past (Clewell D B et al., 1974, J Bacteriol., 117:283-289), the combinatorial nature of this new toolkit makes it possible to test multiple antibiotic resistance markers and promoters, which are more difficult to replace in plasmids that rely on classical cloning approaches.

**[0207]** Standard part definitions enable researchers to customize a toolkit by adding new capabilities for their own applications, as it was done with re-using parts from the yeast toolkit (YTK) (Lee M E et al., 2015, ACS Synth Biol., 4:975-986). Separating antibiotic resistance cassettes and replication origins into different subparts and adding to the library of choices available for each function allows more combinations of antibiotics and origins to be tested when first working with a new species. Gram-positive origins, such as pAMβ1 (Clewell D B et al., 1974, J Bacteriol., 117:283-289), would be especially useful for the manipulation of other common host-associated phyla such as Firmicutes and Actinobacteria (Robinson C J et al., 2010, Microbiol Mol Biol Rev., 74:453-476). Further validation of some BTK parts, such as the dCas9 and Cas9 systems, is needed to conclude that they will function reliably across diverse species. Other established broad-host-range tools—such as Tn7-transposon integration (Choi K H et al., 2005, Nat Meth., 2:443-448), Group II intron-based gene disruption (Enyeart P J et al., 2013, Mol Syst Biol., 9:685-685), and emerging CRISPR methods for targeted mutagenesis (Banno S et al., 2018, Nat Microbiol., 339:819)—could also be incorporated into the BTK-compatible Golden Gate framework in the future.

**[0208]** Application of the BTK to engineering bee gut bacteria enables new approaches to microbiome research in these insect species that are important pollinators and model systems for studying social behavior and learning. For example, gene disruption combined with fluorescent visualization of bacterial cells in living bees can be used to improve understanding of the molecular basis of host-microbe and microbe-microbe interactions and their relevance to host health. The BTK can also be used to implement and test biotechnological approaches for mitigating threats to bee health. For example, it could be used to engineer commensal gut bacteria to degrade pesticides or suppress pathogen populations (i.e., paratransgenesis) (Rangberg A et al., 2012, Integr Comp Biol., 52:89-99). These efforts could one day profoundly affect the health of the bee colonies that sustain modern agriculture.

**[0209]** The materials and methods employed in these experiments are now described.

**[0210]** Bacterial Culture

**[0211]** A complete list of bacterial strains used in this work and their sources is available as FIG. **17**. Unless otherwise specified, bacterial strains *S. alvi* wkB2, *G. apicola* wkB7, *Parasaccharibacter apium* wkB6, *B. apis* PEB0150, *G. apicola* PEB0183, *B. apis* PEB0149, and *S. alvi* PEB0171, *S. marcescens* N10A28 were grown on Columbia agar supplemented with 5% sterile sheep's blood (B-COL) and incubated at 35° C. in a 5% CO2 atmosphere as static cultures. *E. coli* were cultured at 37° C. with orbital shaking at 225 rpm over a 1-inch diameter. *E. coli* MFDpir was grown in LB supplemented with 0.3 mM diaminopimelic acid (DAP). *E. coli* EC100D and *E. coli* DH5α were grown in LB.

**[0212]** For antibiotic selection, the following concentrations were used: ampicillin (100 μg/mL *E. coli*, 30 μg/mL *S. alvi*, 30 μg/mL *G. apicola*, 30 μg/mL *B. apis*, 300 μg/mL *S. marcescens*), kanamycin (50 μg/mL *E. coli*, 20 μg/mL *S. alvi*, 20 μg/mL *G. apicola*, 20 μg/mL *B. apis*), spectinomycin (60 μg/mL *E. coli*, 30 μg/mL for *S. alvi*, 30 μg/mL *G. apicola*, 30 μg/mL *B. apis*, 30 μg/mL *P. apium*, 180 μg/mL *S. marcescens*).

**[0213]** Biparental Conjugation

**[0214]** MFDpir with mobilizable plasmid ("donor strain") was grown overnight, shaking in LB with appropriate selective antibiotics and DAP (0.3 mM) supplementation. Recipient strains (wkB2, wkB7, PEB0150, PEB0183, PEB0171, N10A28, wkB6, wkB12, Snod 2-15, Pens 2-2-5) were grown overnight on solid media. Recipient and donor strains were washed in 1 mL PBS, spun down (1006×g for 5 minutes), and resuspended with 1 mL of PBS. These two suspensions were mixed in a 9:1 OD ratio of recipient:donor and spotted (without filter) onto a B-COL plate supplemented with 0.3 mM DAP. Conjugations proceeded overnight (~12-14 hours) and were scraped from the plate into PBS the next morning. Conjugation mixtures were again gently spun down (1006×g) and washed twice in PBS to remove residual DAP. Approximately 100 μl of this mixture (and 1:10, 1:100 dilutions) was plated onto selective antibiotic plates and incubated 2-3 days to obtain transconjugant colonies. Transconjugants were passaged again on selective media and confirmed by PCR amplification of a plasmid sequence and visible fluorescence, when appropriate. For the initial broad-host-range plasmid screen, transconjugants were further verified by plasmid reisolation and electroporation into *E. coli* DH5α cells. To determine conjugation efficiency, mating mixtures were serially diluted and plated on selective and non-selective plates. Conjugation frequency was calculated as the number of fluorescent transconjugant CFUs on selective plates per total CFUs on non-selective plates

**[0215]** BTK Construction

**[0216]** Construction of the BTK backbone was carried out with Gibson assembly (Gibson D G et al., 2009, Nat Meth., 6:343-345) following established protocols. New part plasmids were constructed using a previously published BsmBI assembly protocol for the yeast toolkit (YTK) (LEE M E et al., 2015, ACS Synth Biol., 4:975-986) with inserts synthesized as doublestranded DNA gBlocks (IDT). New parts were cloned into the pYTK001 entry vector. The BTK kit uses the entry vector plasmid, connector parts (Type 1 and Type 5), and part sequence overhangs of the YTK. In contrast to the YTK, Type 3 parts of the BTK include a stop codon, as the Type 4 terminators do not include a stop codon. A list of BTK plasmids is available in FIG. **18**.

**[0217]** Measuring BGM GFP In Vitro

**[0218]** To measure fluorescence, 50 μL of ~0.2 OD bacterial cultures were pooled on B-COL agar plates and incubated for 48 hours. Cells were scraped into PBS and then loaded into wells of a 96 well plate to measure fluorescent excitation using a Tecan Spark 10M multimode microplate reader at excitation/emission wavelengths of 485/535. Fluorescent readings were corrected with blank values, and then normalized by OD. Gain was set manually and consistent throughout experiments.

**[0219]** Flow Cytometry Analysis of GFP Expression

**[0220]** As with plate reader measurements, 50 μL of ~0.2 OD bacterial culture was pulled onto BCOL agar plates and incubated for 48 hours. Bacteria were scraped into PBS, washed, and then gently spun down (1006×g for 5 minutes). Cells were resuspended vigorously to disrupt any biofilm, and then diluted to ~0.1 OD in HPLC-grade water. Cells were counterstained with SYTO 17 red nucleic acid stain (Thermo-Fisher), and then ran samples on a BD LSR-Fortessa SORP Flow Cytometer. Data were acquired with FACSDiva v6.1.3, and then analyzed with FlowJo v10.4.2. All samples were run under identical conditions. GFP-A voltage was consistent throughout experiments. Nonfluorescent controls were used to determine forward-scatter, side-scatter, and APC-A (counterstain) gates that were then set individually for each species.

**[0221]** Tn7-Transposition in *B. apis*

**[0222]** For the chromosomal insertion of gfp into *B. apis*, a tri-parental mating was performed with *B. apis*, *E. coli* MFDpir with pTNS2, and *E. coli* MFDpir with pTN7-PA1-gfp-kan in an 8:1:1 ratio. Conjugation proceeded for 12 hours, and transformed *B. apis* was selected with kanamycin as in biparental conjugation.

**[0223]** Broad-host-range dCas9 plasmids are created by BsmBI assembly of 3 parts plasmids containing: (1) the sgRNA transcriptional unit (pBTK615), (2) the dCas9 transcriptional unit (pBTK614), and (3) the broad-host-range backbone with ConLE and ConRE connector sequences (pBTK527a). To repress gfp expression in *B. apis*, the gfp nontemplate strand was targeted by using the N20 sequence: 5'-CGTCTAATTCCACGAGGATT (SEQ ID NO:7). The sgRNA plasmid can be retargeted using MEGAWHOP cloning (Miyazaki K et al., 2011, Meth Enz., 498:399-406). Briefly, in MEGAWHOP cloning a double-stranded PCR product containing the sequence change to be introduced, but otherwise identical to a portion of the plasmid, is used as a "megaprimer" to re-amplify the whole plasmid in a second PCR reaction. Because the sgRNA targeting sequence is short, it is possible to include a new target sequence flanked by 20 bp of homology to the plasmid on either side in one of the primers used in the initial PCR reaction to generate the megaprimer. The fully assembled CRISPRi plasmid (pBTK618) was conjugated into *B. apis* with chromosomally integrated PA1-gfp, and GFP fluorescence was measured as above.

**[0224]** Chromosomal Disruption using Cas9 and Homologous Recombination

**[0225]** Plasmid pBTK601 contains Cas9 driven by the kanamycin resistance gene promoter on the broad-host-range backbone. This plasmid was conjugated into *S. alvi* wkB2, *G. apicola* wkB7, and *B. apis* PEB0150 and maintained with spectinomycin. The CP25-driven sgRNA is on plasmid pBTK615 and can be retargeted using MEGA-WHOP cloning (Miyazaki K et al., 2011, Meth Enz., 498:399-406). A full description of homology donor plasmid assembly is available in FIG. **23**. Briefly, a genomic homology segment upstream of the gene of interest to disrupt or replace is amplified with Type 2 part overhangs, and a downstream genomic homology segment is amplified as a Type 4 part. Upstream homology, antibiotic resistance cassette (Type 3), and downstream homology are combined in a single BsaI reaction with ConLE and ConRE to form a Stage 1 assembly of the replacement cassette. The final BsmBI assembly includes: (1) the sgRNA plasmid, (2) the replacement cassette plasmid, and (3) pBTK599 (R6K suicide plasmid backbone). This final assembly must be transformed into pir$^+$ strains, such as EC100D or MFDpir.

**[0226]** Efficiency of Chromosomal Disruption with and without Cas9

**[0227]** Recipient BGM strains (wkB2, wkB2::pBTK601, wkB7, wkB7::pBTK601, PEB0150, PEB0150::pBTK601) were grown on B-COL plates for 48 hours prior to conjugation. Donor *E. coli* strains were grown in liquid culture overnight prior to conjugation. Donor and recipients were washed in PBS and mixed in a 1:9 ratio (by OD), and 100 μL was plated on B-COL+0.3 mM DAP media for overnight conjugation. After 14 hours, the entire conjugation mixtures were scraped into PBS and washed twice to remove residual DAP, and dilutions were plated on selective agar plates (B-COL+Kanamycin 20 μg/mL) and nonselective agar plates (B-COL). Efficiency of gene disruption was calculated as (# of transconjugant cells)/(# of total cells). To identify single-crossover and double-crossover mutants, a series of PCR reactions were conducted as described in FIG. **23**. Briefly, transconjugants were screened for the appropriate upstream and downstream junctions with colony PCR. Potential double-crossover mutants were then further screened for the size of the disrupted region, and loss of the suicide plasmid backbone.

**[0228]** Laboratory Care of Honey Bees

**[0229]** Microbiota-free bees were obtained and raised using methods described previously (Kwong W K et al., 2014, Proc Natl Acad Sci USA., 111:11509-11514). Briefly, pupae were pulled under sterile conditions from brood combs obtained from outdoor hives. These pupae emerged in a sterile incubator (becoming newly emerged adult workers) and were then sorted into individual cup cages for further development in the laboratory. Prior to inoculation, newly emerged workers were allowed to feed on sterile irradiated pollen (Betterbee) and 50% sucrose solution ad libitum. For any individual experiment, all pupae were obtained from the same hive. When raised in this manner, *Apis mellifera* workers remain uncolonized by core BGM bacteria species and show very low levels of environmental

bacteria in their guts (Powell J E et al., 2014. Appl Environ Microbiol., 80:7378-7387). It is critical to pull the pupae from frames at an early stage. before the mouthparts have hardened, as later pupal stages will begin to ingest hive material and may be colonized

**[0230]** Mono- and Co-Innoculation of Engineered BGM into Honey Bees

**[0231]** After obtaining newly emerged workers, bees were chilled at 4° C. for 30 minutes and then coated in sugar syrup containing resuspended bacterial inoculum, transferred to cup cages, and allowed to groom each other. The inoculum generally contained 200 μL of OD ~0.1 bacterial suspension combined with 800 μL of 1:1 sucrose:water solution. Approximately 30 μL of this solution per bee was used for inoculations (corresponding to $10^7$ bacteria per bee to ensure robust inoculation). Plate counts of the inoculum were used to confirm concentrations.

**[0232]** In Vivo Imaging of Bacterial Burden Using E2-Crimson

**[0233]** To visualize in vivo expression of E2-Crimson in living bees. a Syngene G:Box Chemi XX6 gel doc system was used. Bees were chilled on ice for 30 min to minimize movement. then imaged using manufactuers recommended instructions for far-red fluorescent probe visualization: "Red LED" light source and "Filter 705M" emission filter. All bees were imaged under identical conditions: 5 minutes exposure time for whole bee and 30 seconds for bees with dissected guts. Images were saved as TIFF files for further analysis in FIJI (Schindelin J et al., 2012, Nat Meth., 9:676-682). In FIJI. fluorescence intensity was mapped to the "mplmagma" scale. A representative bee for each condition is shown. No further image manipulation was performed. Different scales are used for comparing fluorescent *S. marcescens* and fluorescent BGM species due to the increased fluorescent protein production and titer of *S. marcescens*.

**[0234]** Confocal Fluorescence Microscopy

**[0235]** Fluorescent images were obtained at the UT ICMB Microscopy core on a Zeiss 710 Laser Scanning Confocal microscope. Bees were chilled and then dissected to expose rectum. ileum, and midgut. Without puncturing the gut, the entire gut compartment was transferred to an Ibidi μ-Dish 35 mm (CAT #81156) and then placed on the microscope. Images were taken with a 20× objective and tiled using Zeiss software. Z-stack 2-channel fluorescent images were taken and combined using Imaris software. Intensity on individual channels was false colored to correspond to species-specific coloring. Display intensity of individual channels was scaled linearly to aid in visualization of different species, but no further transformations or background reduction was used.

**[0236]** qPCR to Assess Colonization of StaA Mutant

**[0237]** Absolute quantification of 16S rRNA gene copies specific to *S. alvi* was performed as described previously (Powell J E et al., 2016, Proc Natl Acad Sci USA., 113: 13887-13892). Cohorts of newly emerged bees were hand-fed with equal amounts (~$10^4$ CFU/bee) of either wild-type *S. alvi* or the staA mutant. Control bees were maintained identically but remained uninoculated. After five days, five bees from each group were dissected and DNA was isolated from individual bee guts using the cetyltrimethylammonium bromide (CTAB) extraction method outlined previously (Powell J E et al., 2014. Apl Environ Microbiol., 80:7378-7387). After extraction, *S. alvi*-specific primers were used for quantitative PCR and absolute quantification based on 10-fold dilution of the target sequence in a pGEM-T plasmid vector. Reactions were run in triplicate.

**[0238]** Quantification and Statistical Analysis

**[0239]** All data processing and statistical analyses were done in R. Kruskal-Wallis rank sum tests were used to assess significance in the dCas9 gene repression experiment and the Cas9-assisted genome modification experiments.

**[0240]** The results of the experiments are now described.

**[0241]** BTK Plasmids Function in Diverse Bacterial Species Found in the Bee Gut

**[0242]** It was sought to explore the host range of the RSF1010 origin used as a basis for the BTK in the context of a larger set of bee-associated bacterial strains. Simultaneously, it was needed to identify antibiotic resistance genes able to function in each bacterial strain. To do so, three BTK plasmids were constructed. each with a different antibiotic resistance marker and encoding GFP driven by the PA1 promoter: pBTK501 ($Amp^R$). pBTK519 ($Kan^R$). pBTK520 ($Spec^R$). Biparental matings were performed between *E. coli* MFDpir donors containing each plasmid and bee gut-associated strains (see Methods). Stable transconjugants were obtained for all of the Gram-negative strains tested with at least one of these three plasmids. as verified by further passaging on antibiotic-containing media, PCR amplification of plasmid sequences, and GFP expression (FIG. **10**A). Successfully transformed bacterial species include Alpha-, Beta-, and Gammaproteobacteria and strains isolated from different bee species (*A. mellifera, Bombus terrestris. Bombus impatiens*, and *Bombus pensylvanicus*). Several of the bacterial species (*S. alvi. G. apicola. B. apis*, and *Parasaccharibacter apium*) are phylogenetically distant from any established model organisms and have no previously reported genetic tools. Transfer of the BTK plasmids was efficient, with $>10^{-3}$ transconjugants per CFU for four diverse bacterial species (FIG. **10**B)

**[0243]** Identifying Functional Promoters in BGM Species

**[0244]** While some sequence features of transcriptional promoters are conserved across bacterial species, there is no guarantee that promoters designed to function in model organisms will function effectively in new bacterial isolates from a natural community of interest (Whitaker W R et al., 2017, Cell, 169:538-538). The BTK includes BHR promoters and RBS combinations as Type 2 parts that can be used to build plasmids to identify functional sequences for driving protein expression in new bacterial hosts. The function of the BHR promoters PA1 (pBTK501). PA2 (pBTK509), PA3 (pBTK510), and CP25 (pBTK503) were compared in *S. alvi* wkB2. *G. apicola* wkB7. *B. apis* PEB0150. and *S. marcescens* N10A28, all isolated from honey bee gut communities. Promoters PA1. PA2. PA3 are strong early promoters from bacteriophage T7 (Siebenlist U., 1979, Nucleic Acids Res., 6:1895-1907). The synthetic CP25 promoter was originally designed to function in *Lactococcus* strains (Jensen P R et al., 1998, Appl Environ Microbiol., 64:82-87). and the BTK includes other promoters from this series.

**[0245]** Using flow cytometry, fluorescent protein expression from these promoters (FIG. **10**A) was characterized. These promoters display significant variability in activity across strains when they are all tested with the same RBS. As expected, the promoter-RBS pairs function most strongly in *S. marcescens*, which is most closely related to *E. coli*. In the other BGM strains. expression was weaker. but there was a signal above background for most promoters that were tested with this RBS. Fluorescence is generally lower in *S.*

*alvi*, *G. apicola*, and *B. apis* than it is in *E. coli*. In *E. coli* the distributions of fluorescent per cell for the PA2, PA3, and CP25 promoters are noticeably bimodal. This may be an intrinsic property of the promoter or due to the accumulation of "broken" plasmids with mutations that inactivate burdensome GFP expression (Sleight S C et al., 2010, J Biol Eng., 4:12). In BGM strains, with the exception of CP25 in *G. apicola*, these distributions are unimodal, indicating consistent fluorescent expression across single cells. PA3 expression was strong in *S. alvi*, and this observation was used to design a constitutive E2-Crimson-expressing plasmid (pBTK570) to test expression in vivo, as described in later sections. Validation of additional parts (E2-Crimson, NanoLuc, and other CP-series promoters) is available in FIG. 20, FIG. **21**, FIG. **22**.

**[0246]** Inducible Gene Expression in BGM Species

**[0247]** Induction systems are required for the temporal control of gene expression, and are useful for testing the functional roles of microbes in gut environments (Lim B et al., 2017, Cell, 169:547-558). Two lacI induction systems were tested: one simple system composed of a modified CP25 promoter with lacO sites and a more complex system that uses T7 RNA polymerase (T7 RNAP). IPTG-induction of these systems was tested in *E. coli* MFDpir, *S. alvi* wkB2, *G. apicola* wkB7, *B. apis* PEB0150, and *S. marcescens* N10A28. The simple system (pBTK552) showed robust induction of GFP in all strains tested (FIG. **11B**). Interestingly, *G. apicola* GFP expression with this system surpassed that of *E. coli* and *S. marcescens*.

**[0248]** For the T7 RNAP system, two transcriptional unit plasmids (pBTK549d, pBTK541) were built, one bearing lacI driven by the CP25 promoter and T7 RNAP under control of the inducible lac promoter and the other with GFP expressed from a T7 promoter with lacO sites, and combined them into a composite plasmid (pBTK550d), (FIG. **11C**). Expression was strong in *S. marcescens* N10A28 and *E. coli* MFDpir, with maximal GFP expression after induction surpassing the simpler system in which lacI directly regulates GFP expression. However, in *G. apicola* wkB7, *S. alvi* wkB2, and *B. apis* PEB0150, a weaker induction of GFP was seen compared to the simpler system. The cause of this weak expression is unknown. It may be due to poor transcription from the lac promoter driving T7 RNAP or to an intrinsic incompatibility between T7 RNAP and the intracellular environment in the BGM species tested. In all strains, the inducible T7 RNAP construct showed appreciable background expression when not induced.

**[0249]** CRISPRi Repression of Chromosomal Gene Expression in *Bartonella apis*

**[0250]** BTK was used to suppress gene activity in a BGM bacterium. Catalytic mutants of Cas9 (dCas9) have been used to reduce transcription of target genes, an approach termed CRISPR interference (CRISPRi), in diverse mammalian and bacterial systems (Barrangou R et al., 2017, Nat Microbiol., 2:1-9). To expand this approach to new non-model bacterial species, a modified dCas9 system was established in which targeting is achieved by a BTK part encoding a small guide RNA (sgRNA) (FIG. **12A**) (Bikard D et al., 2013, Nucleic Acids Res., 41:7429-7437). To test the system, the sgRNA was targeted to a PA1-driven GFP gene in *B. apis* PEB0150, which was inserted into the chromosome using Tn7-based integration (Choi K H et al., 2005, Nat Meth., 2:443-448). GFP expression was significantly reduced in the presence of a sgRNA targeted to the GFP sequence (FIG. **12B**). Coupled with the induction system, this ability to repress a target gene enables functional studies of essential genes that cannot be disrupted entirely.

**[0251]** Cas9-Assisted Gene Disruption in the BGM

**[0252]** Gene disruption is an important tool for establishing gene function and for studying interactions between genes. After identifying functional antibiotic cassettes in the earlier plasmid-replication screen, it was attempted to use homologous recombination to disrupt chromosomal genes in the BGM strains. To improve the efficacy of targeted gene disruption, a two-step approach was implemented based on using Cas9 cleavage for chromosomal modifications (Barrangou R et al., 2017, Nat Microbiol., 2:1-9) (see Methods). In step one, Cas9 is introduced into a cell on the BTK backbone (pBTK601) without any targeting sgRNA. In step two, a second round of conjugation is used to deliver a suicide plasmid with the replacement cassette (~1000 bp homology flanking a functional antibiotic resistance gene) and the sgRNA targeting the desired chromosomal location. The suicide plasmid is made with Golden Gate assembly using repurposed Type 2-4 overhangs and an R6K origin of replication (FIG. **13A**, FIG. **13B**). The sgRNA can be retargeted using MEGAWHOP cloning (Miyazaki K, 2011, Meth Enz., 498:399-406) (see Methods). A detailed description of suicide plasmid assembly and validation of mutants is shown in FIG. **23**. It was expected that Cas9 cleavage might facilitate recombination into the chromosome and that it would also select against single-crossover integrations, in which the suicide plasmid backbone is incorporated into the chromosome, because they preserve the cleavage site, whereas double-crossover integrations result in replacement of the targeted gene sequence with just the antibiotic resistance cassette and delete the cleavage site.

**[0253]** To test the utility of this scheme, it was attempted to generate gene disruptions in three BGM species. In *S. alvi* wkB2 staA (SALWKB2_RS11470) was targeted, an adhesion gene previously implicated in a genome-wide screen as important for gut colonization (FIG. **24**) (Powell J E et al., 2016, Proc Natl Acad Sci USA, 113:13887-13892). In *G. apicola* wkB7 acetate kinase ackA was targeted (A9G17_RS12535) (FIG. **25**), and in *B. apis* PEB0150 nitrate reductase narG (PEB0150_RS00755) was targeted (FIG. **26**). Homology regions were designed to be internal to each coding sequence, so that even single-crossover events would disrupt gene function. For *S. alvi* wkB2, the multi-step system showed higher efficiency compared to basic homologous recombination not using Cas9. In the presence of Cas9, wkB2 mutants were obtained more frequently and were more often double-crossover mutants (FIG. **13D**). In contrast, *B. apis* PEB0150 showed relatively high gene disruption efficiency even in the absence of Cas9, and the Cas9 system had little effect on improving the number of double-crossover mutants (FIG. **13C**). In *G. apicola* wkB7 the Cas9 was also not helpful, and no double-crossover mutants were obtained (FIG. **13E**). The *G. apicola* wkB7 mutants isolated showed irregular PCR amplification at the expected junctions (FIG. **25**), indicating that it could not effectively disrupt ackA, perhaps because it is an essential gene in this species. These experiments validated this general approach to gene disruption in multiple BGM species.

**[0254]** Engineered Strains Colonize Bees and can be Directly Visualized in the Ileum

**[0255]** Next the ability of engineered BGM strains to colonize newly emerged worker bees removed from the hive before they acquire a normal microbiota was tested. Previously, *S. alvi* and *G. apicola* have been visualized in bees using fluorescent in situ hybridization (Martinson V G et al., 2012, Apl Environ Microbiol., 78:2830-2840). However, this technique can only be used at one time point because it requires sacrificing the bee. In contrast, fluorescent reporter strains can be used to non-destructively estimate bacterial abundance and observe how bacterial community structure changes over time in live bees. Previous studies have examined how *S. alvi* colonizes the honey bee gut (Kwong W K et al., 2014, Proc Natl Acad Sci USA., 111:11509-11514; Engel P et al., 2013, J of Api Res., 52:1-24), but colonization by *G. apicola, B. apis*, and *S. marcescens* has not been investigated (Raymann K et al., 2017, PLoS Biol., 15:e2001861; Burritt N L et al., 2016, PLoS One., 11:e0167752). Newly emerged workers with ~$10^4$ CFU per bee of either *S. marcescens* N10A28 or *S. alvi* wkB2 was inoculated, each carrying a constitutively expressed E2-Crimson fluorescent protein (pBTK570). After 5 days, bees from each group were dissected and their guts were examined (FIG. **14**). Fluorescent bacteria were successfully imaged directly in guts without preparation or fixation, preserving natural community structure. *S. marcescens* N10A28 shows robust colonization in all gut compartments, while other species show spatially restricted colonization. As previously reported, *S. alvi* wkB2 robustly colonizes the ileum, with little colonization in the midgut and rectum. Additionally, co-inoculations with *S. alvi* wkB2 and either *B. apis* PEB0150 or *G. apicola* wkB7 engineered were performed to express GFP (pBTK520). The guts of colonized bees were again dissected and fluorescently imaged in vivo co-colonization of these defined communities (FIG. **15**A, FIG. **15**B). While both *B. apis* and *G. apicola* are found in the ileum colocated with *S. alvi*, they also colonize the rectum, in contrast to *S. alvi*.

**[0256]** *Snodgrassella* StaA Contributes to Gut Colonization In Vivo

**[0257]** Finally, it was sought to validate the usefulness of the BTK for disrupting specific genes in BGM species in order to investigate their function. StaA belongs to a family of YadA-like adhesion proteins important for colonization and pathogenicity in multiple host-associated species (Linke D et al., 2006, Trends Microbiol., 14:264-270). These trimeric autotransporter proteins localize to the bacterial membrane and form "lollipop" structures that allow bacteria to adhere to epithelial cells (Ribet D et al., 2015, Microbes Infect., 17:173-183; Tahir El Y et al., 2001, Int J Med Microbiol., 291:209-218). Orthologs of these genes are found in multiple *S. alvi* genomes, including those from honey bee- and bumble bee-associated strains (Kwong W K et al., 2014, Proc Natl Acad Sci USA., 111:11509-11514). In the previous works screening a transposon mutant library identified staA (SALWKB2_RS11470) as necessary for the fitness of *S. alvi* during gut colonization (Powell J E et al., 2016, Proc Natl Acad Sci USA., 113:13887-13892). However, it was not able to isolate a mutant from the library with a transposon disrupting staA, and thus it could not fully characterize and validate the role of this gene. Using the BTK, a ΔstaA mutant was generated in *S. alvi* wkB2 (as described above). The ΔstaA mutant and a wild-type control was labeled with a BTK plasmid expressing E2-Crimson (pBTK570) to assess the effects of disrupting this gene in the context of the bee gut. The wkB2 ΔstaA mutant shows reduced colonization efficacy compared to a wild-type control, as measured by qPCR of *S. alvi* 16S rRNA gene copies (FIG. **15**C). The colonization pattern of this mutant in terms of its localization within the gut (FIG. **15**D) is distinct from that of wild-type *S. alvi* (FIG. **14**E). After 6 days, the mutant does not form the contiguous, robust colonization of the ileum wall seen for the wild type strain. Instead, colonization is apparently restricted to small patches, while the majority of the ileum remains uncolonized.

### Example 5. Engineering Bee Guts with Symbiont-Produced dsRNA

**[0258]** These experiments provide data to demonstrate the use of engineered gut bacteria (*Snodgrassella alvi*) to manipulate bee gene expression, behavior, and immune response.

**[0259]** Engineered Symbionts Reduce Viral Replication in Bees.

**[0260]** Emerged bees were engineered with gut bacteria harboring one of six plasmids: (1) "NR"—this is an empty plasmid control, expressing no double-stranded RNA; (2) "dsGFP"—this is a dsRNA control, expressing GFP dsRNA; (3) "DWV T1"—dsRNA with DWV target 1, (4) "DWV T2"—dsRNA with DWV target 2; (5) "DWV T3"—dsRNA with DWV target 3, (6) "DWV T5"—dsRNA with DWV target 5.

**[0261]** After 5 days, bees from each condition were hand fed 5.7e6 viral particles of DWV.

**[0262]** After 48 hours, the fat bodies and hemolymph of the bees was dissected, and RNA was isolated from this tissue. cDNA was generated and then absolute qPCR quantification was performed to determine viral genomes (FIG. **27**).

**[0263]** Engineered Symbionts Reduce Expression of Target Genes Across Body Tissues.

**[0264]** Emerged bees were engineered with gut bacteria harboring one of three plasmids: (1) "NR"—an empty plasmid control, expressing no double-stranded RNA; (2) "dsGFP"-a dsRNA control, expressing GFP dsRNA; (3) "dsTH"—dsRNA targeting Tyrosine Hydroxylase (TH).

**[0265]** At two time points, Day 4 and Day 8, RNA was isolated from the gut and head. cDNA was generated, and relative quantitation was performed to determine expression (FIG. **28**).

**[0266]** Engineered Gut Bacteria Alter Host Behavior.

**[0267]** Behavioral assays were performed on emerged bees engineered with gut bacteria harboring one of three plasmids: (1) "NR"—an empty plasmid control, expressing no double-stranded RNA; (2) "dsGFP"-a dsRNA control, expressing GFP dsRNA; (3) "dsTH"—dsRNA targeting Tyrosine Hydroxylase (TH).

**[0268]** This behavioral assay measured aversive learning, the ability of bees to learn to associate a scent with a shock. Bees colonized with bacteria expressing dsTH learned significantly more slowly than bees colonized with control bacteria (dsGFP) (FIG. **29**).

**[0269]** Suppression of *Varroa* with Engineered Gut Bacteria.

**[0270]** *Varroa* mites are the major bee pest, and suppressing them is a promising application of dsRNA technology. Emerged bees are engineered with gut bacteria expressing at

least one dsRNA with sequence specific to essential *Varroa* genes. Targets are present individually or as a composite of multiple targeting sequences. This dsRNA moves into the bee hemolymph and when *Varroa* mites feed, they will induce a lethal self-targeting RNAi response. This is different from the previous described RNAi work because the RNAi response is in the *varroa* mite, not the bee.

**[0271]** Experimental Design: Colonize bees with gut bacteria expressing *Varroa* targeting constructs (dsVarroa), capture live *Varroa* mites from hives, expose defined number of *varroa* mites to bees, and measure mortality of *varroa* mites fed on dsVarroa bees. Compare to control NR and dsGFP colonized bees.

**[0272]** Suppression of *Nosema* with Engineered Gut Bacteria.

**[0273]** *Nosema* is another pathogen of bees. Suppression of *Nosema* in bees is approached in two ways. (1) use symbiont-mediated RNAi to alter and strengthen the bee immune response, and (2) trigger lethal RNAi in *nosema*

**[0274]** Experimental Design: Colonize bees with gut bacteria expression lethal *nosema* RNAi or immune-strengthening RNAi, expose bees to a defined number of *nosema* spores, after 48-72 hours, count the number of *nosema* spores. Compare to control bees with no RNAi or control dsGFP RNAi

**[0275]** Suppression of Small Hive Beetle with Engineered Gut Bacteria

**[0276]** The small hive beetle is another major pest in beekeeping. Unlike DWV, *Varroa*, and *Nosema*, however, it does not attack bees directly, but instead it feeds on hive components. Therefore, to target this insect with bacterially induced RNAi, the approach is different. For this a different bacterial species that can live in hive materials, such as *Parasaccharibacter apium* or *Lactobacillus* sp. is used. These bacteria are transformed to produce dsRNA identical to an essential hive beetle gene. When these bacteria are consumed by the hive beetle, they would kill the beetles or impair their reproduction.

## Example 6: Persistence of Engineered Bacteria in Host

**[0277]** Two separate cohorts of bees were obtained from different hives and allowed to emerge in lab. Within 24 hours after emergence, bees were inoculated with ~1e04 CFU of *S. alvi* wkB2 engineered to constitutively express GFP (plasmid pBTK520) and separated into individual cups with 5-10 bees. Bees were fed sucrose solution supplemented with 60 ug/mL spectinomycin. Every five days, five to eight bees from each cohort were dissected and their entire gut contents plated on selective media with spectinomycin to estimate the CFU of engineered *S. alvi* remaining in their gut.

**[0278]** Across all three time points, no significant difference existed between time points or hives in this experiment. Over 99% of colonies were fluorescent in each sample, indicating the genetic device remained functional (FIG. 30). This shows that engineered *S. alvi* wkB2 persistently colonizes and functions in the bee gut despite different bee genetic backgrounds. Bees were fed spectinomycin to maintain the plasmid, but other strategies could be used to ensure maintenance and function of the device in engineered strains (ie, chromosomal incorporation).

**[0279]** Engineered *S. alvi* persists and functions over the measured lifetime of the bee in laboratory environments. Without being bound by theory, it is expected that the engineered gut bacteria would persist over the lifetime in bees in their natural environment, as well.

## Example 7: Sequences

**[0280]**

| SEQ ID NO | Description |
|---|---|
| SEQ ID NO: 1 | pMMB67EH |
| SEQ ID NO: 2 | pBTK520 |
| SEQ ID NO: 3 | pBTK570 |
| SEQ ID NO: 4 | pBTK502 |
| SEQ ID NO: 5 | pBTK501 |
| SEQ ID NO: 6 | pBTK599 |
| SEQ ID NO: 8 | pBTK401 |
| SEQ ID NO: 9 | pBTK402 |
| SEQ ID NO: 10 | pBTK403 |
| SEQ ID NO: 11 | pBTK599 |
| SEQ ID NO: 12 | CP25 (lacO) promoter |
| SEQ ID NO: 26 | pBTK001 |
| SEQ ID NO: 27 | T7 promoter + RBS |
| SEQ ID NO: 28 | Lac lacO inducible promoter + RBS |
| SEQ ID NO: 29 | CP25 promoter + RBS |
| SEQ ID NO: 40 | CP6 promoter + RBS |
| SEQ ID NO: 41 | CP12 promoter + RBS |
| SEQ ID NO: 42 | CP32 promoter + RBS |
| SEQ ID NO: 43 | PA1 promoter + RBS |
| SEQ ID NO: 44 | PA2 promoter + RBS |
| SEQ ID NO: 45 | PA3 promoter + RBS |
| SEQ ID NO: 46 | CP25 + RBS reverse |
| SEQ ID NO: 47 | dCas9 |
| SEQ ID NO: 48 | rpoC terminator |
| SEQ ID NO: 49 | Bba_B0015 terminator |
| SEQ ID NO: 50 | T7 terminator |
| SEQ ID NO: 51 | pBTK103 |
| SEQ ID NO: 52 | pBTK105 |
| SEQ ID NO: 53 | pBTK107 |
| SEQ ID NO: 54 | pBTK110 |
| SEQ ID NO: 55 | pBTK112 |
| SEQ ID NO: 56 | pBTK113 |
| SEQ ID NO: 57 | pBTK119 |
| SEQ ID NO: 58 | pBTK120 |
| SEQ ID NO: 59 | pBTK121 |
| SEQ ID NO: 60 | pBTK138 |
| SEQ ID NO: 61 | pBTK200 |
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| SEQ ID NO: 68 | pBTK229 |
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| SEQ ID NO: 71 | pBTK305 |
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| SEQ ID NO: 86 | pBTK564 |
| SEQ ID NO: 87 | pBTK569 |
| SEQ ID NO: 88 | pBTK579 |
| SEQ ID NO: 89 | pBTK601 |
| SEQ ID NO: 90 | pBTK614 |
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| SEQ ID NO: 92 | pBTK619 |

-continued

| SEQ ID NO | Description |
| --- | --- |
| SEQ ID NO: 93 | sBFK6ZL |
| SEQ ID NO: 94 | sBFK6ZI |

**[0281]** All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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accccatgcc gaactcagaa gtgaaacgcc gtagcgccga tggtagtgtg gggtctcccc     180

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&lt;212&gt; TYPE: DNA
&lt;213&gt; ORGANISM: Artificial Sequence
&lt;220&gt; FEATURE:
&lt;223&gt; OTHER INFORMATION: Chemically Synthesized, pDIK399 backbone
      sequence, circular

&lt;400&gt; SEQUENCE: 11

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<223> OTHER INFORMATION: Chemically Synthesized, CP25 lacO sequence

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<210> SEQ ID NO 14
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<400> SEQUENCE: 16

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<223> OTHER INFORMATION: Chemically Synthesized

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<210> SEQ ID NO 18
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<223> OTHER INFORMATION: Chemically Synthesized

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 19

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<223> OTHER INFORMATION: Chemically Synthesized

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<223> OTHER INFORMATION: Chemically Synthesized

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<210> SEQ ID NO 22
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 22

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<210> SEQ ID NO 23
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 23

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<210> SEQ ID NO 24
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<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 24

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<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesised

<400> SEQUENCE: 29

cttagagata ggagagtg 18

<210> SEQ ID NO 30
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesised

<400> SEQUENCE: 30

taatgatggc aactaatgac aa 22

<210> SEQ ID NO 31
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 31

cccaatcctc gtggaattag acg 23

<210> SEQ ID NO 32
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

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<400> SEQUENCE: 32

gacttagacg aatcagactc 20

<210> SEQ ID NO 33
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 33

ttccatttca tacgagactc 20

<210> SEQ ID NO 34
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 34

acaccatgtc catgcgaaaa 20

<210> SEQ ID NO 35
<211> LENGTH: 49
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized

<400> SEQUENCE: 35

atgtcttttt caatgggtac gtatgtatct ctaaagtaat caacataat 49

<210> SEQ ID NO 36
<211> LENGTH: 2481
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chemically synthesized, pKD3

<400> SEQUENCE: 36

agcgagctcg atatcaaatt acgccccgcc ctgccactca tcgcagtact gttgtaattc 60

attaagcatt ctgccgacat ggaagccatc acaaacggca tgatgaacct gaatcgccag 120

cggcatcagc accttgtcgc cttgcgtata atatttgccc atggtgaaaa cgggggcgaa 180

gaagttgtcc atattggcca cgtttaaatc aaaactggtg aaactcaccc agggattggc 240

tgagacgaga aacatattct caataaaccc tttagggaaa taggccaggt tttcaccgta 300

acacgccaca tcttgcgaat atatgtgtag aaactgccgg aaatcgtcgt ggtattcact 360

ccagagcgat gaaaacgttt cagtttgctc atggaaaacg gtgtaacaag ggtgaacact 420

atcccatatc accagctcac cgtctttcat tgccatacga aattccggat gagcattcat 480

caggcgggca agaatgtgaa taaaggccgg ataaaacttg tgcttatttt tctttacggt 540

ctttaaaaag gccgtaatat ccagctgaac ggtctggtta taggtacatt gagcaactga 600

ctgaaatgcc tcaaaatgtt ctttacgatg ccattgggat atatcaacgg tggtatatcc 660

agtgattttt ttctccattt tagcttcctt agctcctgaa aatctcgata actcaaaaaa 720

tacgcccggt agtgatctta tttcattatg gtgaaagttg gaacctctta cgtgccgatc 780

continued

```
aacctaacct aggccaagcc aacccgacca gaatcaagca atatgaagct aaccccagtg     840

gtggcgaacc aagacaggcc tataaagata aaaggcgttc aaccccggcg gatcccatgt     900

gcgctctcct gttcctgcct ttcggtttac cggtgtcatt ccgctgttat ggccgcgttt     960

gtctcattcc acgcctgaca ctcagttccg ggtaggcagt tcgctccaag ctggactgta    1020

tgcacgaacc ccccgttcag tccgaccgct gcgccttatc cggtaactat cgtcttgagt    1080

ccaacccgga aagacatgca aaagcaccac tggcagcagc cactggtaat tgatttagag    1140

gagttagtct tgaagtcatg cgccggttaa ggctaaactg aaaggacaag ttttggtgac    1200

tgcgctcctc caagccagtt acctcggttc aaagagttgg tagctcagag aaccttcgaa    1260

aaaccgccct gcaaggcggt ttttcgtttt tcagagcaag agattacgcg cagaccaaaa    1320

cgatctcaac ccctgattct gtggataacc gtagtcggcc agacggaaag tgaaacgtga    1380

tttcatgcgt cattttgaac atttggtaaa tcttatttaa taatggtgtc ggccattcac    1440

atttaattta tgtttgtttt attaacatcg aggcaatcca agttacggcc ggttcggatc    1500

ttagctacta gagtaagtgg agttatacta gatgcgtata ggcgaagagc tgttcaatgg    1560

tgtcgtcccc attcctggtg aactggatgg tgatgtcaac ggtcataagt tttccgtgcg    1620

tggcgagggc gaaggtgacg caactaatgg taaactgacg ctgaagttca tctgtactac    1680

tggtaaactg ccggttcctt ggccgactct ggtaacgacg ctgacttatg gtgttcagtg    1740

ctttgctcgt tatccggacc atatgaagca gcatgacttc ttcaagtccg ccatgccgga    1800

aggctatgtg caggaacgca cgatttcctt taaggatgac ggcacgtaca aaacgcgtgc    1860

ggaagtgaaa tttgaaggcg ataccctggt aaaccgcatt gagctgaaag gcattgactt    1920

taaagaggac ggcaatatcc tgggccataa gctggaatac aattttaaca gccacaatgt    1980

ttacatcacc gccgataaac aaaaaaatgg cattaaagcg aattttaaaa ttcgccacaa    2040

cgtggaggat ggcagcgtgc agctggctga tcactaccag caaaacactc caatcggtga    2100

tggtcctgtt ctgctgccag acaatcacta tctgagcacg caaagcgttc tgtctaaaga    2160

tccgaacgag aaacgcgatc atatggttct gctggagttc gtaaccgcag cgggcatcac    2220

gcatggtatg gatgaactgt acaaatgacc aggcattaaa taaaacgaaa ggctcagtcg    2280

aaagactggg cctttcgttt tatctgttgt ttgtcggtga acgctctcta ctagagtcac    2340

actggctcac cttcgggtgg gcctttctgc gtttatacgt ctctgaccag accaataaaa    2400

aacgccccgc ggcaaccgag cgttctgaac aaatccagat ggagttctga ggtcattact    2460

ggatctatca acaggagtcc a                                              2481
```

<210> SEQ ID NO 37
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically synthesized, T7 + RBS promoter from pET41b

<400> SEQUENCE: 37

```
aaggtaatac gactcactat agggcaacga aaccgaggcg atataccata tg              52
```

<210> SEQ ID NO 38
<211> LENGTH: 64
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, lac lacO + RBS from
      pBTK103

<400> SEQUENCE: 38

aacgtttaca ctttatgctt ccggctcgta tgttgtgtgg aattgtgagc ggataacaat      60

ttcaaggagg agaaattaac tatg                                             84


<210> SEQ ID NO 39
<211> LENGTH: 92
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, cp25 + RBS from pBTK107

<400> SEQUENCE: 39

aacgctttgg cagtttattc ttgacatgta gtgagggggc tggtataatc acatagtact      60

gttatacaga aacagaggag atattaacta tg                                    92


<210> SEQ ID NO 40
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, CP6 + RBS from pBTK110

<400> SEQUENCE: 40

aacgcatgtg ggagtttatt cttgacaccg atattttcgg atgctataat aactgagtac      60

tgttatacag aaacagagga gatattaact atg                                   93


<210> SEQ ID NO 41
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, cp25 + RBS from
      pBTK112

<400> SEQUENCE: 41

aacgcatata caagtttatt cttgacacta gtcggccaaa atgatataat acctgagtac      60

tgttatacag aaacagagga gatattacat atg                                   93


<210> SEQ ID NO 42
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, cp32 + RBS from pBTK113

<400> SEQUENCE: 42

aacgcatacg ggagtttatt cttgacatat tgccggtgtg ttggtataat aacttagtac      60

tgttatacag aaacagagga gatattaact atg                                   93


<210> SEQ ID NO 43
<211> LENGTH: 103
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, PA1 + RBS from pBTK119
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<400> SEQUENCE: 43

aacgttatca aaacgagtaa tgaccttaag tataacataa aggataactt aagccatagc 60

gagggacagg gcgaatacag aaacagagga gatattacat atg 103

<210> SEQ ID NO 44
<211> LENGTH: 104
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, P42 + RBS from pBTK120

<400> SEQUENCE: 44

aacgcacgaa aaacaggtat tgacaacatg aagtaacatg cagtaagata caaatcgcta 60

ggtaacacta gcagcataca gaaacagagg agatattaca tatg 104

<210> SEQ ID NO 45
<211> LENGTH: 103
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, P43 + RBS from pBTK121

<400> SEQUENCE: 45

aacgggtgaa acaaaacggt tgacaacatg aagtaaacac ggtacgatgt accacatgaa 60

acgacagtga gtcaatacag aaacagagga gatattacat atg 103

<210> SEQ ID NO 46
<211> LENGTH: 102
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, CP25 + RBS reverse
      promoter from pBTK103

<400> SEQUENCE: 46

gagtacctct cctgtatctt gtgtacttgc gtaccgtaat atctcctctg tttctgtata 60

aacgtactaa gtgattatac aagcccactc actacatgtc aagtataacc tgccaaagcc 120

ga 102

<210> SEQ ID NO 47
<211> LENGTH: 4115
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, dCas9 from pBTK209

<400> SEQUENCE: 47

tatgatggat aagaaatact caataggctt agctatcggc acaaatagcg tcggatgggc 60

ggtgatcact gatgaatata aggttccgtc taaaaagttc aaggttctgg gaaatacaga 120

ccgccacagt atcaaaaaaa atcttatagg ggctctttta tttgacagtg gagagacagc 180

ggaagcgact cgtctcaaac ggacagctcg tagaaggtat acacgtcgga agaatcgtat 240

ttgttatcta caggagattt tttcaaatga gatggcgaaa gtagatgata gtttctttca 300

tcgacttgaa gagtcttttt tggtggaaga agacaagaag catgaacgtc atcctatttt 360

tggaaatata gtagatgaag ttgcttatca tgagaaatat ccaactatct atcatctgcg 420

aaaaaaattg gtagattcta ctgataaagc ggatttgcgc ttaatctatt tggccttagc 480

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gcatatgatt aagtttcgtg gtcatttttt gattgaggga gatttaaatc ctgataatag     540

tgatgtggac aaactattta tccagttggt acaaacctac aatcaattat ttgaagaaaa     600

ccctattaac gcaagtggag tagatgctaa agcgattctt tctgcacgat tgagtaaatc     660

aagacgatta gaaaatctca ttgctcagct ccccggtgag aagaaaaatg gcttatttgg     720

gaatctcatt gctttgtcat tgggtttgac ccctaatttt aaatcaaatt ttgatttggc     780

agaagatgct aaattacagc tttcaaaaga tacttacgat gatgatttag ataatttatt     840

ggcgcaaatt ggagatcaat atgctgattt gtttttggca gctaagaatt tatcagatgc     900

tattttactt tcagatatcc taagagtaaa tactgaaata actaaggctc ccctatcagc     960

ttcaatgatt aaacgctacg atgaacatca tcaagacttg actcttttaa aagctttagt    1020

tcgacaacaa cttccagaaa agtataaaga aatctttttt gatcaatcaa aaaacggata    1080

tgcaggttat attgatgggg gagctagcca agaagaattt tataaattta tcaaaccaat    1140

tttagaaaaa atggatggta ctgaggaatt attggtgaaa ctaaatcgtg aagatttgct    1200

gcgcaagcaa cggacctttg acaacggctc tattccccat caaattcact tgggtgagct    1260

gcatgctatt ttgagaagac aagaagactt ttatccattt ttaaaagaca atcgtgagaa    1320

gattgaaaaa atcttgactt ttcgaattcc ttattatgtt ggtccattgg cgcgtggcaa    1380

tagtcgtttt gcatggatga ctcggaagtc tgaagaaaca attaccccat ggaattttga    1440

agaagttgtc gataaaggtg cttcagctca atcatttatt gaacgcatga caaactttga    1500

taaaaatctt ccaaatgaaa aagtactacc aaaacatagt ttgctttatg agtattttac    1560

ggtttataac gaattgacaa aggtcaaata tgttactgaa ggaatgcgaa aaccagcatt    1620

tctttcaggt gaacagaaga aagccattgt tgatttactc ttcaaaacaa atcgaaaagt    1680

aaccgttaag caattaaaag aagattattt caaaaaaata gaatgttttg atagtgttga    1740

aatttcagga gttgaagata gatttaatgc ttcattaggt acctaccatg atttgctaaa    1800

aattattaaa gataaagatt ttttggataa tgaagaaaat gaagatatct tagaggatat    1860

tgttttaaca ttgaccttat ttgaagatag ggagatgatt gaggaaagac ttaaaacata    1920

tgctcacctc tttgatgata aggtgatgaa acagcttaaa cgtcgccgtt atactggttg    1980

gggacgtttg tctcgaaaat tgattaatgg tattagggat aagcaatctg gcaaaacaat    2040

attagatttt ttgaaatcag atggttttgc caatcgcaat tttatgcagc tgatccatga    2100

tgatagtttg acatttaaag aagacattca aaaagcacaa gtgtctggac aaggcgatag    2160

tttacatgaa catattgcaa atttagctgg tagccctgct attaaaaaag gtattttaca    2220

gactgtaaaa gttgttgatg aattggtcaa agtaatgggg cggcataagc cagaaaatat    2280

cgttattgaa atggcacgtg aaaatcagac aactcaaaag ggccagaaaa attcgcgaga    2340

gcgtatgaaa cgaatcgaag aaggtatcaa agaattagga agtcagattc ttaaagagca    2400

tcctgttgaa aatactcaat tgcaaaatga aaagctctat ctctattatc tccaaaatgg    2460

aagagacatg tatgtggacc aagaattaga tattaatcgt ttaagtgatt atgatgtcga    2520

tcacattgtt ccacaaagtt tccttaaaga cgattcaata gacaataagg tcttaacgcg    2580

ttctgataaa aatcgtggta aatcggataa cgttccaagt gaagaagtag tcaaaaagat    2640

gaaaaactat tggagacaac ttctaaacgc caagttaatc actcaacgta agtttgataa    2700

tttaacgaaa gctgaacgtg gaggtttgag tgaacttgat aaagctggtt ttatcaaacg    2760
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aaaatggtta gaaactagcc aaatcaatca gcatgtggca aaatttttgg atacgtcgat   2820

gaaaaataaa tacgatgaaa atgaaaaaca tatttgtagg gttaaagtga ttacctaaac   2880

atctaaatta gtttctgact tccgaaaaga tttccaattc tataaagtac gtgagattaa   2940

caattaccat catgcccatg atgcgtatct aaatgccgtc gttggaactg ctttgattaa   3000

gaaaaatcca aaacttgaat cggagtttgt ctatggtgat tataaagttt atgatgttcg   3060

taaaatgatt gctaagtctg agcaagaaat aggcaaagca accgcaaaat atttctttta   3120

atctaatatc atgtaattct taaaaaatga aattacaatt gaaaatggtg agattcgaaa   3180

aagcaatcta atcgaaacta atggggaaac tggagaaatt gtctgggata aagggcgaga   3240

ttttgccaca gtgcgcaaag tattgtccat gcgccaagtc aatattgtca agaaaacaga   3300

agtacagaca gggggattct ccaaggagtc aatttaccca aaaagaaatt cggacaagct   3360

tattgctcgt aaaaaagact gggatccaaa aaaatatggt ggttttgata gtccaacggt   3420

agcttattca gtcctagtgg ttgctaaggt ggaaaaaggg aaatcgaaga agttaaaatc   3480

agttaaagag ttactaggga tcacaattat ggaaagaagt tcctttgaaa aaaatccgat   3540

tgacttttta gaagctaaag gatataagga agttaaaaaa gacttaatca ttaaactacc   3600

taaatatagt cttttgagtt tagaaaacgg tcgtaaacgg atgctggcta gtgccggaga   3660

attacaaaaa ggaaatgagc tggctctgcc aagcaaatat gtgaattttt tatatttagc   3720

tagtcattat gaaaagttga agggtagtcc agaagataac gaacaaaaac aattgtttgt   3780

ggagcagcat aagcattatt tagatgagat tattgagcaa atcagtgaat tttctaagcg   3840

tgttatttta gcagatgcca atttagataa agttcttagt gcatataaca aacatagaga   3900

caaaccaata cgtgaacaag cagaaaatat tattcattta tttacgttga cgaatcttgg   3960

agctcccgct gcttttaaat atttcgatac aacaattgat cgtaaacgat atacgtctac   4020

aaagaagttt ttagatgcca ctcttatcca tcaatccatc actggtcttt atgaaacacg   4080

cattgatttg agtcagctag gaggtgactg aatcc                               4115
```

<210> SEQ ID NO 18
<211> LENGTH: 91
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, rpoC terminator from pBTK300

<400> SEQUENCE: 18

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atccgtaatc gttcatacgc aactaaagta aaaaccagcc taggctggtt ttttcatggg     60

gggagtttag ggaaagagca tttgtcagca g                                    91
```

<210> SEQ ID NO 19
<211> LENGTH: 137
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, BBa_B0015 terminator from pBTK301

<400> SEQUENCE: 19

```
tacaccaggc atcaaataaa acgaaaggct cagtcgaaag actgggcctt tcgttttatc     60

tgttgtttgt cggtgaacgc tctctactag agtcacactg gctcaccttc gggtgggcct    120
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ttctgagttc atccgga 137

<210> SEQ ID NO 50
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, T7 terminator from
      pBTK305

<400> SEQUENCE: 50

atccaaacta gcataacccc ttggggcctc taaacgggtc ttgaggggtt ttttgctggc 60

tg 62

<210> SEQ ID NO 51
<211> LENGTH: 1710
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pBTK102

<400> SEQUENCE: 51

tcaccgtctt tcattgccat acgaaattcc ggatgagcat tcatcaggcg ggcaagaatg 60

tgaataaagg ccggataaaa cttgtgctta tttttcttta cggtctttaa aaaggccgta 120

atatccagct gaacggtctg gttataggta cattgagcaa ctgactgaaa tgcctcaaaa 180

tgttctttac gatgccattg ggatatatca acggtggtat atccagtgat ttttttctcc 240

attttagctt ccttagctcc tgaaaatctc gataactcaa aaaatacgcc cggtagtgat 300

cttatttcat tatggtgaaa gttggaacct cttacgtgcc gatcaatctc tgaccaaaat 360

cccttaacgt gagttttcgt tccactgagc gtcagacccc gtagaaaaga tcaaaggatc 420

ttcttgagat cctttttttc tgcgcgtaat ctgctgcttg caaacaaaaa aaccaccgct 480

accagcggtg gtttgtttgc cggatcaaga gctaccaact ctttttccga aggtaactgg 540

cttcagcaga gcgcagatac caaatactgt tcttctagtg tagccgtagt taggccacca 600

cttcaagaac tctgtagcac cgcctacata cctcgctctg ctaatcctgt taccagtggc 660

tgctgccagt ggcgataagt cgtgtcttac cgggttggac tcaagacgat agttaccgga 720

taaggcgcag cggtcgggct gaacgggggg ttcgtgcaca cagcccagct tggagcgaac 780

gacctacacc gaactgagat acctacagcg tgagctatga gaaagcgcca cgcttcccga 840

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ggagcttcca gggggaaacg cctggtatct ttatagtcct gtcgggtttc gccacctctg 960

acttgagcgt cgatttttgt gatgctcgtc aggggggcgg agcctatgga aaaacgccag 1020

caacgcggcc tttttacggt tcctggcctt ttgctggcct tttgctcaca tgttctttcc 1080

tgcgttatcc cctgattctg tggataaccg tagtcggtcc caaacgtaat acgactcact 1140

ataggatcca gatccagcgg agatattcca tatgcgagcc caggccaatc aattacgacc 1200

ggcggcaacc gagcgttctg aaccaaatcc agatggagtt ctgaggtcat tactggatct 1260

tacacaggag taccagagag atcgatatca aattacgccc cgccctgcca ctcatcgcag 1320

tactgttgta attcattaag cattctgccg acatggaagc catcacaaac ggcatgatga 1380

acctgaatcg ccagcggcat cagcaccttg tcgccttgcg tataatattt gcccatggtg 1440

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aaaacggggg cgaagaagtt gtccatattg gccacgttta aatcaaaact ggtgaaactc 1500

acccagggat tggctgagac gaaaaacata ttctcaataa accctttagg gaaataggcc 1560

aggttttcac cgtaacacgc cacatcttgc gaatatatgt gtagaaactg ccggaaatcg 1620

tcgtggtatt cactccagag cgatgaaaac gtttcagttt gctcatggaa aacggtgtaa 1680

caagggtgaa cactatccca tatcaccagc 1710

<210> SEQ ID NO 52
<211> LENGTH: 1742
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDIK103

<400> SEQUENCE: 52

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tatttcatta tggtgaaagt tggaacctct tacgtgcccg atcaatcatg accaaaatcc 120

cttaacgtga gttttcgttc cactgagcgt cagaccccgt agaaaagatc aaaggatctt 180

cttgagatcc tttttttctg cgcgtaatct gctgcttgca aacaaaaaaa ccaccgctac 240

cagcggtggt ttgtttgccg gatcaagagc taccaactct ttttccgaag gtaactggct 300

tcagcagagc gcagatacca aatactgttc ttctagtgta gccgtagtta ggccaccact 360

tcaagaactc tgtagcaccg cctacatacc tcgctctgct aatcctgtta ccagtggctg 420

ctgccagtgg cgataagtcg tgtcttaccg ggttggactc aagacgatag ttaccggata 480

aggcgcagcg gtcgggctga acggggggtt cgtgcacaca gcccagcttg gagcgaacga 540

cctacaccga actgagatac ctacagcgtg agctatgaga aagcgccacg cttcccgaag 600

ggagaaaggc ggacaggtat ccggtaagcg gcagggtcgg aacaggagag cgcacgaggg 660

agcttccagg gggaaacgcc tggtatcttt atagtcctgt cgggtttcgc cacctctgac 720

ttgagcgtcg atttttgtga tgctcgtcag gggggcggag cctatggaaa aacgccagca 780

acgcggcctt tttacggttc ctggcctttt gctggccttt tgctcacatg ttctttcctg 840

agttatcccc tgattctgtg gataaccgta gtcggtatca aacgcttacc atttacgatt 900

ccggctcgta tgttgtgtgg aattgtgagc ggataacaat tttaaagagg agaaattaac 960

tatgtgagac cagaccaata aaaaacgccc ggcggcaacc gagcgttctg aacaaatcca 1020

gatggagttc tgaggtcatt actggatcta tcaacaggag tccaagcgag ctcgatatca 1080

aattacgccc cgccctgcca ctcatcgcag tactgttgta attcattaag cattctgccg 1140

acatggaagc catcacaaac ggcatgatga acctgaatcg ccagcggcat cagcaccttg 1200

tcgccttgcg tataatattt gcccatggtg aaaacggggg cgaagaagtt gtccatattg 1260

gccacgttta aatcaaaact ggtgaaactc acccagggat tggctgagac gaaaaacata 1320

ttctcaataa accctttagg gaaataggcc aggttttcac cgtaacacgc cacatcttgc 1380

gaatatatgt gtagaaactg ccggaaatcg tcgtggtatt cactccagag cgatgaaaac 1440

gtttcagttt gctcatggaa aacggtgtaa caagggtgaa cactatccca tatcaccagc 1500

tcaccgtctt tcattgccat acgaaattcc ggatgagcat tcatcaggcg ggcaagaatg 1560

tgaataaagg ccggataaaa cttgtgctta tttttcttta cggtctttaa aaaggccgta 1620

atatccagct gaacggtctg gttataggta cattgagcaa ctgactgaaa tgcctcaaaa 1680

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tgttctttac gatgccattg ggatatatca acggtggtat atccagtgat ttttttctcc 1740

at 1742

<210> SEQ ID NO 53
<211> LENGTH: 1750
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pBTK107

<400> SEQUENCE: 53

tactgacccc aatccattca agtgagtttt agttccactg agcgtcagac cccgtagaaa 60

agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa 120

aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc 180

cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt 240

agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc 300

tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac 360

gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca 420

gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg 480

ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag 540

gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt 600

ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat 660

ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc 720

acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtagg tatcaaaagc 780

tttggcagtt tattcttgac atgtagtgag ggggctggta taatcacata gtactgttat 840

acagaaacag aggagatatt acatatgtga gaccagacca ataaaaaacg cccggcggca 900

accgagcgtt ctgaacaaat ccagatggag ttctgaggtc attactggat ctatcaacag 960

gagtccaagc gagctcgata tcaaattacg ccccgccctg ccactcatcg cagtactgtt 1020

gtaattcatt aagcattctg ccgacatgga agccatcaca aacggcatga tgaacctgaa 1080

tcgccagcgg catcagcacc ttgtcgcctt gcgtataata tttgcccatg gtgaaaacgg 1140

gggcgaagaa gttgtccata ttggccacgt ttaaatcaaa actggtgaaa ctcacccagg 1200

gattggctga gacgaaaaac atattctcaa taaacccttt agggaaatag gccaggtttt 1260

caccgtaaca cgccacatct tgcgaatata tgtgtagaaa ctgccggaaa tcgtcgtggt 1320

attcactcca gagcgatgaa aacgtttcag tttgctcatg gaaaacggtg taacaagggt 1380

gaacactatc ccatatcacc agctcaccgt ctttcattgc catacggaat tccggatgag 1440

cattcatcag gcgggcaaga atgtgaataa aggccggata aaacttgtgc ttatttttct 1500

ttacggtctt taaaaaggcc gtaatatcca gctgaacggt ctggttatag gtacattgag 1560

caactgactg aaatgcctca aaatgttctt tacgatgcca ttgggatata tcaacggtgg 1620

tatatccagt gatttttttc tccattttag cttccttagc tcctgaaaat ctcgataact 1680

caaaaaatac gcccggtagt gatcttattt cattatggtg aaagttggaa cctcttacgt 1740

gcccgatcaa 1750

<210> SEQ ID NO 54

continued

<211> LENGTH: 1751
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesised, pDTK110

<400> SEQUENCE: 54

ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca gcttggagcg 60

aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg ccacgcttcc 120

cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag gagagcgcac 180

gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt ttcgccacct 240

ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat ggaaaaacgc 300

cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc acatgttctt 360

tcctgcgtta tcccctgatt ctgtggataa ccgtagtcgg tctcaaagcg atgtgggagt 420

ttattcttga cacagatatt tccggatgat ataataactg agtactgtta tacagaaaca 480

gaggagatat taccatgtgg agcccagccc aatcaaaaac gcccggaggc aaacgagagt 540

tatgaaacca taccgatgga gttccgaggc catcactgga tatccaaacc ggacgccaag 600

cgagctcgat atcaaattac gccccgcccc gccactcatc gcagtactgt tgtaattcat 660

taagcattct gccgacatgg aagccatcac aaacggcatg atgaacctga atcgccagcg 720

gcatcagcac cttgtcgcct tgcgtataat atttgcccat ggtgaaaacg ggggcgaaga 780

agttgtccat attggccacg tttaaatcaa aactggtgaa actcacccag ggattggctg 840

agacgaaaaa catattctca ataaaccctt tagggaaata ggccaggttt tcaccgtaac 900

acgccacatc ttgcgaatat atgtgtagaa actgccggaa atcgtcgtgg tattcactcc 960

agagcgatga aaacgtttca gtttgctcat ggaaaacggt gtaacaaggg tgaacactat 1020

cccatatcac cagctcaccg tctttcattg ccatacgaaa ttccggatga gcattcatca 1080

ggcgggcaag aatgtgaata aaggccggat aaaacttgtg cttatttttc tttacggtct 1140

ttaaaaaggc cgtaatatcc agctgaacgg tctggttata ggtacattga gcaactgact 1200

gaaatgcctc aaaatgttct ttacgatgcc attgggatat atcaacggtg gtatatccag 1260

tgattttttt ctccatttta gcttccttag ctcctgaaaa tctcgataac tcaaaaaata 1320

cgcccggtag tgatcttatt tcattatggt gaaagttgga acctcttacg tgccgatcaa 1380

atcatgacca aaatccctta acgtgagttt tcgttccact gagcgtcaga ccccgtagaa 1440

aagatcaaag gatcttcttg agatcctttt tttctgcgcg taatctgctg cttgcaaaca 1500

aaaaaaccac cgctaccagc ggtggtttgt ttgccggatc aagagctacc aactcttttt 1560

ccgaaggtaa ctggcttcag cagagcgcag ataccaaata ctgttcttct agtgtagccg 1620

tagttaggcc accacttcaa gaactctgta gcaccgccta catacctcgc tctgctaatc 1680

ctgttaccag tggctgctgc cagtggcgat aagtcgtgtc ttaccgggtt ggactcaaga 1740

cgatagttac c 1751

<210> SEQ ID NO 55
<211> LENGTH: 1751
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesised, pDTK110

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<400> SEQUENCE: 55

```
tcttgaccaa aatcccttaa cgtgagtttt cgttccactg agcgtcagac cccgtagaaa      60
agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa     120
aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc     180
cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240
agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc     300
tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac     360
gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca     420
gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg     480
ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag     540
gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt     600
ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat     660
ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc     720
acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtagg tatcaaaagc     780
atatacaagt ttattcttga cactagtggc ccaaaatgat ataatacctg agtactgtta     840
tacagaaaca gaggagatat tacatatgtg agaacagaac aataaaaaac gcccggcggc     900
aaccgagcgt tctgaacaaa tccagatgga gttctgaggt cattactgga tctatcaaca     960
ggagtccaag cgagctcgat atcaaattac gccccgccct gccactcatc gcagtactgt    1020
tgtaattcat taagcattct gccgacatgg aagccatcac aaacggcatg atgaacctga    1080
atcgccagcg gcatcagcac cttgtcgcct tgcgtataat atttgcccat ggtgaaaacg    1140
ggggcgaaga agttgtccat attggccacg tttaaatcaa aactggtgaa actcacccag    1200
ggattggctg agacgaaaaa catattctca ataaaccctt tagggaaata ggccaggttt    1260
tcaccgtaac acgccacatc ttgcgaatat atgtgtagaa actgccggaa atcgtcgtgg    1320
tattcactcc agagcgatga aaacgtttca gtttgctcat ggaaaacggt gtaacaaggg    1380
tgaacactat cccatatcac cagctcaccg tctttcattg ccatacgaat ttccggatga    1440
gcattcatca ggcgggcaag aatgtgaata aaggccggat aaaacttgtg cttatttttc    1500
tttacggtct ttaaaaaggc cgtaatatcc agctgaacgg tctggttata ggtacattga    1560
gcaactgact gaaatgcctc aaaatgttct ttacgatgcc attgggatat atcaacggtg    1620
gtatatccag tgattttttt ctccatttta gcttccttag ctcctgaaaa tctcgataac    1680
tcaaaaaata cgcccggtag tgatcttatt tcattatggt gaaagttgga acctcttacg    1740
tgcccgatca a                                                          1751
```

<210> SEQ ID NO 56
<211> LENGTH: 1751
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized. pBTK113

<400> SEQUENCE: 56

```
tcttgaccaa aatcccttaa cgtgagtttt cgttccactg agcgtcagac cccgtagaaa      60
agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa     120
```

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aataaaaacc gataaaagcg gtggtttgtt tgccggatca agagctacca actctttttc     180
cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240
agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc     300
tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac     360
gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca     420
gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg     480
ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag     540
gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt     600
ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat     660
ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc     720
acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtcgg tctcaaacgc     780
atacgggagt ttattcttga catattgccg gtgtgttggt ataataactt agtaccgtta     840
tacagaatca gaggagatct taccatgtgc agcccagacc aatcaaaatc gaccggaggc     900
aaccgagcgc tatgaaacca taccgatgga gttcagaggc aattactggc tatttcaacc     960
ggagtccaag cgagctcgat atcaaattac gccccgccct gccactcatc gcagtactgt    1020
tgtaattcat taagcattct gccgacatgg aagccatcac aaacggcatg atgaacctga    1080
atcgccagcg gcatcagcac cttgtcgcct tgcgtataat atttgcccat ggtgaaaacg    1140
ggggcgaaga agttgtccat attggccacg tttaaatcaa aactggtgaa actcacccag    1200
ggattggctg agacgaaaaa catattctca ataaaccctt tagggaaata ggccaggttt    1260
tcaccgtaac acgccacatc ttgcgaatat atgtgtagaa actgccggaa atcgtcgtgg    1320
tattcactcc agagcgatga aaacgtttca gtttgctcat ggaaaacggt gtaacaaggg    1380
tgaacactat cccatatcac cagctcaccg tctttcattg ccatacgaaa ttccggatga    1440
gcattcatca ggcgggcaag aatgtgaata aaggccggat aaaacttgtg cttatttttc    1500
tttacggtct ttaaaaaggc cgtaatatcc agctgaacgg tctggttata ggtacattga    1560
gcaactgact gaaatgcctc aaaatgttct ttacgatgcc attgggatat atcaacggtg    1620
gtatatccag tgattttttt ctccatttta gcttccttag ctcctgaaaa tctcgataac    1680
tcaaaaaata cgcccggtag tgatcttatt tcattatggt gaaagttgga acctcttacg    1740
tgcccgatca a                                                         1751
```

<210> SEQ ID NO 57
<211> LENGTH: 1761
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pRK119

<400> SEQUENCE: 57

```
aacaaaaccg aactgagcta aatacagcgt gagctatgag aaagcgccac gcttcccgaa      60
gggagaaagg cggacaggta tccggtaagc ggcagggtcg gaacaggaga gcgcacgagg     120
gagcttccag ggggaaacgc ctggtatctt tatagtcctg tcgggtttcg ccacctctga     180
cttgagcgtc gatttttgtg atgctcgtca ggggggcgga gcctatggaa aaacgccagc     240
aacgcggcct ttttacggtt cctggccttt tgctggcctt ttgctcacat gttctttcct     300
```

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gagttatccc atgcttatgt ggataaacgt agtcggtatc aaacggtatc aaacagagta     360

ttgacttaaa gtctaaccta taggatactt acagccatcg agagggacac ggcgaatacc     420

gaaacagagg agatattaca tatgtgagac cagaccaata aaaaacgccc ggcggcaacc     480

gagcgtttcg aacaaatcca gatggagttc tgaggtcatt actggatcta tcaacaggag     540

tccaagcgag ctcgatatca aattacgccc cgccctgcca ctcatcgcag tactgttgta     600

attcattaag cattctgccg acatggaagc catcacaaac ggcatgatga acctgaatcg     660

ccagcggcat cagcaccttg tcgccttgcg tataatattt gcccatggtg aaaacggggg     720

cgaagaagtt gtccatattg gccacgttta aatcaaaact ggtgaaactc acccagggat     780

tggctgagac gaaaaacata ttctcaataa accctttagg gaaataggcc aggttttcac     840

cgtaacacgc cacatcttgc gaatatatgt gtagaaactg ccggaaatcg tcgtggtatt     900

cactccagag cgatgaaaac gtttcagttt gctcatggaa aacggtgtaa caagggtgaa     960

cactatccca tatcaccagc tcaccgtctt tcattgccat acgaaattcc ggatgagcat    1020

tcatcaggcg ggcaagaatg tgaataaagg ccggataaaa cttgtgctta tttttcttta    1080

cggtctttaa aaaggccgta atatccagct gaacggtctg gttataggta cattgagcaa    1140

ctgactgaaa tgcctcaaaa tgttctttac gatgccattg ggatatatca acggtggtat    1200

atccagtgat ttttttctcc attttagctt ccttagctcc tgaaaatctc gataactcaa    1260

aaaatacgcc cggtagtgat cttatttcat tatggtgaaa gttggaacct cttacgtgcc    1320

cgatcaatca tgaccaaaat cccttaacgt gagttttcgt tccactgagc gtcagacccc    1380

gtagaaaaga tcaaaggatc ttcttgagat cctttttttc tgcgcgtaat ctgctgcttg    1440

caaacaaaaa aaccaccgct accagcggtg gtttgtttgc cggatcaaga gctaccaact    1500

ctttttccga aggtaactgg cttcagcaga gcgcagatac caaatactgt tcttctagtg    1560

tagccgtagt taggccacca cttcaagaac tctgtagcac cgcctacata cctcgctctg    1620

ctaatcctgt taccagtggc tgctgccagt ggcgataagt cgtgtcttac cgggttggac    1680

tcaagacgat agttaccgga taaggcgcag cggtcgggct gaacgggggg ttcgtgcaca    1740

cagcccagct tggagcgaac g                                               1761
```

<210> SEQ ID NO 50
<211> LENGTH: 1762
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized. pBTK120

<400> SEQUENCE: 58

```
cagcccagct tggagcgaac gacctacacc gaactgagat acctacagcg tgagctatga       60

gaaagcgcca cgcttcccga agggagaaag gcggacaggt atccggtaag cggcagggtc      120

ggaacaggag agcgcacgag ggagcttcca gggggaaacg cctggtatct ttatagtcct      180

gtcgggtttc gccacctctg acttgagcgt cgatttttgt gatgctcgtc aggggggcgg      240

agcctatgga aaaacgccag caacgcggcc tttttacggt tcctggcctt ttgctggcct      300

tttgctcaca tgttctttcc tgcgttatcc cctgattctg tggataaccg tagtcggtat      360

caaacgcacg aaaaacaggt attgacaaca tgaagtaaca tgcagtaaga tacaaatcgc      420

taggtaacac tagcagcata cagaaacaga ggagatatta catatgtgag accagaccaa      480
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ataaaaacgc ccggcggcaa ccgagcgttc tgaacaaatc cagatggagt tctgaggtca     540
ttactggatc tatcaacagg agtccaagcg agctcgatat caaattacgc cccgccctgc     600
cactcatcgc agtactgttg taattcatta agcattctgc cgacatggaa gccatcacaa     660
acggcatgat gaacctgaat cgccagcggc atcagcacct tgtcgccttg cgtataatat     720
ttgcccatgg tgaaaacggg ggcgaagaag ttgtccatat tggccacgtt taaatcaaaa     780
ctggtgaaac tcacccaggg attggctgag acgaaaaaca tattctcaat aaacccttta     840
gggaaatagg ccaggttttc accgtaacac gccacatctt gcgaatatat gtgtagaaac     900
tgccggaaat cgtcgtggta ttcactccag agcgatgaaa acgtttcagt ttgctcatgg     960
aaaacggtgt aacaagggtg aacactatcc catatcacca gctcaccgtc tttcattgcc    1020
atacgaaatt ccggatgagc attcatcagg cgggcaagaa tgtgaataaa ggccggataa    1080
aacttgtgct tatttttctt tacggtcttt aaaaaggccg taatatccag ctgaacggtc    1140
tggttatagg tacattgagc aactgactga aatgcctcaa aatgttcttt acgatgccat    1200
tgggatatat caacggtggt atatccagtg atttttttct ccattttagc ttccttagct    1260
cctgaaaatc tcgataactc aaaaaatacg cccggtagtg atcttatttc attatggtga    1320
aagttggaac ctcttacgtg ccgatcaact catgaccaaa atcccttaac gtgagttttc    1380
gttccactga gcgtcagacc ccgtagaaaa gatcaaagga tcttcttgag atcctttttt    1440
tctgcgcgta atctgctgct tgcaaacaaa aaaaccaccg ctaccagcgg tggtttgttt    1500
gccggatcaa gagctaccaa ctctttttcc gaaggtaact ggcttcagca gagcgcagat    1560
accaaatact gttcttctag tgtagccgta gttaggccac cacttcaaga actctgtagc    1620
accgcctaca tacctcgctc tgctaatcct gttaccagtg gctgctgcca gtggcgataa    1680
gtcgtgtctt accgggttgg actcaagacg atagttaccg gataaggcgc agcggtcggg    1740
ctgaacgggg ggttcgtgca ca                                             1762
```

<210> SEQ ID NO 59
<211> LENGTH: 1701
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDTK121

<400> SEQUENCE: 59

```
ctgagatacc tacagcgtga gctatgagaa agcgccacgc ttcccgaagg gagaaaggcg      60
gacaggtatc cggtaagcgg cagggtcgga acaggagagc gcacgaggga gcttccaggg     120
ggaaacgcct ggtatcttta tagtcctgtc gggtttcgcc acctctgact tgagcgtcga     180
tttttgtgat gctcgtcagg ggggcggagc ctatggaaaa acgccagcaa cgcggccttt     240
ttacggttcc tggccttttg ctggcctttt gctcacatgt tctttcctgc gttatcccct     300
gattctgtgg ataaccgtag tcggtctcaa acgggtgaaa caaaacggtt gacaacatga     360
agtaaaaacg gtacgatgta ccacatgaaa cgacagtgag tcaccaaaga aaccgaggga     420
atattaacta tgtgagacca gaccaataaa aaacgcccgg cggcaaccga gcgttctgaa     480
aaaaaaaaga tggagttctg aggtcattac tggatctatc aacaggagtc caagcgagct     540
cgatatcaaa ttacgccccg ccctgccact catcgcagta ctgttgtaat tcattaagca     600
ttctgccgac atggaagcca tcacaaacgg catgatgaac ctgaatcgcc agcggcatca     660
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continued

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gatcctgtc gactcgagta tactacttgc aattggtgca aacgggggcg aagcagttgt     720

aatcattggc aacgcttcca tcaccaatgg tgcaactaac aatgggattg gatgaaaagc     780

aaaacatatt ctcaataaac cctttaggga aatagcccag gttttcaccg taacacgcca     840

catcttgcga atatatgtgt agaaactgcc ggaaatcgtc gtggtattca ctccagagcg     900

atgaaaacgt ttcagtttgc tcatggaaaa cggtgtaaca agggtgaaca ctatcccata     960

tcaccagctc accgtctttc attgccatac gaaattccgg atgagcattc atcaggcggg    1020

caagaatgtg aataaaggcc ggataaaact tgtgcttatt tttctttacg gtctttaaaa    1080

aggccgtaat atccagctga acggtctggt tataggtaca ttgagcaact gactgaaatg    1140

cctcaaaatg ttctttacga tgccattggg atatatcaac ggtggtatat ccagtgattt    1200

ttttctccat tttagcttcc ttagctcctg aaaatctcga taactcaaaa aatacgcccg    1260

gtagtgatct tatttcatta tggtgaaagt tggaacctct tacgtgcccg atcaatcatg    1320

accaaaatcc cttaacgtga gttttcgttc cactgagcgt cagaccccgt agaaaagatc    1380

aaaggatctt cttgagatcc tttttttctg cgcgtaatct gctgcttgca aacaaaaaaa    1440

accaccgcta ccagcggtgg tttgtttgcc ggatcaagag ctaccaactc tttttccgaa    1500

gtaactggct tcagcagagc gcagatacca aatactgttc ttctagtgta gccgtagtta    1560

ggccaccact tcaagaactc tgtagcaccg cctacatacc tcgctctgct aatcctgtta    1620

ccagtggctg ctgccagtgg cgataagtcg tgtcttaccg ggttggactc aagacgatag    1680

ttaccggata aggcgcagcg gtcgggctga acggggggtt cgtgcacaca gcccagcttg    1740

gagcgaacga cctacaccga a                                               1761
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<210> SEQ ID NO 60
<211> LENGTH: 1700
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pBTK138

<400> SEQUENCE: 60

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tactgaacca aatcccttca agtgagtttt agttccactg agcgtcagac cccgtagaaa      60

agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa     120

aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc     180

cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240

agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc     300

tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac     360

gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca     420

gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg     480

ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag     540

gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt     600

ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat     660

ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc     720

acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtattacc gcctttgagt     780

gagctgatac cgctcgccgc agccgaacga ccgagcgcag cgagtcagtg agcgaggaag     840
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aatatgtgtt tattccagcc aactcaattc atgtcaagta tattttgact aagccgatgt      900

gacccagacc attaaaattg aacggcggca aacgagagtt atgaacaaat aacgatgggg      960

ttctgaggtc attactggat ctatcaacag gagtccaagc gagctcgata tcaaattacg     1020

ccccgccctg ccactcatcg cagtactgtt gtaattcatt aagcattctg ccgacatgga     1080

agccatcaca aacggcatga tgaacctgaa tcgccagcgg catcagcacc ttgtcgcctt     1140

gcgtataata tttgcccatg gtgaaaacgg gggcgaagaa gttgtccata ttggccacgt     1200

ttaaatcaaa actggtgaaa ctcacccagg gattggctga gacgaaaaac atattctcaa     1260

taaacccttt agggaaatag gccaggtttt caccgtaaca cgccacatct tgcgaatata     1320

tgtgtagaaa ctgccggaaa tcgtcgtggt attcactcca gagcgatgaa aacgtttcag     1380

tttgctcatg gaaaacggtg taacaagggt gaacactatc ccatatcacc agctcaccgt     1440

ctttcattgc catacggaat tccggatgag cattcatcag gcgggcaaga atgtgaataa     1500

aggccggata aaacttgtgc ttatttttct ttacggtctt taaaaaggcc gtaatatcca     1560

gctgaacggt ctggttatag gtacattgag caactgactg aaatgcctca aaatgttctt     1620

tacgatgcca ttgggatata tcaacggtgg tatatccagt gatttttttc tccattttag     1680

cttccttagc tcctgaaaat ctcgataact caaaaaatac gcccggtagt gatcttattt     1740

cattatggtg aaagttggaa cctcttacgt gcccgatcaa                           1780
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<210> SEQ ID NO 61
<211> LENGTH: 4315
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pR 620

<400> SEQUENCE: 61

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agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa      120

aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc      180

cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt      240

agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc      300

tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac      360

gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca      420

gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg      480

ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag      540

gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt      600

ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat      660

ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc      720

acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtattacc gcctttgagt      780

acacgattca catcgctaag aacgacttct ctgacatcga actggctgct atcccgttca      840

aacctatggc tgcccattcc ggtgagcgtc tagctcgaga aacgctggcc attgagcatg      900

agtcctacga gatgggtgaa gcacgcttcc gcaagatgtt tgagcgtcaa cttaaagctg      960

gtgaggttgc ggataacgct gccgccaagc ctctcatcac taccctactc cctaagatga     1020
```

continued

```
ttgcaagcct aatcgaatgg tttgaggacg tgccagctca gagcggaacg agcccgaacg    1080
actaccagtc aatgcaagca atccagacgg aagccgtagc gtccatcacc attcagaccc    1140
ctccggcttg cctaaccagc gctgacaata caaccgttca ggctgtagca agcgcaatcg    1200
gtcggcgcac tgaggacgag gctcgcttcg gtcgcatccg tgacctgaag gctaagcact    1260
tcaagaaaaa cgttgaggaa caactcaaca agcgcgtagg gcacgctcac aagcaagcat    1320
ttatgcaagt tgtcgaggct gacatgctct ctaagggtct actcggtggc gaggcgtggt    1380
attcgtggca tacggaagcc tatcccactg taggagtacg atgcatacag atgcccattg    1440
agtcaaacgg aatggttagc ttccacagcc aacccgatgg agtagtaggt cacgactatg    1500
agactatcga actcgcaccc gaatacgctg aggctatcgc aacccgtgca ggtgcgctgg    1560
ctggcatctc tccgatgttc caacccgcgc tagttcctcc taagccgtgg actggcatta    1620
ctggtggtgg ctattgggct aacggtcgtc gtccactggc gctggtgcgt actcacagta    1680
agaaagcact gatgcgctac gaagacgttt acatgcctga ggtgtacaaa gcgattaaca    1740
ttgcgcaaca accgcaatgg aaaatcaaca agcaagtact agcggtagcc aacgcaatca    1800
accagtggca gactcgtccg gtcgaggcca tcccgcagca tgcgcgtgca gaacccaagc    1860
tgaaaccgga agacatcgac atgaatcctg aggctctcac cgcgtggaaa cgtgctgccg    1920
ctgctgtgta ccgcaaggac aaggctcgca agtctcgccg tatcagcctt gagttcatgc    1980
ttgagcaagc caataagttt gctaaccata aggccatctg gttcccttac aacatggact    2040
ggcgcggtcg tgtttacgct gtgtcaatgt tcaacccgca aggtaacgat atgaccaaag    2100
gactgcttac gctggcgaaa ggtaaaccaa tcggtaagga aggttactac tggctgaaaa    2160
tccacggtgc aaactgtgcg ggtgtcgata aggttccgtt ccctgagcgc atcaagttca    2220
ttgaggaaaa ccacgagaac atcatggctt gcgctaagtc tccactggag aacacttggt    2280
gggctgagca agattctccg ttctgcttcc ttgcgttctg ctttgagtac gctggggtac    2340
agcaccacgg cctgagctat aactgctccc ttccgctggc gtttgacggg tcttgctctg    2400
gcatccagca cttctccgcg atgctccgag atgaggtagg tggtcgcgcg gttaacttgc    2460
ttcctagtga aaccgttcag gacatctacg ggattgttgc taagaaagtc aacgagattc    2520
tacaagcaga cgcaatcaat gggaccgata acgaagtagt taccgtgacc gatgagaaca    2580
ctggtgaaat ctctgagaaa gtcaagctgg gcactaaggc actggctggt caatggctgg    2640
cttacggtgt tactcgcagt gtgactaagc gttcagtcat gacgctggct tacgggtcca    2700
aagagttcgg cttccgtcaa caagtgctgg aagataccat tcagccagct attgattccg    2760
gcaagggtcc gatgttcact caggccgctc aggctgctgg atacatggct aagctgattt    2820
gggaatctgt gagcgtgacg gtggtagctg cggttgaagc aatgaactgg cttaagtctg    2880
ctgctaagct gctggctgct gaggtcaaag ataagaagac tggagagatt cttcgcaagc    2940
gttgcgctgt gcattgggta actcctgatg gtttccctgt gtggcaggaa tacaagaagc    3000
ctattcagac gcgcttgaac ctgatgttcc tcggtcagtt ccgcttacag cctaccatta    3060
acaccaacaa agatagcgag attgatgcac acaaacagga gtctggtatc gctcctaact    3120
ttgtacacag ccaagacggt agccacctta gtacgactgt agtgtgggca cacgagaagt    3180
acggaatcga atctttgcac ctgattcacg actccttcgg taccattccg gctgacgctg    3240
cgaacctgtt caaagcagtg cgcgaaacta tggttgacac atatgagtct tgtgatgtac    3300
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tggctgattt ctacgaccag ttcgctgacc agttgcaaga gtctcaattg gaccaaatgc   3360

aagcaattcc ggctaaaggt aactggaccc taagtgacct attcgagtcg gacttcgagt   3420

tcgcgtaaat cctgagacca gaccaataaa aaacgcccgg cggcaaccga gcgttctgaa   3480

caaatccaga tggagttctg aggtcattac tggatctatc aacaggagtc caagcgagct   3540

cgatatcaaa ttacgccccg ccctgccact catcgcagta ctgttgtaat tcattaagca   3600

ttctgccgac atggaagcca tcacaaacgg catgatgaac ctgaatcgcc agcggcatca   3660

gcaccttgtc gccttgcgta taatatttgc ccatggtgaa aacgggggcg aagaagttgt   3720

ccatattggc cacgtttaaa tcaaaactgg tgaaactcac ccagggattg gctgagacga   3780

aaaacatatt ctcaataaac cctttaggga aataggccag gttttcaccg taacacgcca   3840

catcttgcga atatatgtgt agaaactgcc ggaaatcgtc gtggtattca ctccagagcg   3900

atgaaaacgt ttcagtttgc tcatggaaaa cggtgtaaca agggtgaaca ctatcccata   3960

tcaccagctc accgtctttc attgccatac gaaattccgg atgagcattc atcaggcggg   4020

caagaatgtg aataaaggcc ggataaaact tgtgcttatt tttctttacg gtctttaaaa   4080

aggccgtaat atccagctga acggtctggt tataggtaca ttgagcaact gactgaaatg   4140

cctcaaaatg ttctttacga tgccattggg atatatcaac ggtggtatat ccagtgattt   4200

ttttctccat tttagcttcc ttagctcctg aaaatctcga taactcaaaa aatacgcccg   4260

gtagtgatct tatttcatta tggtgaaagt tggaacctct tacgtgcccg atcaa        4315
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<210> SEQ ID NO 62
<211> LENGTH: 2746
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDIK203

<400> SEQUENCE: 62

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agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa    120

aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc    180

cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt    240

agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc    300

tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac    360

gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca    420

gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg    480

ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag    540

gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt    600

ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat    660

ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc    720

acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtcgg tctcatatga    780

aaccagtaac gttatacgat gtcgcagagt atgccggtgt ctcttatcag accgtttccc    840

gcgtggtgaa ccaggccagc cacgtttctg cgaaaacgcg ggaaaaagtg gaagcggcga    900

tggcggagct gaattacatt cccaaccgcg tggcacaaca actggcgggc aaacagtcgt    960
```

continued

```
tgcagattgg agttgaaacc taaagaatgg aactgcaagc gacgacgaac attgacgagg   1020
agaaaaaatc tagcgaagaa aaacagggtg aaagcgtggc ggtgacgatg gtagaaagaa   1080
gcggcgtcga agcccgtaaa gcggccgtgc acaatcttcc cgcgcaacgc gtcagtgggc   1140
tgatcattaa ctatccgctg gatgaccagg atgccattgc tgtggaagct gcctgcacta   1200
atgttccggc gttatttctt gatgtctctg accagacacc catcaacagt attattttct   1260
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tcgcgctgtt agcgggccca ttaagttctg tctcggcgcg tctgcgtctg gctggctggc   1380
ataaatatct cactcgcaat caaattcagc cgatagcgga acgggaaggc gactggagtg   1440
ccatgtccgg ttttcaacaa accatgcaaa tgctgaatga gggcatcgtt cccactgcga   1500
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tgcgcgttgg tgcggatatc tcggtagtgg gatacgacga taccgaagac agctcatgtt   1620
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accgcttgct gcaactctct cagggccagg cggtgaaggg caatcagctg ttgcccgtct   1740
cactggtgaa aagaaaaacc accctggcgc ccaatacgca aaccgcctct ccccgcgcgt   1800
tggccgattc attaatgcag ctggcacgac aggtttcccg actggaaagc gggcagtgaa   1860
tcctgagacc agaccaataa aaaacgcccg gcggcaaccg agcgttctga acaaatccag   1920
atggagttct gaggtcatta ctggatctat caacaggagt ccaagcgagc tcgatatcaa   1980
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cgccttgcgt ataatatttg cccatggtga aaacgggggc gaagaagttg tccatattgg   2160
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aatatatgtg tagaaactgc cggaaatcgt cgtggtattc actccagagc gatgaaaacg   2340
tttcagtttg ctcatggaaa acggtgtaac aagggtgaac actatcccat atcaccagct   2400
caccgtcttt cattgccata cgaaattccg gatgagcatt catcaggcgg gcaagaatgt   2460
gaataaaggc cggataaaac ttgtgcttat ttttctttac ggtctttaaa aaggccgtaa   2520
tatccagctg aacggtctgg ttataggtac attgagcaac tgactgaaat gcctcaaaat   2580
gttctttacg atgccattgg gatatatcaa cggtggtata tccagtgatt tttttctcca   2640
ttttagcttc cttagctcct gaaaatctcg ataactcaaa aaatacgccc ggtagtgatc   2700
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<210> SEQ ID NO 63
<211> LENGTH: 2386
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pK 6205

<400> SEQUENCE: 63

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aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc    180
```

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cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240
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tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac     360
gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca     420
gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg     480
ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag     540
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gtaaaggaga agagcttttc accggagttg tcccaatcct cgtggaattg gacggtgatg     840
ttaatgggca caagttctct gtcagtggag agggtgaagg cgacgcaaca tatggcaagc     900
tgacccttaa atttatttgc accactggta aactacctgt tccatggcca acactggtca     960
ctacgttcgg gtatggggtt cagtgctttg cgcgctaccc agatcacatg aaacagcacg    1020
actttttcaa gagtgccatg cccgaaggct atgtacagga gagaaccatc tttttcaagg    1080
atgacggcaa ctataagaca cgcgccgaag tgaagttcga gggtgatacc cttgttaata    1140
gaatcgagtt aaagggtatt gacttcaagg aagatggaaa tattttaggc cacaaactgg    1200
aatataacta taactcccat aatgtgtaca ttatggccga caagcaaaag aacggtatca    1260
aggttaactt caagattaga cacaacattg aggatggaag cgttcaactc gccgaccatt    1320
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gaccagacca ataaaaaacg cccggcggca accgagcgtt ctgaacaaat ccagatggag    1560
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tttgctcatg gaaaacggtg taacaagggt gaacactatc ccatatcacc agctcaccgt    2040
ctttcattgc catacgaaat tccggatgag cattcatcag gcgggcaaga atgtgaataa    2100
aggccggata aaacttgtgc ttatttttct ttacggtctt taaaaaggcc gtaatatcca    2160
gctgaacggt ctggttatag gtacattgag caactgactg aaatgcctca aaatgttctt    2220
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cttccttagc tcctgaaaat ctcgataact caaaaaatac gcccggtagt gatcttattt    2340
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<210> SEQ ID NO 64

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<211> LENGTH: 2179
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDIK206

<400> SEQUENCE: 64

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aaaaaaaccc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc 180

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<210> SEQ ID NO 65
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<223> OTHER INFORMATION: Chemically Synthesized, pR 6209

<400> SEQUENCE: 65

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cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240

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aaaaaatgga tggtactgag gaattattgg tgaaactaaa tcgtgaagat ttgctgcgca 1980

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<210> SEQ ID NO 66
<211> LENGTH: 2749
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDTK211

<400> SEQUENCE: 66

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cttaacgtga gttttcgttc cactgagcgt cagaccccgt agaaaagatc aaaggatctt     180

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<210> SEQ ID NO 67
<211> LENGTH: 2380
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pEK204

<400> SEQUENCE: 67

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<210> SEQ ID NO 68
<211> LENGTH: 2673
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDTK229

<400> SEQUENCE: 68

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cttggagcga acgacctaca ccgaactgag atacctacag cgtgagctat gagaaagcgc     120

cacgcttccc gaagggagaa aggcggacag gtatccggta agcggcaggg tcggaacagg     180

agagcgcacg agggagcttc cagggggaaa cgcctggtat ctttatagtc ctgtcgggtt     240

tcgccacctc tgacttgagc gtcgattttt gtgatgctcg tcaggggggc ggagcctatg     300

gaaaaacgcc agcaacgcgg cctttttacg gttcctggcc ttttgctggc cttttgctca     360

catgttcttt cctgcgttat cccctgattc tgtggataac cgtattaccg cctttgagtg     420

taccgagcgg ccgcgtgtta caaccaatta accaattctg attagaaaaa ctcatcgagc     480

atcaaatgaa actgcaattt attcatatca ggattatcaa taccatattt ttgaaaaagc     540

cgtttctgta atgaaggaga aaactcaccg aggcagttcc ataggatggc aagatcctgg     600

tatcggtctg cgattccgac tcgtccaaca tcaatacaac ctattaattt cccctcgtca     660

aaaataaggt tatcaagtga gaaatcacca tgagtgacga ctgaatccgg tgagaatggc     720

aaaagtttat gcatttcttt ccagacttgt tcaacaggcc agccattacg ctcgtcatca     780

aaatcactcg catcaaccaa accgttattc attcgtgatt gcgcctgagc gagacgaaat     840

acgcgatcgc tgttaaaagg acaattacaa acaggaatcg aatgcaaccg gcgcaggaac     900

actgccagcg catcaacaat attttcacct gaatcaggat attcttctaa tacctggaat     960

gctgttttcc cggggatcgc agtggtgagt aaccatgcat catcaggagt acggataaaa    1020

tgcttgatgg tcggaagagg cataaattcc gtcagccagt ttagtctgac catctcatct    1080

gtaacatcat tggcaacgct acctttgcca tgtttcagaa acaactctgg cgcatcgggc    1140

ttcccataca atcgatagat tgtcgcacct gattgcccga cattatcgcg agcccattta    1200

tacccatata aatcagcatc catgttggaa tttaatcgcg gcctggagca agacgtttcc    1260

cgttgaatat ggctcataac accccttgta ttactgttta tgtaagcaga cagttttatt    1320
```

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gttcatgatg atatattttt atcttgtgca atgtaacatc agagattttg agacacaacg    1380
tggctttgtt gaataaatcg aacttttgct gagttgaagg atcagatcat gagtccagtc    1440
caataaaaaa cgcccggcgg caaccgagcg ttctgaacaa atccagatgg agttctgagg    1500
tcattactgg atctatcaac aggagtccaa gcgagctcga tatcaaatta cgccccgccc    1560
tgccactcat cgcagtactg ttgtaattca ttaagcattc tgccgacatg gaagccatca    1620
caaacggcat gatgaacctg aatcgccagc ggcatcagca ccttgtcgcc ttgcgtataa    1680
tatttgccca tggtgaaaac gggggcgaag aagttgtcca tattggccac gtttaaatca    1740
aaactggtga aactcaccca gggattggct gagacgaaaa acatattctc aataaaccct    1800
ttagggaaat aggccaggtt ttcaccgtaa cacgccacat cttgcgaata tatgtgtaga    1860
aactgccgga aatcgtcgtg gtattcactc cagagcgatg aaaacgtttc agtttgctca    1920
tggaaaacgg tgtaacaagg gtgaacacta tcccatatca ccagctcacc gtctttcatt    1980
gccatacgga attccggatg agcattcatc aggcgggcaa gaatgtgaat aaaggccgga    2040
taaaacttgt gcttattttt ctttacggtc tttaaaaagg ccgtaatatc cagctgaacg    2100
gtctggttat aggtacattg agcaactgac tgaaatgcct caaaatgttc tttacgatgc    2160
cattgggata tatcaacggt ggtatatcca gtgatttttt tctccatttt agcttcctta    2220
gctcctgaaa atctcgataa ctcaaaaaat acgcccggta gtgatcttat ttcattatgg    2280
tgaaagttgg aacctcttac gtgccgatca aatcatgacc aaaatccctt aacgtgagtt    2340
ttcgttccac tgagcgtcag accccgtaga aaagatcaaa ggatcttctt gagatccttt    2400
ttttctgcgc gtaatctgct gcttgcaaac aaaaaaacca ccgctaccag cggtggtttg    2460
tttgccggat caagagctac caactctttt tccgaaggta actggcttca gcagagcgca    2520
gataccaaat actgttcttc tagtgtagcc gtagttaggc caccacttca agaactctgt    2580
agcaccgcct acatacctcg ctctgctaat cctgttacca gtggctgctg ccagtggcga    2640
taagtcgtgt cttaccgggt tggactcaag acg                                 2673
```

<210> SEQ ID NO 69
<211> LENGTH: 1749
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pDIK200

<400> SEQUENCE: 69

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tcatgaccaa aatcccttaa cgtgagtttt cgttccactg agcgtcagac cccgtagaaa      60
agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa     120
aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc     180
cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt     240
agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc     300
tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac     360
gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca     420
gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg     480
ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag     540
gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt     600
```

-continued

```
ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat     660
ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc     720
acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtcgg tctcaatccg     780
taatcgttaa tccgcaaata acgtaaaaac ccgcttcggc gggttttttt atggggggag     840
tttagggaaa gagcatttgt cagctgtgag accgagacca taaaaaacgc ccggcggcaa     900
ccgagcgttc tgaacaaatc cagatggagt tctgaggtca ttactggatc tatcaacagg     960
agtccaagcg agctcgatat caaattacgc cccgccctgc cactcatcgc agtactgttg    1020
taattcatta agcattctgc cgacatggaa gccatcacaa acggcatgat gaacctgaat    1080
cgccagcggc atcagcacct tgtcgccttg cgtataatat ttgcccatgg tgaaaacggg    1140
ggcgaagaag ttgtccatat tggccacgtt taaatcaaaa ctggtgaaac tcacccaggg    1200
attggctgag acgaaaaaca tattctcaat aaacccttta gggaaatagg ccaggttttc    1260
accgtaacac gccacatctt gcgaatatat gtgtagaaac tgccggaaat cgtcgtggta    1320
ttcactccag agcgatgaaa acgtttcagt ttgctcatgg aaaacggtgt aacaagggtg    1380
aacactatcc catatcacca gctcaccgtc tttcattgcc atacggaatt ccggatgagc    1440
attcatcagg cgggcaagaa tgtgaataaa ggccggataa aacttgtgct tatttttctt    1500
tacggtcttt aaaaaggccg taatatccag ctgaacggtc tggttatagg tacattgagc    1560
aactgactga aatgcctcaa aatgttcttt acgatgccat tgggatatat caacggtggt    1620
atatccagtg atttttttct ccattttagc ttccttagct cctgaaaatc tcgataactc    1680
aaaaaatacg cccggtagtg atcttatttc attatggtga aagttggaac ctcttacgtg    1740
ccgatcaac                                                            1749
```

<210> SEQ ID NO 70
<211> LENGTH: 1795
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized, pBTK201

<400> SEQUENCE: 70

```
tcatgaccaa aatcccttaa cgtgagtttt cgttccactg agcgtcagac cccgtagaaa       60
agatcaaagg atcttcttga gatccttttt ttctgcgcgt aatctgctgc ttgcaaacaa      120
aaaaaccacc gctaccagcg gtggtttgtt tgccggatca agagctacca actctttttc      180
cgaaggtaac tggcttcagc agagcgcaga taccaaatac tgttcttcta gtgtagccgt      240
agttaggcca ccacttcaag aactctgtag caccgcctac atacctcgct ctgctaatcc      300
tgttaccagt ggctgctgcc agtggcgata agtcgtgtct taccgggttg gactcaagac      360
gatagttacc ggataaggcg cagcggtcgg gctgaacggg gggttcgtgc acacagccca      420
gcttggagcg aacgacctac accgaactga gatacctaca gcgtgagcta tgagaaagcg      480
ccacgcttcc cgaagggaga aaggcggaca ggtatccggt aagcggcagg gtcggaacag      540
gagagcgcac gagggagctt ccagggggaa acgcctggta tctttatagt cctgtcgggt      600
ttcgccacct ctgacttgag cgtcgatttt tgtgatgctc gtcagggggg cggagcctat      660
ggaaaaacgc cagcaacgcg gcctttttac ggttcctggc cttttgctgg ccttttgctc      720
acatgttctt tcctgcgtta tcccctgatt ctgtggataa ccgtagtcgg tctcatacac      780
```

continued

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aaggcatcca atccaacgca aggcccagtc gaccgaatgg gacttccgtt ttatccgttg     840
tttgccgggtg aacgctatcc actcgagtca aactggatca acttcgggtg ggcccctatg     900
cgtttatacc gatgagacca gaccaataaa aaaccccggc cggcaaccga gcgttctgaa     960
caaatccaga tggagttctg aggtcattac tggatctatc aacaggagtc caagcgagct    1020
cgatatcaaa ttacgccccg ccctgccact catcgcagta ctgttgtaat tcattaagca    1080
ttctgccgac atggaagcca tcacaaacgg catgatgaac ctgaatcgcc agcggcatca    1140
gcaccttgtc gccttgcgta taatatttgc ccatggtgaa aacgggggcg aagaagttgt    1200
ccatattggc cacgtttaaa tcaaaactgg tgaaactcac ccagggattg gctgagacga    1260
aaaacatatt ctcaataaac cctttaggga aataggccag gttttcaccg taacacgcca    1320
catcttgcga atatatgtgt agaaactgcc ggaaatcgtc gtggtattca ctccagagcg    1380
atgaaaacgt ttcagtttgc tcatggaaaa cggtgtaaca agggtgaaca ctatcccata    1440
tcaccagctc accgtctttc attgccatac gaaattccgg atgagcattc atcaggcggg    1500
caagaatgtg aataaaggcc ggataaaact tgtgcttatt tttctttacg gtctttaaaa    1560
aggccgtaat atccagctga acggtctggt tataggtaca ttgagcaact gactgaaatg    1620
cctcaaaatg ttctttacga tgccattggg atatatcaac ggtggtatat ccagtgattt    1680
ttttctccat tttagcttcc ttagctcctg aaaatctcga taactcaaaa aatacgcccg    1740
gtagtgatct tatttcatta tggtgaaagt tggaacctct tacgtgcccg atcaa          1795
```

<210> SEQ ID NO 71
<211> LENGTH: 1720
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesised, pDTK005

<400> SEQUENCE: 71

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ggtcgggctg aacggggggt tcgtgcacac agcccagctt ggagcgaacg acctacaccg      60
aactgagata cctacagcgt gagctatgag aaagcgccac gcttcccgaa gggagaaagg     120
aggacaggta tccggtaagc ggcagggtcg gaacaggaga gcgcacgagg gagcttccag     180
ggggaaacgc ctggtatctt tatagtcctg tcgggtttcg ccacctctga cttgagcgtc     240
gatttttgtg atgctcgtca ggggggcgga gcctatggaa aaacgccagc aacgcggcct     300
ttttacggtt cctggccttt tgctggcctt ttgctcacat gttctttcct gcgttatccc     360
ctgattctgt ggataaccgt attaccgcct ttgagtgagc tgataccgct cgccgcagcc     420
gaacgaccga gcgcagcgag tcagtgagcg aggaagcgga agagcgccca atacgcaaac     480
cgcctctccc cgcgcgttgg ccgattcatt aatgcagctg gcacgacagg tttcccgact     540
ggaaagcggg cagtgagcgc aacgcaatta atgtgagtta gctcactcat taggcaccc      600
actgttgtaa ttcattaagc attctgccga catggaagcc atcacaaacg gcatgatgaa     660
cctgaatcgc cagcggcatc agcaccttgt cgccttgcgt ataatatttg cccatggtga     720
aaacgggggc gaagaagttg tccatattgg ccacgtttaa atcaaaactg gtgaaactca     780
cccagggatt ggctgagacg aaaaacatat tctcaataaa ccctttaggg aaataggcca     840
ggttttcacc gtaacacgcc acatcttgcg aatatatgtg tagaaactgc cggaaatcgt     900
cgtggtattc actccagagc gatgaaaacg tttcagtttg ctcatggaaa acggtgtaac     960
```

-continued

```
aagggtgaac actatcccat atcaccagct caccgtcttt cattgccata cgaaattccg    1020

gatgagcatt catcaggcgg gcaagaatgt gaataaaggc cggataaaac ttgtgcttat    1080

ttttctttac ggtctttaaa aaggccgtaa tatccagctg aacggtctgg ttataggtac    1140

attgagcaac tgactgaaat gcctcaaaat gttctttacg atgccattgg gatatatcaa    1200

cggtggtata tccagtgatt tttttctcca ttttagcttc cttagctcct gaaaatctcg    1260

ataactcaaa aaatacgccc ggtagtgatc ttatttcatt atggtgaaag ttggaacctc    1320

ttacgtgccc gatcaatcat gaccaaaatc ccttaacgtg agttttcgtt ccactgagcg    1380

tcagaccccg tagaaaagat caaaggatct tcttgagatc ctttttttct gcgcgtaatc    1440

tgctgcttgc aaacaaaaaa accaccgcta ccagcggtgg tttgtttgcc ggatcaagag    1500

ctaccaactc tttttccgaa ggtaactggc ttcagcagag cgcagatacc aaatactgtt    1560

cttctagtgt agccgtagtt aggccaccac ttcaagaact ctgtagcacc gcctacatac    1620

ctcgctctgc taatcctgtt accagtggct gctgccagtg gcgataagtc gtgtcttacc    1680

gggttggact caagacgata gttaccggat aaggcgcagc                          1720
```

<210> SEQ ID NO 72
<211> LENGTH: 7536
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Chemically Synthesized. pBTK327

<400> SEQUENCE: 72

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ggctggaccg aatgcggggc ttatcctgct gacgctgggc atgctcgatc tgctggaccg      60

aatgctgacc aagcgaaggg aaacgcgtgg aggtcatgcc attggattcc agcaggcagc     120

ccgacggctg ataaccggcg cgggtggtgc gcttgtcctt gcggttggtg aagcccgcca     180

agcgcccata gtggcggctg tcggcgctgg ccgggtcggc gtcgtactcg ctggccagcg     240

tccgggcaat ctgcccccga agttcaccgc ctgcggcgtc ggccaccttg acccatgcct     300

gatagttctt cgggctggtt tccactacca gggcaggctc ccggccctcg gctttcatgt     360

aatccaggtc aaccgagctg aggtcgtcca accgcaaccg aacctgaagc tactgctagg     420

cgggcctgac atacacgtca ttgccctggg cattcatccg cttgagccat ggcgtgttct     480

ggagcacttc ggcggctgac cattcccggt tcatcatctg gccggtggtg gcgtccctga     540

cgccgatatc gaagcgctca cagcccatgg ccttgagctg tcggcctatg gcctgcaaag     600

tcctgtcgtt cttcatcggg ccacccagcg cagccagatc gagccgtcct cggttgtcag     660

tggcgtaccg tagagaacga gaaacgatgc gatcagaagc aaaaccgtag gaatcatggc     720

agccagaatc aaggtaagcc atagcataca gtgccaaacc agcgacgagc taccgggcgt     780

atgcgagggc atgctaaccc aggcggatac ataccgaacc tatttggacc gatccaaacc     840

tgccgccccc gtctggcgcc gggccttcag ccacccggcc gcctgcgccc cgctggcctg     900

attggtatgg ataccgaccc gaagggattc gtaggccaag gtagccatgc tatggcaacg     960

cggttcgatc tgctccgcta actcgttgat gcctctggat ttcttcactc tgtcgattgc    1020

gttcatggtc tattgaatcc aggtatacct gtacgtagcc gatccgggcg ttggccgtgt    1080

cgatgttccg ggccacgtct gccccgtcgg tgcggatgcc ccggccttcc atctccacca    1140

cgttcggccc caggtgaaca ccgggcaggc gctcgatgcc ctgcgcctca agtgctctgt    1200
```

continued

```
ggtcaatgcg gggcaagtgg aacgccagcc ataccgaacg gttggcatgg tagggccatg   1260
aatcgagggc atgccaacgc aatgccttgg gatttgagac ttcggcattc tgtgccaagc   1320
ccttctcggc ggtccttgcg ttgtaccgcc tgaaccactg agcggcgggc cgctcgatgc   1380
cgtcattgac ccgcccggac atcatcaggc ggcagccgcg gttcccgccg ccacccgcat   1440
ggacggccag cgtacacggc aggcgctcgg cacccggtcg gtgcacggcg aactcggacg   1500
ccagcgccta ctgcaggtcg agggacagca cgacccgccg ggcaaattcg aactccttga   1560
aacgccgccc attggcgcgc taatacaggc aggcagcatc aacgcagtcg gagggcagct   1620
agacgaactc aggcatgtgc aaggactcgg agtgcaagcc ttcaccaatg tagcgggact   1680
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tgccggtttt cgccgtaagg tgataaatcg ccatgctgcc tcgccgttgc ttttgctttt   1800
cggcaccatg caatggccca cggcgagcgc accgcccgaa gggtggccgt taggccagtt   1860
tctcgaagcg aaacccgtaa gtgcgccctc ccctacaacg tagggacggg attgccgccg   1920
atgacgatcc atgacagccc aagacgaagc aaataaaaca tggggcgtcc agatggttac   1980
ggggcgaacc aagggcgcgg atcggctggc aacgccagca gacccaacgc agcgaatacc   2040
tgccgaaatt cagccggagc gggcaaggga acagcagcaa gagccgaaga acgaaacaag   2100
gcgcaaggtc ctggcggggc ccatgatttt ggccaaggtc aacagcagcg agtggccgga   2160
ggacacggct atggcggcca tggacgcgta ccttgaacgc gacccacgac gcgccctgtt   2220
cggactgccg ccacgccaga aggacggacc gggcaggaat atcgacccga acaggccctg   2280
agggggtgca aacgcgaccc aacccatcgg gtacggggca aggccgatcc agcggctacc   2340
agcgctaacg agtacttctg aggggattgg tgtgggattc agcgggcttt gaccgcattt   2400
cccactgccg cgcagcggtg gggcggtgtg tagccagccg cagccaatag accagctatc   2460
cggcctctgg ccgggcatac tgggcaaggg cagcagcgcc ccacaagggc gctgatcaac   2520
gcgcctagtg gattattcta agataatcaa ggatggatta ttccaacacc ccgccagccc   2580
ccgcccctgc tgggattgca ggttaggggg cgtgacagta attgcagggg ttcgagacag   2640
ttacagacgg ggggcgtgac agttactgca ggggacagtg aacgacagtc agggagtgcc   2700
gggcactggc tggcaatgtc tagcaacggc aggcatttcg gctgagggta aaagaacttt   2760
ccgctaaggc atagactgta tgtaaacaca gtattgcaag gacgccgaac atgcctcatg   2820
tggcggccag gacggccagc cgggaacggg atacaggtcg ttacccagac cacccgaccg   2880
agcaaaccca tctcaatcag atcgaagacg agtaaaaccc ggcaaacgct gcgcaaatgg   2940
aagacaaggc aaacgaattg aagggctatg tgcaacggga atttgaagcc tttcacaact   3000
gagggaggca ggagcatggc tttcaagggc ttcgccgaga gtctgaaacc gacgagaacc   3060
tggccgattc aagcaatcca tatcaagtca atatgagtca aattggtatg aacggcaact   3120
gaattcgcat ctagactgat gagacgtggc agagccacaa acagccggta caagcaacga   3180
tatccaggac aatccgaatc atgcgcggca gaccggaacc aacgacgggc atcacagacc   3240
ttaaccccaa gtacagaccc tgcgacaacg tggcaattcg tcgcaatacc acgtaacggg   3300
attccaatcc aatcgattcg agatagtacc agcccgtgcc tgcccgaact tatcgcgagt   3360
tataacccat ttatacccat ataaatcagc atccatgttg gaatttaatc gcgtgagcct   3420
atgcaacggg cttcccatac aatcgattag agattgtcac cgcacctgat tgcccgacat   3480
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-continued

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tatcgagagc tattaaactt tttataccct attaattagc atcaatgttg gacttttatc    3540
gagagagcca tacgtaatcg ttattccgca aattacgtta aatcccgatt aggcgggttt    3600
ttttatgggg ggagtttagg gaaagagcat ttgtcagctg gaaatctgct cgtcagtggt    3660
gctcacactg acgaatcatg tacagatcat acggatgact gcctgggcga tcacaactaa    3720
gcaagaacgc cggaaccagc gccggcgaac accacctgca atatggcata ttcacaacgt    3780
ccacgtctca agccgttaca gagactgttc gaacccactg tgcacctgcg tacaccaggc    3840
atcaaatata acgtaaggct aagtcgaacg aatgggaatc tagtattatc tgttgattgt    3900
aggtgaaagc tatctaatag agtcacactg gatcacattc gggtggcact ttatgcgttt    3960
ataccgagcg gccgcgtgtt acaaccaatt aaccaattct gattagaaaa actcatcgag    4020
catcaaatga aactgcaatt tattcatatc aggattatca ataccatatt tttgaaaaag    4080
ccgtttctgt aatgaaggag aaaactcacc gaggcagttc cataggatgg caagatcctg    4140
gtatcggtct gcgattccga ctcgtccaac atcaatacaa cctattaatt tcccctcgtc    4200
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caaaagctta tgcatttctt tccagacttg ttcaacaggc cagccattac gctcgtcatc    4320
aaaatcactc gcatcaacca aaccgttatt cattcgtgat tgcgcctgag cgagacgaaa    4380
tacgcgatcg ctgttaaaag gacaattaca aacaggaatc gaatgcaacc ggcgcaggaa    4440
cactgccagc gcatcaacaa tattttcacc tgaatcagga tattcttcta atacctggaa    4500
tgctgttttc ccggggatcg cagtggtgag taaccatgca tcatcaggag tacggataaa    4560
atgcttgatg gtcggaagag gcataaattc cgtcagccag tttagtctga ccatctcatc    4620
tgtaacatca ttggcaacgc tacctttgcc atgtttcaga aacaactctg gcgcatcggg    4680
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What is claimed is:

**1**. A microbial composition comprising one or more bacteria genetically engineered to express at least one heterologous nucleic acid, wherein the one or more bacteria are native to the microbiome of a host insect.

**2**. The composition of claim **1**, wherein the host insect is selected from the group consisting of a honey bee and a bumble bee.

**3**. The composition of claim **1**, wherein the one or more bacteria are selected from the group consisting of *Snodgrassella alvi*, *Bartonella apis*, *Gilliamella apicola*, *Serratia marcescens*, *Parasaccharibacter apium*, and *Lactobacillus* sp.

**4**. The composition of claim **1**, wherein the composition comprises 2, 3, 4, or 5 bacterial species.

**5**. The composition of claim **1**, wherein the one or more bacteria express at least two heterologous nucleic acids.

**6**. The composition of claim 1, wherein the heterologous nucleic acid encodes a polypeptide that improves the health of a host insect.

**7**. The composition of claim **6**, wherein the heterologous nucleic acid encodes a pesticide degrading polypeptide or a cytochrome.

**8**. The composition of claim 1, wherein the heterologous nucleic acid is an inhibitory nucleic acid.

**9**. The composition of claim **8**, wherein the inhibitory nucleic acid is selected from the group consisting of an antisense DNA, dsRNA, siRNA, shRNA, sgRNA and a miRNA.

**10**. The composition of claim 1, wherein at least one heterologous nucleic acid is a broad host range plasmid.

**11**. The composition of claim **10**, wherein the broad host range plasmid comprises at least one regulatory sequence selected from the group consisting of an RSF1010 origin of replication, a PA1 promoter sequence, a PA2 promoter sequence, a PA3 promoter sequence, a cp25 promoter sequence, and a detectable marker.

**12**. The composition of claim 1, wherein the composition is a bee-ingestible composition.

**13**. The composition of claim **12**, wherein the composition comprises at least one selected from the group consisting of: the bacteria are present as a live suspension, the bacteria are present as a lyophilized powder, the composition is in solid form, the composition is in liquid form, the composition comprises protein, the composition comprises pollen, the composition is a sucrose solution, and the composition is a corn syrup solution.

**14**. The composition of claim **13**, further comprising a carbohydrate or sugar supplement.

**15**. An insect comprising the composition of claim 1.

**16**. The insect of claim **15**, wherein the insect is a honey bee.

**17**. A method for producing composition of claim 1, comprising transfecting said bacterial species with an expression cassette comprising at least one heterologous nucleic acid.

**18**. A method for downregulating expression of a target gene product, comprising administering an effective amount of a composition of claim **1** to an insect, wherein said bacteria express an inhibitor of said target gene product.

**19**. The method of claim **18**, wherein the target gene product is a gene from an organism selected from the group consisting of a pathogen, a parasite, a virus, a mite, Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, Deformed Wing Virus, *Varroa destructor* mite, and Small Hive Beetle.

**20**. The method of claim **18**, wherein the insect is selected from the group consisting of a bee, a honey bee, a forager, a hive bee, a pupae, an adult bee, and a bee colony parasite.

**21**. The method of claim **18**, wherein the target gene is selected from the group consisting of TOM70, TIM22, TOM40, Imp2, mitochondrial Hsp70, ATM1-ABC transporter proteins, Frataxin, Ferredoxin, ERV1, ferredoxin, NADPH oxido-reductase [FNR], pyruvate dehydrogenase α subunit, pyruvate dehydrogenase β subunit, mitochondrial glycerol-3-phosphate dehydrogenase (mtG3PDH), manganese-containing superoxide dismutase (MnSOD), DNAJ (Hsp70 interacting), Iron Sulfur cluster ISU1, Cystein desulfurase Nfl1, NAR1, RLI1, ATPase subunit A, RNA polymerase I, RNA polymerase III, Inhibitor of apoptosis (IAP), and FAS apoptotic.

**22**. A method for reducing the susceptibility of a bee to a disease or disorder selected from the group consisting of Colony Collapse Disorder (CCD) and infection, comprising administering an effective amount of a composition of claim 1 to said bee, wherein said bacteria express an inhibitor of a pathogen or parasite specific gene product.

**23**. The method of claim **22**, wherein the pathogen or parasite is selected from the group consisting of Acute Bee Paralysis Virus (ABPV), Kashmir Bee Virus (KBV), Israeli Acute Paralysis Virus (IAPV), *Nosema ceranae*, *Nosema cerana*, *Nosema apis*, Deformed Wing Virus, and *Varroa destructor* mite.

**24**. The method of claim **22**, wherein the bacteria express at least two non-contiguous dsRNAs downregulating expression of a pathogen or parasite specific gene product.

**25**. A method for reducing the susceptibility of a bee colony to infestation by the Small Hive Beetle, comprising administering an effective amount of a composition of claim **1** to hive components, wherein said bacteria express an inhibitor of a Small Hive Beetle specific gene product.

**26**. The method of claim **25**, wherein the bacteria express at least two non-contiguous dsRNAs downregulating expression of a Small Hive Beetle specific gene product.

**27**. A method for expression of a heterologous nucleic acid sequence in a bee, the method comprising administering to the bee at least one modified *Snodgrassella alvi* bacterium comprising an expression plasmid for expression of the heterologous nucleic acid sequence.

**28**. The method of claim **27**, wherein the heterologous nucleic acid sequence encodes a molecule selected from the group consisting of a protein, a peptide, an antisense DNA, an inhibitory RNA, a dsRNA, a siRNA, a shRNA, a sgRNA and a miRNA.

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