US 20150045412A1

(54) **USE OF THE CHROMOSOME 19 MICRORNA CLUSTER (C19MC) FOR TREATING MICROBIAL DISEASE AND PROMOTING AUTHOPHAGY**

(71) Applicant: **University of Pittsburgh - Of the Commonwealth System of Higher Education**, Pittsburgh, PA (US)

(72) Inventors: **Yoel Sadovsky**, Pittsburgh, PA (US); **Carolyn Coyne Candrilli**, Jefferson Hills, PA (US)

Publication Classification

(51) **Int. Cl.**
      C12N 15/113 (2006.01)
(52) **U.S. Cl.**
      CPC *C12N 15/1131* (2013.01); *C12N 15/1132* (2013.01); *C12N 15/1133* (2013.01); *C12N 2310/141* (2013.01)
      USPC .... **514/44 A**; 435/375; 514/44 R

(57) **ABSTRACT**

It is disclosed herein that cultured primary placental human trophoblast (PHT) cells are highly resistant to infection by a number of disparate viruses, and confer this resistance to non-placental recipient cells by exosome-mediated delivery of microRNAs (miRs). PHT cells express high levels of unique, primate-specific miRNAs, expressed from the chromosome 19 miRNA cluster (C19MC). It is further disclosed herein that C19MC miRNAs are packaged within PHT-derived exosomes and attenuate viral replication in recipient cells by inducing autophagy. Thus, provided herein are methods of inhibiting, treating or preventing microbial infections by administering one or more miRs of the C19MC. Also provided are methods of inducing autophagy in a cell by contacting the cell with one or more miRs of the C19MC.

FIG. 1A
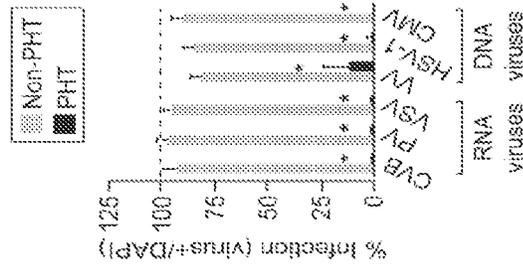
FIG. 1B
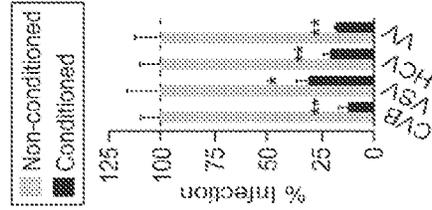
FIG. 1C
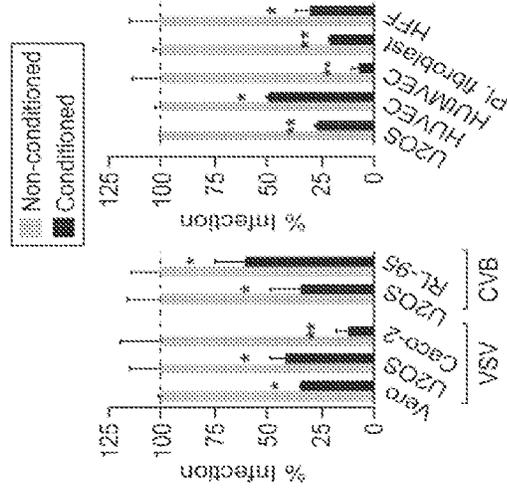
FIG. 1D
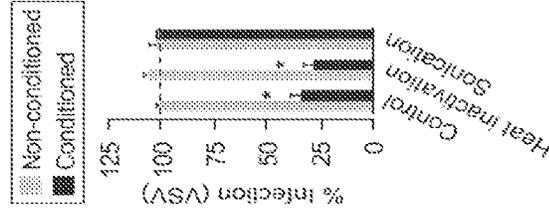
FIG. 1E
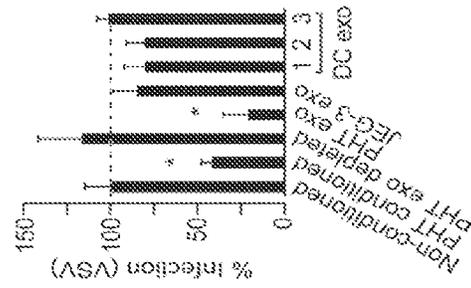
FIG. 2A
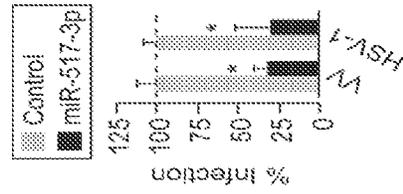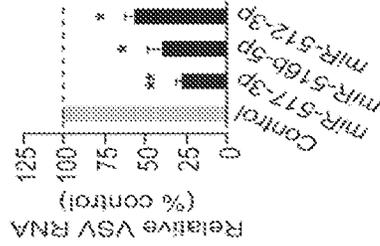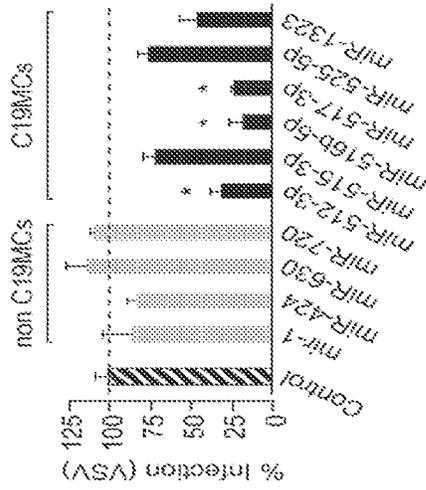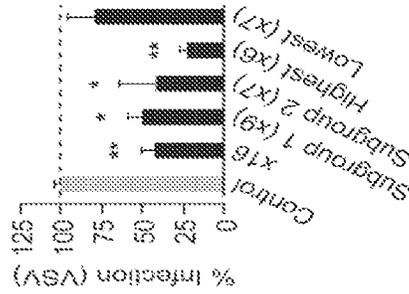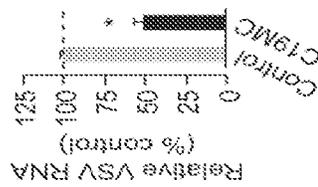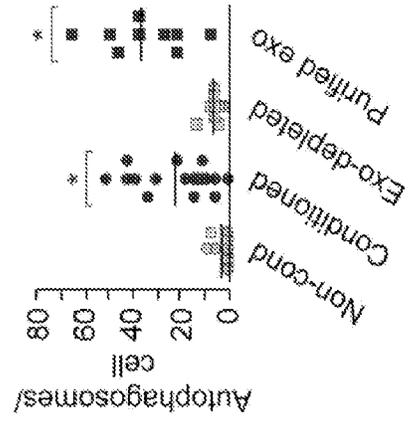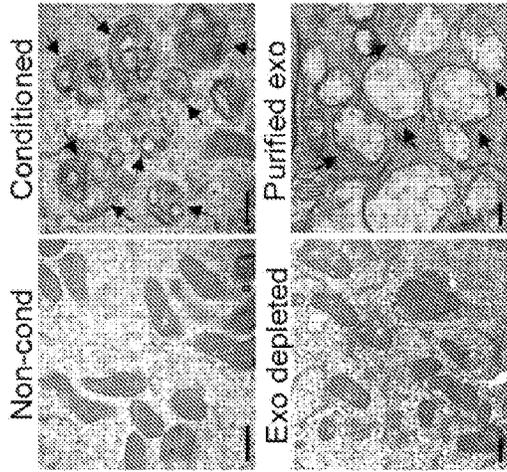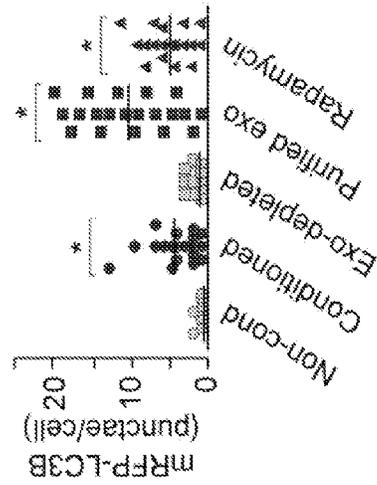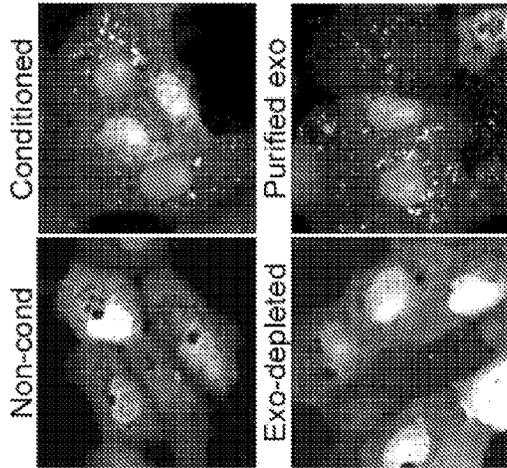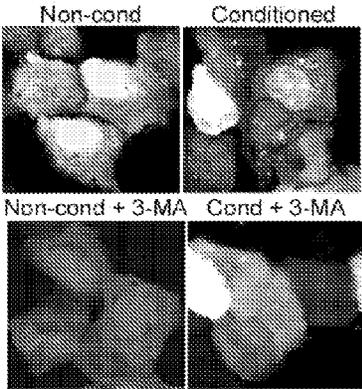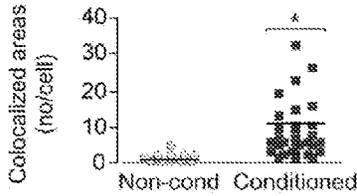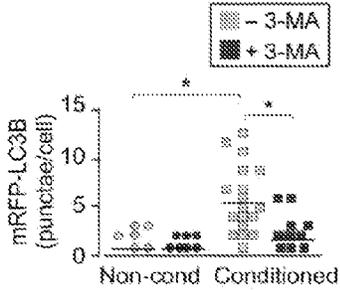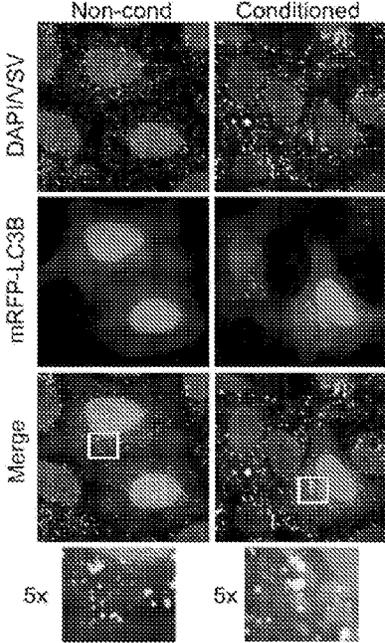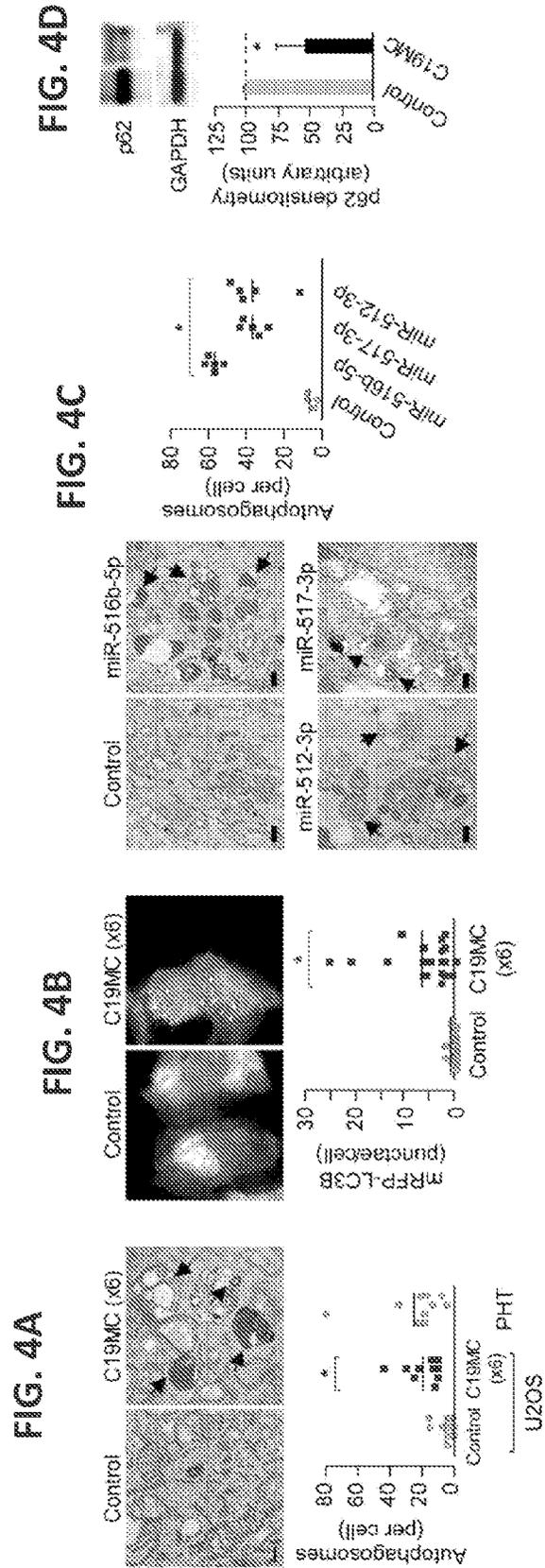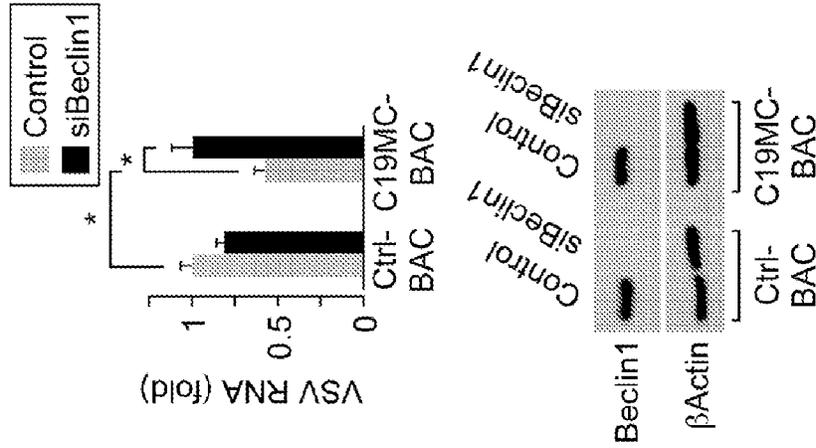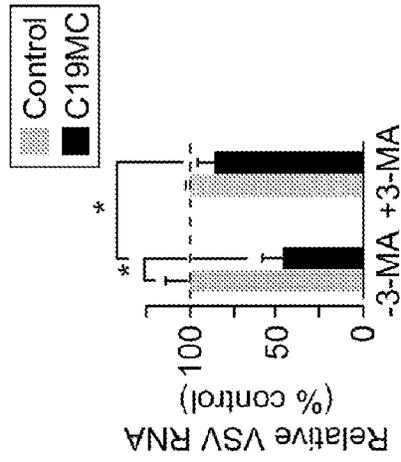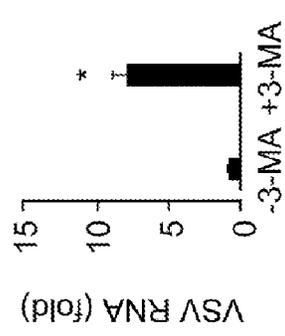
FIG. 2B

FIG. 2C

FIG. 2D

FIG. 2E

FIG. 3A

FIG. 3B

FIG. 3C

FIG. 3D

FIG. 4D

FIG. 4C

FIG. 4B

FIG. 4A

FIG. 5B

FIG. 5A

FIG. 5C

FIG. 6C

VSV Titer (pfu/ml)

6.0E+07
4.0E+0.7
2.0E+0.7
0

Cond

Non-cond

FIG. 6B

% Infection (VSV)

125
100
75
50
25
0

Cond

Non-cond

FIG. 6A

Mock 10⁻⁹ 10⁻⁸ 10⁻⁷ 10⁻⁶ 10⁻⁵ 10⁻⁴ 10⁻³ 10⁻²

Non-cond
1
2
3

Cond
1
2
3

FIG. 6E

FIG. 6D

FIG. 6C

FIG. 6H

FIG. 6G

FIG. 6F

FIG. 7A

FIG. 7B

FIG. 7C

FIG. 7D

FIG. 8

FIG. 9

TZM with conditioned media n=2
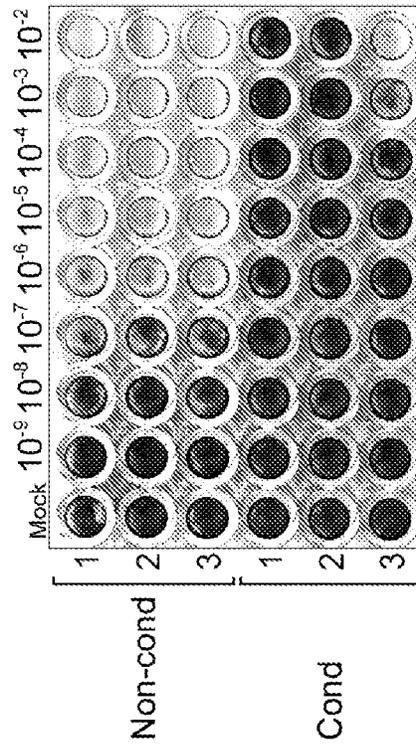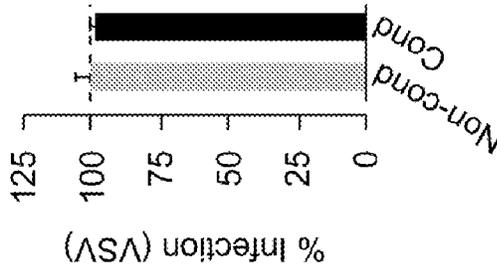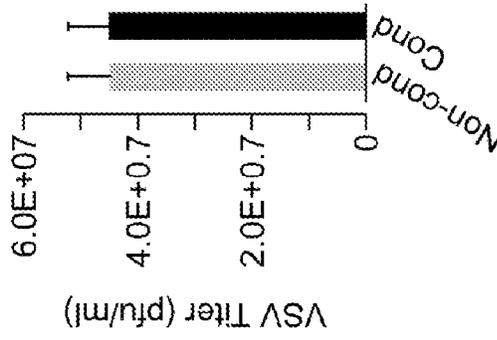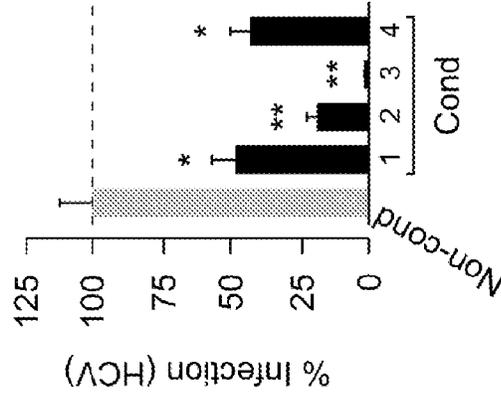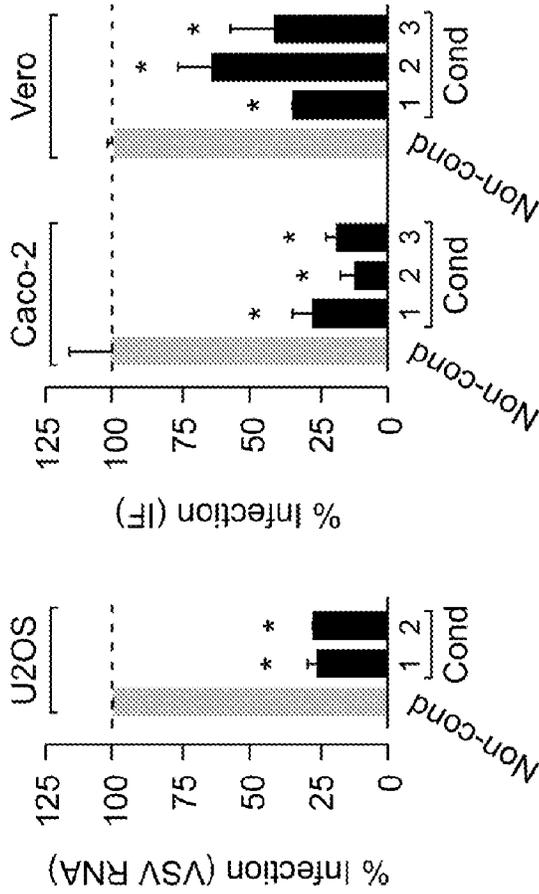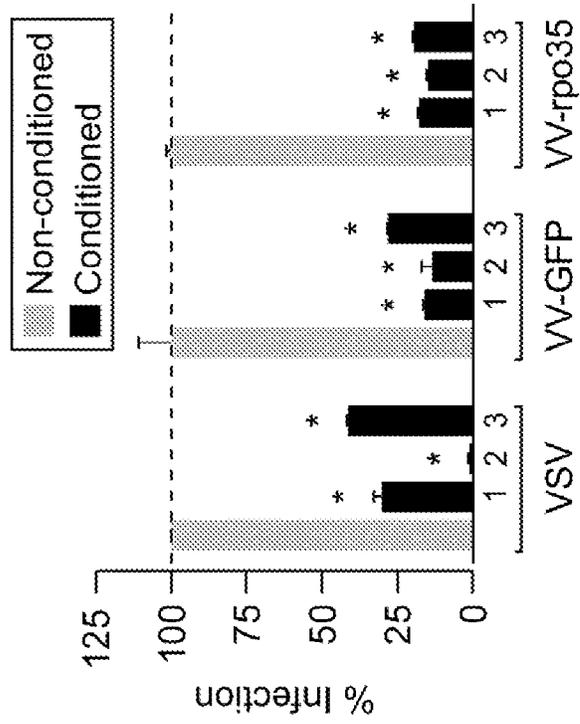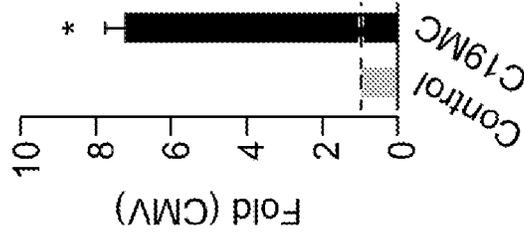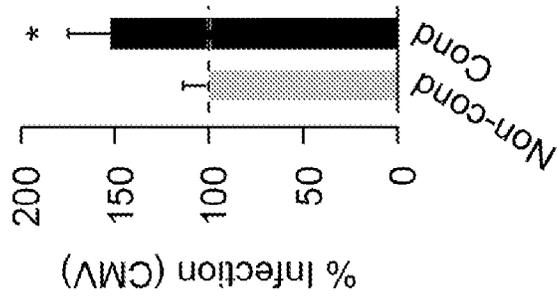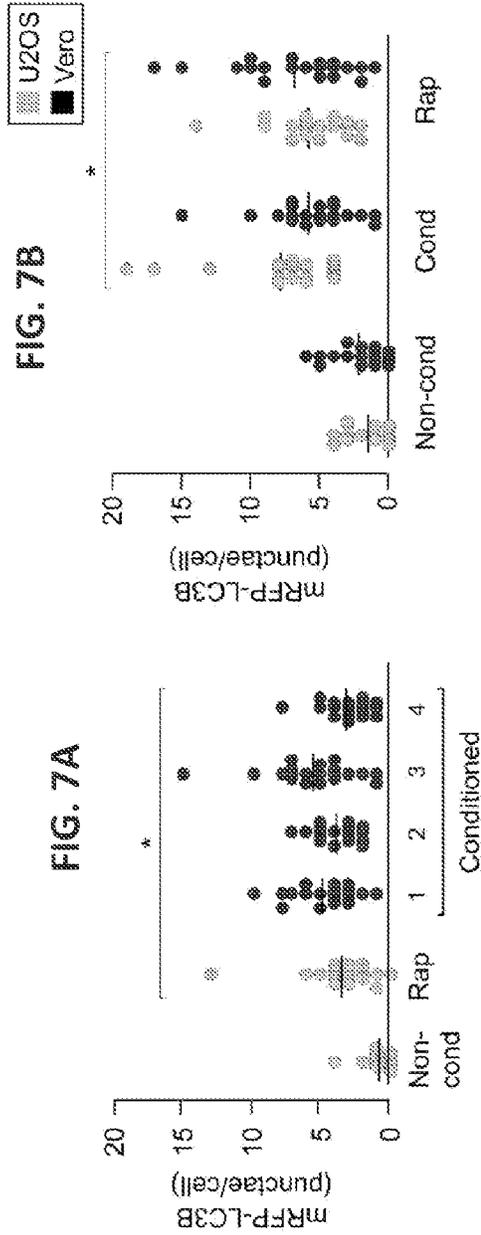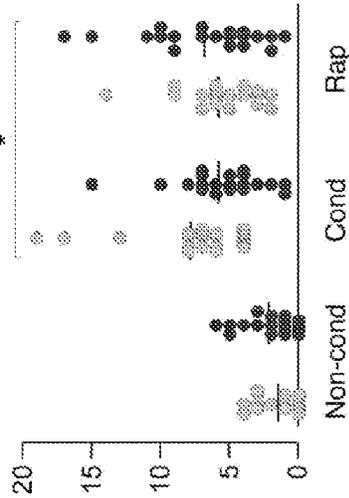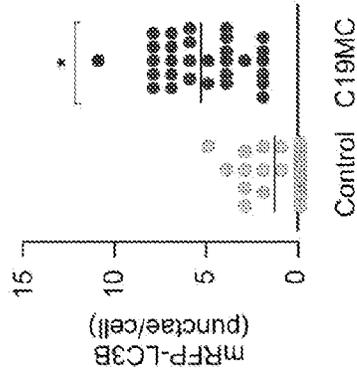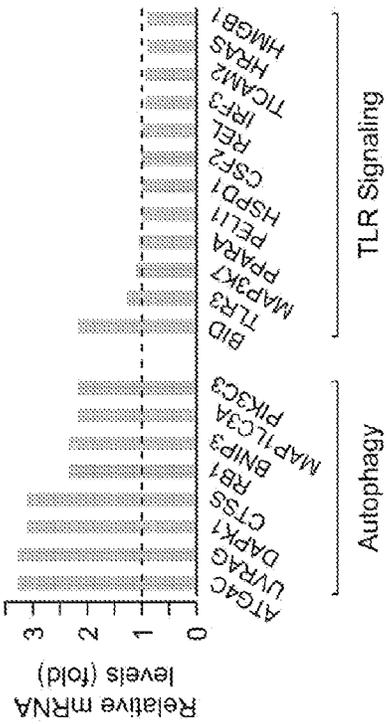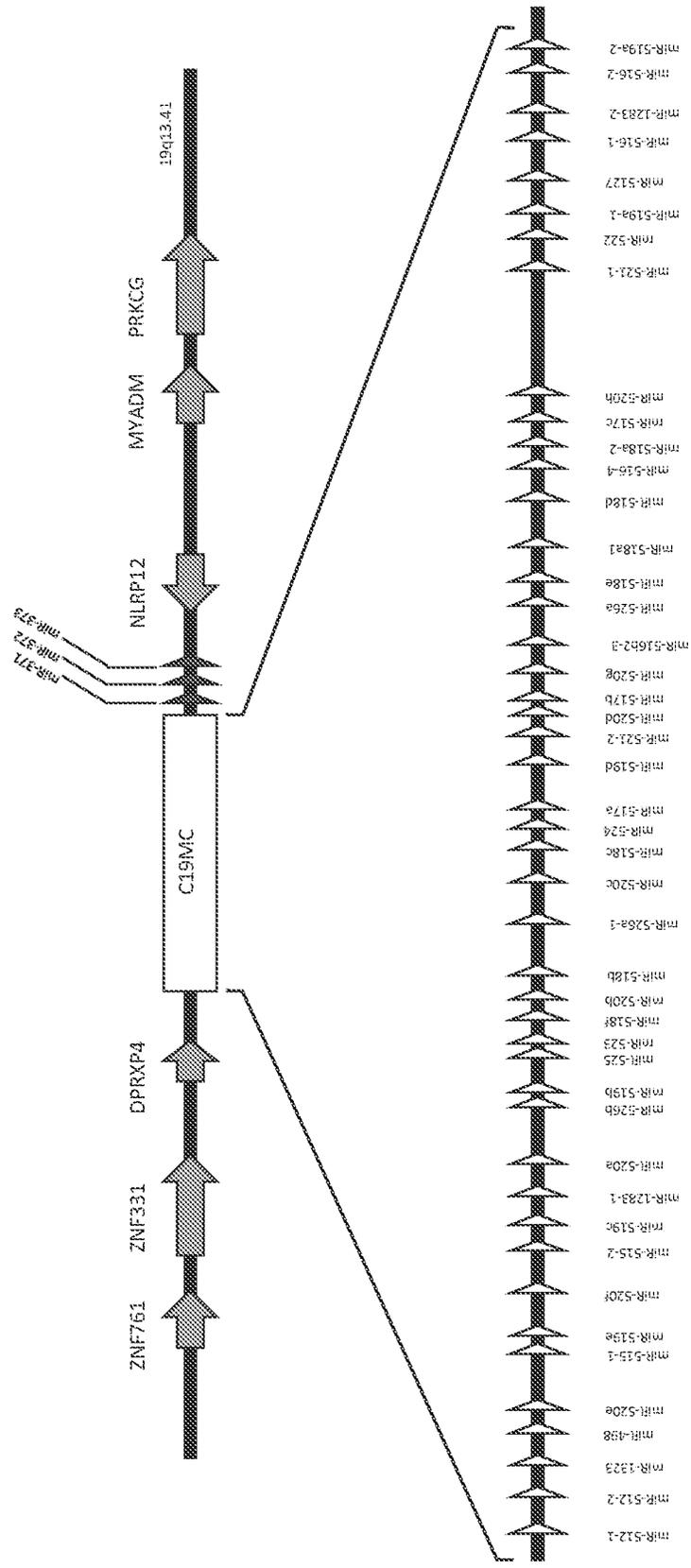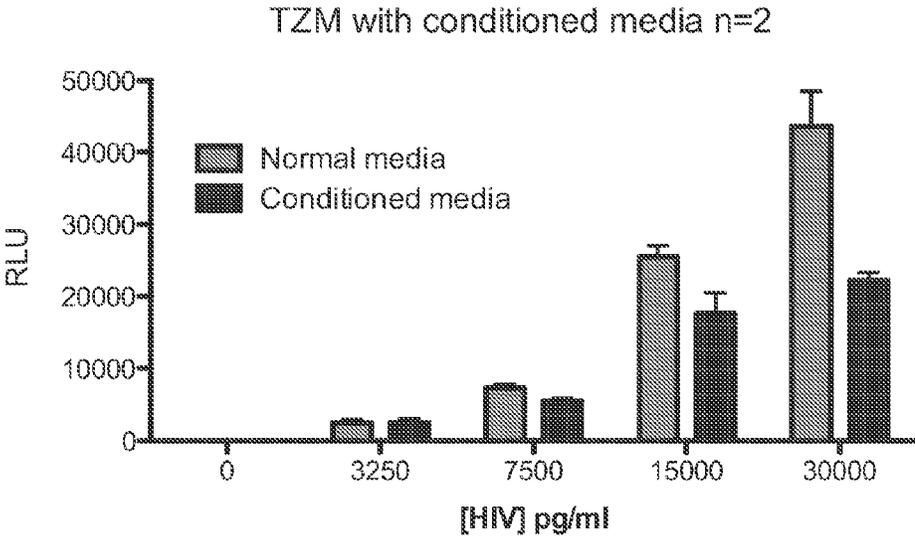
FIG. 10
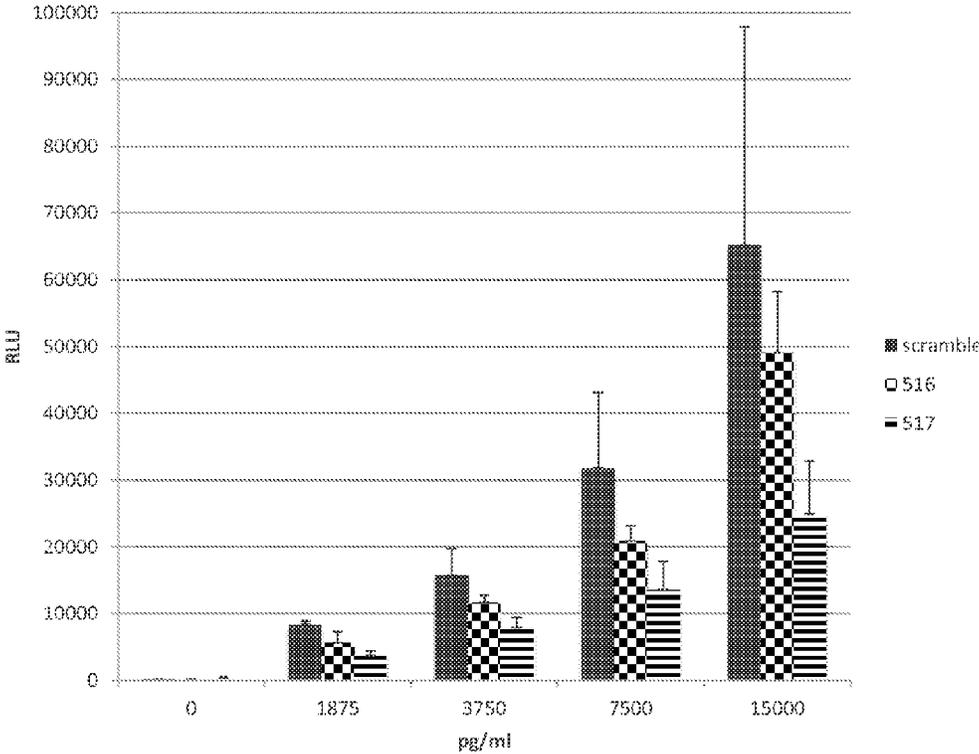
USE OF THE CHROMOSOME 19 MICRORNA CLUSTER (C19MC) FOR TREATING MICROBIAL DISEASE AND PROMOTING AUTHOPHAGY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/607,899, filed Mar. 7, 2012, which is herein incorporated by reference in its entirety.

ACKNOWLEDGMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant numbers A1081759 and HD065893 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

[0003] This disclosure concerns the use of microRNAs encoded by the primate-specific chromosome 19 miRNA cluster (C19MC) for the prophylaxis and/or treatment of microbial infection and diseases associated with autophagy.

BACKGROUND

[0004] Strategies to reduce the risk of fetal infection are of critical importance during pregnancy, where maternal to fetal transmission of microbes can have devastating consequences to the developing embryo, ranging from fetal infection, induced preterm delivery, structural or functional congenital anomalies, miscarriages and stillbirths (Ornoy and Tenenbaum, *Reprod Toxicol* 21, 446-457, 2006; Silingardi et al., *Am J Forensic Med Pathol* 30, 394-397, 2009; Euscher et al., *Obstet Gynecol* 98, 1019-1026, 2001). Additionally, pathogenic infections can compromise maternal health and jeopardize the pregnancy even in the absence of fetal transmission. The physical barrier interfacing the maternal and fetal blood systems within human hemochorial placenta villi include the trophoblast bilayer, basement membrane, stromal cells and fetal capillary endothelial cells. The multinucleated, terminally differentiated villous syncytiotrophoblasts are bathed directly in the maternal blood, and mediate the crucial exchange of gases, nutrients, and waste products between the mother and fetus, produce crucial hormones, and immunologically guard the developing fetus. These cells, along with the less differentiated cytotrophoblasts, constitute the first line of feto-placental defense against invading microbes.

[0005] Intrauterine transmission of viruses is likely to occur by at least four potential routes: (a) transmission across the placental villous trophoblasts by hematogenous spread or ascending infection, (b) placental transfer of infected macrophages from the maternal blood, (c) transfer of viruses via paracellular routes and/or (d) transmission of viruses from the infected maternal endothelial microvasculature to endovascular extravillous cytotrophoblasts. In general, little is known regarding the defense mechanisms employed by placental trophoblasts to defend against viral infections. Additionally, as antiviral therapeutics are generally ineffective in preventing intrauterine viral infections, elucidating the nature of these mechanism(s), as well as the underpinnings of viral counter-measures, is critical for designing therapeutic strategies aimed at preventing fetal and maternal viral disease.

[0006] Mammalian cells utilize diverse defense mechanisms to combat microbial pathogens. One crucial mechanism is the induction of autophagy, an evolutionarily conserved lysosomal degradation pathway that has been associated with an array of cellular functions, including cell death (Beaulation and Lockshin, *J Morphol* 154:39-57, 1977; Liang et al., *Nature* 402:672-676, 1999), tumorigenesis (Qu et al., *J Clin Invest* 112:1809-1820, 2003), and neurodegeneration (Hara et al., *Nature* 441:885-889, 2006; Komatsu et al., *Nature* 441:880-884, 2006). Autophagy also degrades intracellular foreign microbial invaders (a process sometimes referred to as xenophagy or virophagy). The cascade of events that culminate in autophagy begin with the formation of a double membrane organelle, the autophagosome, and ends in the degradation of engulfed material via the fusion of autophagosomes with late endosomes and/or lysosomes. The degradation of microbes via the fusion of autophagosomes with lysosomes is a key component in the antimicrobial effects of autophagy, yet the sequestration of viruses into autophagosomes can also direct MHC class II presentation (English et al., *Nat Immunol* 10:480-487, 2009), the production of antiviral type I interferons downstream of toll-like receptor 7 engagement (Lee et al., *Science* 315:1398-1401, 2007), and even altered T-cell signaling (Nedjic et al., *Nature* 455:396-400, 2008). It is becoming clear that autophagy functions at the crossroads of many aspects of cell survival, and is likely a fundamental component of antiviral signaling.

SUMMARY

[0007] It is disclosed herein that microRNAs (miRs) of the C19MC cluster promote viral resistance and induce autophagy of recipient cells.

[0008] Provided herein is a method of inhibiting or treating a microbial infection in a subject by selecting a subject with a microbial infection or at risk for contracting a microbial infection; and administering to the subject a therapeutically effective amount of one or more miRs encoded by the C19MC, thereby inhibiting or treating the microbial infection. In some embodiments, the one or more miRs are administered by administering a nucleic acid molecule encoding the entire C19MC or a biologically active portion thereof, for example a portion that encodes one or more miRs that promote viral resistance and induce autophagy. In non-limiting examples, the one or more miRs include miR-517-3p, miR-1323, miR-516b-5p, miR-525-5p, miR-512-3p, or miR-515-3p, or any combination thereof.

[0009] Also provided herein is a method of inducing autophagy in a cell by contacting the cell with an effective amount of one or more miRs encoded by the C19MC, thereby inducing autophagy in the cell. In some embodiments, the method is an in vitro method. In other embodiments, the method is an in vivo method that includes administering to a subject an effective amount of one or more miRs encoded by the C19MC, or a nucleic acid molecule encoding the C19MC or a biologically active portion thereof. In non-limiting examples, the subject suffers from a disease associated with a deficiency in autophagy and/or a disease that may be ameliorated by enhancing autophagy.

[0010] The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIGS. 1A-1E: Conditioned primary human tropho-blast (PHT) medium and exosomes confer viral resistance to recipient cells. (FIG. 1A) PHT or non-PHT cells were infected with a panel of viruses, including coxsackievirus B (CVB), poliovirus (PV), vesicular stomatitis virus (VSV), vaccinia virus (VV), herpes simplex virus-1 (HSV-1), or cytomegalovirus (CMV). Non-PHT cells were as follows: HeLa (CVB, PV), U2OS (VSV, HSV-1, and VV), and human foreskin fibroblasts (HFF, CMV). Shown are the percent infected cells (assessed by immunofluorescence (IF); *p<0. 0001). (FIG. 1B) Non-PHT recipient cells were exposed for 24 h to non-conditioned or conditioned PHT medium, and then infected with CVB, VSV, HCV, or VV. Non-PHT cells were as follows: HFF (CVB), U2OS (VSV, VV), and Huh 7.5 (HCV). Shown are the percent of infected cells, assessed by IF (CVB, VSV), luciferase assay (HCV), or RT-qPCR (VV); *p<0.05, **p<0.005. (FIG. 1C, left) Cells were exposed to non-conditioned or conditioned PHT medium for 24 h, then infected with VSV or CVB. (FIG. 1C, right) Primary cells were infected with VSV following exposure to non-conditioned or conditioned PHT medium (*p<0.05, **p<0.005). (FIG. 1D) Conditioned PHT medium was subjected to heat inactivation or sonication prior to 24 h exposure to Vero cells, then infected with VSV. Percent infection assessed as in (A); (*p<0.0001). (FIG. 1E) U2OS cells were exposed for 24 h to non-conditioned, conditioned, exosome-depleted conditioned medium, exosomes purified from PHT, JEG-3, or from three preparations of murine dendritic cell (DC), and then infected with VSV. Percent infection assessed as in (A); (*p<0.0005), each PHT exosome preparation was derived from a different placental preparation.

[0012] FIGS. 2A-2E: PHT and exosomal C19MC miRNAs confer viral resistance to recipient cells. (FIG. 2A) U2OS cells stably expressing control- or C19MC-bacterial artificial chromosome (BAC) were infected with VSV (infection levels assessed by RT-qPCR, *p<0.0001). (FIG. 2B) U2OS cells were transfected with C19MC miRNA mimics that represent the miRNA sub-groups detailed in Table 2 or control mimics, and then infected with VSV (shown as percent infected cells, assessed by IF; *p<0.05, **p<0.001). (FIG. 2C) U2OS cells, transfected with mimics of the six highest expressed C19MC miRNAs, scrambled control, or non-C19MC (miR-1, -424, -630, -720) miRNA mimics, were infected with VSV (infection level assessed by IF or qPCR; *p<0.0005). (FIG. 2D) U2OS cells, transfected with mimics of the top three antiviral C19MC miRNAs or with scrambled control mimics, were infected with VSV (infection assessed by RT-qPCR; *p<0.05, **p<0.0001). (FIG. 2E) U2OS cells, transfected with scrambled control or miR-517-3p mimic, were infected with VV or HSV-1; infection assessed as in (D) (*p<0.0001).

[0013] FIGS. 3A-3D: PHT-derived exosomes induce autophagy in recipient cells. (FIG. 3A) U2OS cells trans-fected with mRFP-LC3b were exposed to non-conditioned-, PHT conditioned-, exosome-depleted conditioned PHT medium, or purified PHT exosomes for 24 h, and LC3b punc-tae formation was assessed by confocal microscopy. Shown are confocal micrographs (top) and quantification of mRFP-LC3b punctae per cell (bottom) (*p<0.0001). (FIG. 3B, top) Electron micrographs of cells exposed to non-conditioned or conditioned PHT medium (Vero), exosome-depleted condi-tioned PHT medium (Vero), or purified PHT exosomes (U2OS). Arrows denote autophagosomes. Bar=500 nm. (FIG. 3B, bottom) Quantification of electron micrographs of

cells exposed to non-conditioned (Vero and U2OS), condi-tioned PHT media samples (Vero and U2OS), exosome-de-pleted conditioned medium (Vero), or purified PHT exo-somes (U2OS) (*p<0.0001). (FIG. 3C) U2OS cells transfected with mRFP-LC3b were exposed to non-condi-tioned or conditioned PHT medium in the absence or pres-ence of 3-methyladenine (3-MA) for 8 h, and LC3b punctae formation was assessed by confocal microscopy. Shown are confocal micrographs (top) and quantification of mRFP-LC3b punctae (bottom) (*p<0.0005). (FIG. 3D, top) Immu-nofluorescence images of VSV entry into U2OS cells tran-siently transfected with mRFP-LC3b exposed to non-conditioned (left) or conditioned (right) PHT medium (inset, 5× magnification). (FIG. 3D, bottom) Quantification of the extent of colocalization between VSV particles and mRFP-LC3B positive punctae (*p<0.0001).

[0014] FIGS. 4A-4D: C19MC miRNAs induce autophagy. (FIG. 4A, top) Electron micrographs of U2OS cells trans-fected with scrambled control or the six highest expressed C19MC miRNA mimics (Table 2). Black arrows denote autophagosomes and/or autolysosomes. Bar=500 nm. (FIG. 4A, bottom) Quantification of electron micrographs shown at top (*p<0.005), or in PHT cells. (FIG. 4B) U2OS cells were transfected with mRFP-LC3b and either scrambled control or the six highest expressed C19MC miRNA mimics. Shown are confocal micrographs (top) and quantification of mRFP-LC3b punctae per cell (bottom) (*p=0.0005). (FIG. 4C, left) Electron micrographs of U2OS cells transfected with scrambled control or the most potent antiviral miRNA mim-ics. Black arrows denote autophagosomes and/or autolysos-omes. Bar=500 nm. (FIG. 4C, right) Quantification of adja-cent electron micrographs (*p<0.005). (FIG. 4D, top) A representative immunoblot for p62 or GAPDH in U2OS cells stably transfected with either control Del- or C19MC-BAC. (FIG. 4D, bottom) Densitometry of p62 levels (normalized to GAPDH) from three independent immunoblots as described above (*p<0.05).

[0015] FIGS. 5A-5C: Suppression of autophagy restores C19MC-medated antiviral effects. (FIG. 5A) U2OS cells transfected with scrambled control or miRNA mimics of the six most prevalent C19MC miRNA mimics. Cells were exposed to 3-MA before and during VSV infection. Relative VSV RNA was analyzed by RT-qPCR (*p<0.0005). (FIG. 5B, top) U2OS cells stably expressing control- or C19MC-BAC transfected with scrambled control siRNA or beclin-1 siRNA for 72 h were infected with VSV, and relative infection was determined by RT-qPCR (*p<0.05, determined using ANOVA with Bonferroni correction). (FIG. 5B, bottom) Immunoblots for beclin-1 or actin in cells transfected as described above. (FIG. 5C) PHT cells were treated with 3-MA for 60 min prior to infection with green fluorescent protein (GFP)-VSV (in the presence of 3-MA). Relative VSV RNA was analyzed by RT-qPCR (*p<0.005). Data are repre-sentative of four independent experiments.

[0016] FIGS. 6A-6H: Medium from different preparations of PHT cells confers an antiviral effect on recipient cells. (FIG. 6A) Tissue culture infectious dose 50 (TCID50) assays for VSV in Vero cells pretreated for 24 h with non-condi-tioned medium (top, in triplicate) or three independent prepa-rations of conditioned PHT medium (bottom). Cells were infected in the indicated dilution of virus in the presence of non-conditioned or conditioned medium for approximately 40-45 h and then stained with crystal violet. (FIG. 6B) Vero cells were exposed to non-conditioned (Non-cond) or condi-

tioned (Cond) medium isolated from BeWo cells for 24 h and then infected with VSV. Shown is the percent of infected cells (as assessed by IF). (FIG. **6C**) VSV was incubated in non-conditioned or conditioned PHT medium (in the absence of cells) for 1 h at 37° C. then a plaque assays performed. Shown are VSV titers (in pfu/mL). (FIG. **6D**, left) U2OS cells were exposed to non-conditioned (Non-cond) or conditioned media (Cond) from two independent PHT preparations and infected with VSV. Relative VSV RNA was assessed by RT-qPCR (*p<0.0001). (FIG. **6D**, right) Caco-2 or Vero cells were exposed to conditioned (Cond) medium isolated from four independent preparations of PHT cells for 24 h prior to infection with VSV. Shown is the percent of infected cells (as assessed by IF; *p<0.0005). (FIG. **6E**) Huh7.5 cells were exposed to non-conditioned or conditioned medium isolated from four independent preparations of PHT cells for 24 h prior to infection with HCV. Shown is percent infection as assessed by luciferase assay (*p<0.005, **p≤0.0005). (FIG. **6F**) U2OS cells exposed to non-conditioned or conditioned PHT medium were infected with VSV or VV for approximately 6 h. Relative VSV or VV (early gene rpo35 or early gene GFP) RNA was assessed by RT-qPCR (*p<0.0001). (FIG. **6G**) HFF cells were exposed to non-conditioned (Non-cond) or conditioned (Cond) PHT media for 24 h before and during infection with CMV. Shown is the percent of infected cells (assessed by IF; *p<0.05). (FIG. **6H**) U2OS cells stably expressing control- or C19MC-BAC were infected with CMV, and infection levels assessed by RT-qPCR. Data are shown as fold-change over control (*p<0.0001). In all panels, data are displayed as mean±SD, and are representative of experiments performed a minimum of three times.

[0017] FIGS. **7A-7D**: Medium from PHT cells induces autophagy in recipient cells. (FIG. **7A**) Vero cells were transfected with mRFP-LC3b and at 24 h post-transfection were exposed for 24 h to either non-conditioned (Non-cond) or conditioned medium isolated from four independent PHT preparations. Cells were exposed to rapamycin (Rap) as a positive control. Shown are the levels of autophagic induction as determined by quantification of mRFP-LC3b positive punctae by confocal microscopy (*p<0.0001). (FIG. **7B**) Vero and U2OS cells were transfected with mRFP-LC3b and then exposed to non-conditioned (Non-cond) or conditioned PHT medium (Cond) 24 h post-transfection. Cells were exposed to rapamycin (Rap) as a positive control. Shown are the levels of autophagic induction as determined by quantification of mRFP-LC3b positive punctae by confocal microscopy (*p<0.0001). (FIG. **7C**) Relative mRNA levels in U2OS cells exposed to non-conditioned or conditioned PHT medium for 24 h, and analyzed using autophagy or toll-like receptor (TLR)-targeted RT-qPCR arrays. (FIG. **7D**) U2OS cells stably expressing a control- or C19MC-BAC were transfected with mRFP-LC3b, fixed after 48 h, and analyzed for mRFP-LC3b punctae by confocal microscopy (*p<0.0001).

[0018] FIG. **8** is a schematic of the genomic organization of the primate-specific C19MC.

[0019] FIG. **9** is a graph showing inhibition of human immunodeficiency virus (HIV) replication by medium from PHT cells. TZM-bl cells were pre-incubated with PHT conditioned medium or control medium for 24 h prior to infection with HIV-1. Cells were then infected with serial dilutions of HIV for 48 h, and infection levels were assessed by Tat-induced luciferase reporter gene expression, in triplicate. The results represent two independent experiments.

[0020] FIG. **10** is a graph showing inhibition of HIV replication in cells transfected with control (scrambled), miR-517-3p (517), or miR-516-5p (516) mimics. TZM-bl cells were transfected for 48 h prior to infection with HIV-1. Cells were then infected with serial dilutions of HIV for 48 h, and infection levels were assessed by Tat-induced luciferase reporter gene expression, in triplicate. The results represent one independent experiment, performed in triplicate.

SEQUENCE LISTING

[0021] The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three letter code for amino acids, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand. The Sequence Listing is submitted as an ASCII text file, created on Feb. 25, 2013, 217 KB, which is incorporated by reference herein. In the accompanying sequence listing:

[0022] SEQ ID NOs: 1-59 are nucleotide sequences of miRNAs found in the C19MC.

[0023] SEQ ID NO: 60 is the nucleotide sequence of the human genomic DNA insert in the BAC RP11-1055O17 clone containing region q13-42 of chromosome 19.

[0024] SEQ ID NOs: 61-82 are qPCR primers.

DETAILED DESCRIPTION

I. Abbreviations

[0025] BAC bacterial artificial chromosome
[0026] C19MC chromosome 19 microRNA cluster
[0027] CMV cytomegalovirus
[0028] Ct cycle threshold
[0029] CTB cholera toxin B
[0030] CVB coxsackievirus B
[0031] DAPI 4',6-diamino-2-phenylindole
[0032] DC dendritic cell
[0033] ELISA enzyme-linked immunosorbent assay
[0034] EM electron microscopy
[0035] FBS fetal bovine serum
[0036] GFP green fluorescent protein
[0037] hCG human chorionic gonadotropin
[0038] HCV hepatitis C virus
[0039] HFF human foreskin fibroblast
[0040] HIV human immunodeficiency virus
[0041] HSV herpes simplex virus
[0042] IF immunofluorescence
[0043] IFN interferon
[0044] ISRE interferon stimulated responsive element
[0045] 3-MA 3-methyladenine
[0046] miR microRNA
[0047] miRNA microRNA
[0048] MOI multiplicity of infection
[0049] PEI polyethylenimine
[0050] PHT primary human trophoblasts
[0051] PV poliovirus
[0052] RNAi RNA interference
[0053] RT-qPCR reverse transcriptase quantitative polymerase chain reaction
[0054] TCID50 tissue culture infectious dose 50
[0055] TLR toll-like receptor
[0056] VSV vesicular stomatitis virus

4

[0057] VV vaccinia virus

[0058] YFP yellow fluorescent protein

II. Terms and Methods

[0059] Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19-854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8).

[0060] In order to facilitate review of the various embodiments of the disclosure, the following explanations of specific terms are provided:

[0061] Administration: To provide or give a subject an agent, such as a therapeutic agent (e.g. a nucleic acid molecule or a microRNA), by any effective route. Exemplary routes of administration include, but are not limited to, injection (such as subcutaneous, intramuscular, intradermal, intraperitoneal, intrathecal and intravenous), oral, intraductal, sublingual, rectal, transdermal, intranasal, vaginal and inhalation routes.

[0062] Autophagy: A lysosomal degradation pathway that is one of the primary mechanisms for maintaining cellular homeostasis. Autophagy, which means "to eat oneself," is a self-cannibalization pathway that is known to be anti-microbial, functioning as a key innate immune pathway to degrade intracellular foreign microbial pathogens by a process termed antimicrobial autophagy or xenophagy. A diverse group of RNA and DNA viruses, bacteria and protozoa are sensitive to autophagy. Autophagy is also known to be deficient in a number of human diseases, such as inflammatory bowel disease, Crohn's disease, alcoholic liver disease, Parkinson's disease, Alzheimer's disease, heart disease, diabetes and obesity.

[0063] Chromosome 19 miRNA cluster (C19MC): A unique cluster of 46 primate-specific miRNA genes encoded by an approximately 100 kb region on chromosome 19 (19q13.41). The genomic organization of C19MC is shown in FIG. **8**. A list of the mature miRNAs (miRs) encoded by the genes in the cluster, as well as their sequences, is provided in section V below. In the context of the present disclosure, a "biologically active portion" of the C19MC refers to any portion of the cluster (or any single miR or combination of multiple miRs encoded by the C19MC) that confers increased viral resistance and/or autophagy in a cell. In the context of the present disclosure, an "inhibitory miR" is a miR encoded by the C19MC with anti-microbial activity (and/or the ability to induce autophagy in a cell). Thus, in some examples, an inhibitory miR is a miR that increases viral resistance and/or induces autophagy in a cell. In some embodiments, the inhibitory miR does not inhibit CMV (or does not increase viral resistance to CMV).

[0064] Contacting: Placement in direct physical association; includes both in solid and liquid form. As used herein, "contacting" is used interchangeably with "exposed." In some cases, "contacting" includes transfecting, such as transfecting a nucleic acid molecule into a cell.

[0065] Exosomes: Small (30-120 nm) endosome-derived membrane vesicles. Exosomes are enriched in miRNAs.

[0066] Isolated: An "isolated" biological component (such as a nucleic acid molecule, miRNA, protein, or cell) has been substantially separated or purified away from other biological components in the cell, blood or tissue of the organism, or the organism itself, in which the component naturally occurs, such as other chromosomal and extra-chromosomal DNA and RNA, proteins and cells. Nucleic acid molecules and proteins that have been "isolated" include those purified by standard purification methods. The term also embraces nucleic acid molecules and proteins prepared by recombinant expression in a host cell as well as chemically synthesized nucleic acid molecules and proteins.

[0067] Microbial infection: Infection by any type of microorganism, including viral, bacterial, fungal and protozoan infections. In some embodiments disclosed herein, the microbial infection is caused by any one of the following viruses, bacteria, fungi or protozoans:

[0068] Examples of viruses include, but are not limited to those in the following virus families: Retroviridae (for example, human immunodeficiency virus (HIV), human T-cell leukemia viruses; Picornaviridae (for example, poliovirus, hepatitis A virus, enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses, foot-and-mouth disease virus); Caliciviridae (such as strains that cause gastroenteritis, including Norwalk virus); Togaviridae (for example, alphaviruses (including chikungunya virus, equine encephalitis viruses, Simliki Forest virus, Sindbis virus, Ross River virus, rubella viruses); Flaviridae (for example, hepatitis C virus, dengue viruses, yellow fever viruses, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus and other encephalitis viruses); Coronaviridae (for example, coronaviruses, severe acute respiratory syndrome (SARS) virus; Rhabdoviridae (for example, vesicular stomatitis viruses, rabies viruses); Filoviridae (for example, Ebola virus, Marburg virus); Paramyxoviridae (for example, parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (for example, influenza viruses); Bunyaviridae (for example, Hantaan viruses, Sin Nombre virus, Rift Valley fever virus, bunya viruses, phleboviruses and Nairo viruses); Arenaviridae (such as Lassa fever virus and other hemorrhagic fever viruses, Machupo virus, Junin virus); Reoviridae (e.g., reoviruses, orbiviurses, rotaviruses); Birnaviridae; Hepadnaviridae (hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses, BK-virus); Adenoviridae (adenoviruses); Herpesviridae (herpes simplex virus (HSV)-1 and HSV-2; cytomegalovirus; Epstein-Barr virus; varicella zoster virus; and other herpes viruses, including HSV-6); Poxyiridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (such as African swine fever virus); Astroviridae; and unclassified viruses or agents (for example, the etiological agents of spongiform encephalopathies, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus).

[0069] Examples of bacterial pathogens include, but are not limited to: *Helicobacter pylori, Escherichia coli, Vibrio cholerae, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria* sps (such as. *M. tuberculosis, M. avium, M. intracellulare, M. kansaii, M. gordonae*), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A *Streptococcus*), *Streptococcus agalactiae* (Group B *Streptococcus*), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Strepto-*

coccus pneumoniae, pathogenic *Campylobacter* sp., *Enterococcus* sp., *Haemophilus influenzae*, *Bacillus anthracis*, *corynebacterium diphtheriae*, *corynebacterium* sp., *Erysipelothrix rhusiopathiae*, *Clostridium perfringers*, *Clostridium tetani*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pasturella multocida*, *Bacteroides* sp., *Fusobacterium nucleatum*, *Streptobacillus moniliformis*, *Treponema pallidium*, *Treponema pertenue*, *Leptospira*, *Bordetella pertussis*, *Shigella flexnerii*, *Shigella dysenteriae* and *Actinomyces israelli*.

[0070] Examples of fungal pathogens include, but are not limited to: *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Chlamydia trachomatis* and *Candida albicans*.

[0071] Other pathogens (such as parasitic pathogens) include, but are not limited to: *Plasmodium falciparum*, *Plasmodium vivax*, *Trypanosoma cruzi* and *Toxoplasma gondii*.

[0072] MicroRNA: MicroRNAs (also known as miRNAs and miRs) are short RNA sequences expressed from longer transcripts found in the genomes of animals, plants and viruses and at least one single-celled eukaryote (Molnar et al., *Nature* 447:1126-1129, 2007; Zhao et al., *Genes Dev.* 21:1190-1203, 2007). MicroRNAs regulate the expression of target genes by binding to complementary sites in the target gene transcripts to cause translational repression or transcript degradation (Pillai et al., *Trends Cell Biol.* 17:118-126, 2007). These small RNA molecules have been implicated in a number of biological processes related to development, cell proliferation, apoptosis, metabolism, morphogenesis and diseases (Kloosterman and Plasterk, *Dev. Cell* 11:441-450, 2006).

[0073] A gene encoding a microRNA is transcribed to form a primary transcript microRNA (pri-miRNA), which is processed to form a short stem-loop molecule, termed a precursor microRNA (pre-miRNA), followed by endonucleolytic cleavage to form the mature microRNA. Mature microRNAs are approximately 19-24 nucleotides in length and are partially complementary to the 3'UTR (or other regions such as introns, exons or 5'UTR) of one or more target messenger RNAs (mRNAs).

[0074] A nomenclature scheme has been well established for microRNAs (Griffiths-Jones et al., *Nucleic Acids Res.* 34:D140-D144, 2006; Ambros et al., RNA 9:277-279, 2003; Griffiths-Jones, *Nucleic Acids Res.* 32:D109-D111, 2004). For example, a microRNA name includes a three or four letter species prefix, such as "hsa" for *Homo sapiens*, and a numeric suffix, such as "150," resulting in a complete name of "hsa-miR-150." Mature miRNA sequences expressed from more than one hairpin precursor molecule are distinguished by "−1" and "−2" (such as miR-6-1 and miR-6-2). Related hairpin loci expressing related mature microRNA sequences have lettered suffixes (such as miR-181a and miR-181b). In some cases, mature miRNAs from both the 5' and 3' arms of the hairpin precursor are identified, which are designated "3p" or "5p" (such as miR-768-3p and miR-768-5p).

[0075] MicroRNA gene product sequences are well described throughout the scientific and patent literature and are available online through miRBase (world wide web at mirbase.org), provided by the University of Manchester (previously provided by the Sanger Institute). The miRBase registry provides the nucleotide sequences of all published animal, plant and viral microRNAs (Griffiths-Jones et al., *Nucleic Acids Res.* 36:D154-D158, 2008). Provided by miRBase are the sequences of precursor microRNAs (stem-loop miRNAs), mature miRNAs and minor microRNA species (miR*). Precursor miRNAs predominantly express one species of miRNA, referred to as the mature miRNA. However, minor miRNA sequences have also been detected and are referred to as miR**, which are sometimes identified by their "3p" or "5p" annotation, as described above.

[0076] In the context of the present disclosure, administering a "miR" to a subject or contacting a cell with a "miR" encompasses administration or contacting with a pri-miRNA, pre-miRNA or mature miRNA, or a nucleic acid molecule encoding a pri-miRNA, pre-miRNA or mature miRNA.

[0077] Operably linked: A first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein-coding regions, in the same reading frame.

[0078] Pharmaceutically acceptable vehicles: The pharmaceutically acceptable carriers (vehicles) useful in this disclosure are conventional. Remington's Pharmaceutical Sciences, by E. W. Martin, Mack Publishing Co., Easton, Pa., 15th Edition (1975), describes compositions and formulations suitable for pharmaceutical delivery of one or more therapeutic compounds, molecules or agents (such as a miR or vector encoding a miR).

[0079] In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (for example, powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

[0080] Preventing, treating or ameliorating a disease: "Preventing" a disease refers to inhibiting the full development of a disease. "Treating" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. "Ameliorating" refers to the reduction in the number or severity of signs or symptoms of a disease.

[0081] Promoter: A promoter is an array of nucleic acid control sequences that directs transcription of a nucleic acid. A promoter includes necessary nucleic acid sequences near the start site of transcription, such as in the case of a polymerase II type promoter (a TATA element). A promoter also optionally includes distal enhancer or repressor elements which can be located as much as several thousand base pairs from the start site of transcription. Both constitutive and inducible promoters are included (see e.g., Bitter et al., *Methods in Enzymology* 153:516-544, 1987).

[0082] Sequence identity/similarity: The identity/similarity between two or more nucleic acid sequences, or two or more amino acid sequences, is expressed in terms of the identity or similarity between the sequences. Sequence iden-

tity can be measured in terms of percentage identity; the higher the percentage, the more identical the sequences are. Sequence similarity can be measured in terms of percentage similarity (which takes into account conservative amino acid substitutions); the higher the percentage, the more similar the sequences are. Homologs or orthologs of nucleic acid or amino acid sequences possess a relatively high degree of sequence identity/similarity when aligned using standard methods. This homology is more significant when the orthologous proteins or cDNAs are derived from species which are more closely related (such as human and mouse sequences), compared to species more distantly related (such as human and *C. elegans* sequences).

[0083] Methods of alignment of sequences for comparison are well known in the art. Various programs and alignment algorithms are described in: Smith & Waterman, *Adv. Appl. Math.* 2:482, 1981; Needleman & Wunsch, *J. Mol. Biol.* 48:443, 1970; Pearson & Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444, 1988; Higgins & Sharp, *Gene,* 73:237-44, 1988; Higgins & Sharp, *CABIOS* 5:151-3, 1989; Corpet et al., *Nuc. Acids Res.* 16:10881-90, 1988; Huang et al. *Computer Appls. in the Biosciences* 8, 155-65, 1992; and Pearson et al., *Meth. Mol. Bio.* 24:307-31, 1994. Altschul et al., *J. Mol. Biol.* 215: 403-10, 1990, presents a detailed consideration of sequence alignment methods and homology calculations.

[0084] The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul et al., *J. Mol. Biol.* 215:403-10, 1990) is available from several sources, including the National Center for Biological Information (NCBI) and on the internet, for use in connection with the sequence analysis programs blastp, blastn, blastx, tblastn and tblastx. Additional information can be found at the NCBI web site.

[0085] Recombinant: A recombinant nucleic acid molecule is one that has a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination can be accomplished by chemical synthesis or by the artificial manipulation of isolated segments of nucleic acid molecules, such as by genetic engineering techniques.

[0086] Subject: Living multi-cellular vertebrate organisms, a category that includes human and non-human mammals.

[0087] Therapeutically effective amount: A quantity of a specified composition, pharmaceutical or therapeutic agent (such as a miR or nucleic acid molecule encoding a miR) sufficient to achieve a desired effect in a subject, or in a cell, being treated with the agent. The effective amount of the agent will be dependent on several factors, including, but not limited to the subject being treated, the disease or condition being treated, and the manner of administration of the therapeutic composition. In some embodiments of the present disclosure, the therapeutically effective amount (or effective amount) of a miR is the amount required to increase viral resistance or induce autophagy.

[0088] Transduce, transform or transfect: To introduce a nucleic acid molecule into a cell, such as a miR or a vector encoding a miR. These terms encompass all techniques by which a nucleic acid molecule can be introduced into a cell, including but not limited to, transduction with viral vectors, transfection with plasmid vectors, liposomal-mediated transfection and introduction of naked DNA by electroporation and particle gun acceleration. A transfected or transformed cell is a cell into which has been introduced a nucleic acid molecule by molecular biology techniques. In some examples, the nucleic acid molecule becomes stably repli-

cated by the cell, for example by incorporation of the nucleic acid molecule into the cellular genome, or by episomal replication. In other examples, the nucleic acid molecule is transiently expressed in the cell.

[0089] Vector: A vector is a nucleic acid molecule allowing insertion of foreign nucleic acid without disrupting the ability of the vector to replicate and/or integrate in a host cell. A vector can include nucleic acid sequences that permit it to replicate in a host cell, such as an origin of replication. A vector can also include one or more selectable marker genes and other genetic elements. An expression vector is a vector that contains the necessary regulatory sequences to allow transcription and translation of inserted gene or genes. In some embodiments herein, the vector is a plasmid vector. In other embodiments, the vector is a viral vector.

[0090] Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Hence "comprising A or B" means including A, or B, or A and B. It is further to be understood that all base sizes or amino acid sizes, and all molecular weight or molecular mass values, given for nucleic acids or polypeptides are approximate, and are provided for description. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including explanations of terms, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

III. Introduction

[0091] Described herein is the finding that cultured primary human trophoblasts (PHT) are highly resistant to infection by diverse and unrelated viruses. The studies disclosed herein also determined that conditioned PHT culture medium confers resistance to viral infections in permissive non-placental cells, indicating that trophoblast-associated viral resistance is transmissible, and is transferred to recipient cells. It was found that a unique cluster of primate-specific microRNAs (miRNAs), which are highly expressed in human trophoblasts from the human chromosome 19 miRNA cluster (C19MC) (Noguer-Dance et al., *Hum Mol Genet.* 19, 3566-3582, 2010), are packaged within PHT-derived exosomes and confer this viral resistance to recipient cells. It is further shown herein that PHT cells exhibit high rates of resting autophagy, a process involved in the maintenance of cellular homeostasis and an effective cellular countermeasure to suppress viral infections. PHT-derived exosomes and several C19MC miRNAs robustly induce autophagy in non-placental recipient cells, which is required for their resistance to viral infection. Unlike the other viruses that were tested, CMV infection is greatly enhanced by C19MC miRNAs. These findings illuminate a previously unknown pathway employed by human trophoblasts to suppress viral infections and confer viral resistance to non-placental recipient cells, suggesting a novel mechanism for shielding the placenta and maternal-derived recipient cells against viral infections during pregnancy.

IV. Overview of Several Embodiments

[0092]   Provided herein is a method of inhibiting or treating a microbial infection in a subject. In some embodiments, the method includes selecting a subject with a microbial infection, or at risk for contracting a microbial infection, and administering to the subject a therapeutically effective amount of one or more microRNAs (miRs) encoded by the chromosome 19 miRNA cluster (C19MC). In some embodiments, the method includes direct administration of the one or more miRs encoded by the C19MC. In other embodiments, administering the one or more miRs encoded by the C19MC comprises administering a nucleic acid molecule encoding the C19MC or a biologically active portion thereof. In some examples, the nucleic acid molecule comprises a vector, such as a plasmid vector or a viral vector.

[0093]   In some embodiments, the microbial infection is a viral infection. The viral infection can be an infection caused by any type of virus. In some examples, the virus is an RNA virus. RNA viruses include, for example, coxsackieviruses (e.g. coxsackievirus A and coxsackievirus B), poliovirus, vesicular stomatitis virus, human immunodeficiency virus, hepatitis C virus, rubella virus and morbilliviruses (such as measles virus). In particular examples, the RNA virus is a coxsackievirus, poliovirus, vesicular stomatitis virus, human immunodeficiency virus or hepatitis C virus. In other examples, the virus is a DNA virus. DNA viruses include, for example, vaccinia virus, herpes simplex viruses (HSV-1 and -2), Epstein-Ban virus, hepatitis B virus, parvovirus and varicella zoster. In particular examples, the DNA virus is a vaccinia virus or a herpes simplex virus. In some embodiments, the virus is not cytomegalovirus (CMV).

[0094]   In some embodiments, the microbial infection is a bacterial infection. In some examples, the bacteria is *Staphylococcus aureus*, Group A *Streptococcus*, *Listeria monocytogenes, Bacillus anthracis, Burkholderia pseudomallei, Helicobacter pylori, Salmonella enterica* or *Vibrio cholerae.*

[0095]   In some embodiments, the microbial infection is a parasitic infection. In some examples, the parasite is the protozoan parasite *Toxoplasma gondii.*

[0096]   In some embodiments, inhibiting the microbial infection comprises preventing the microbial infection.

[0097]   In some embodiments, the method comprises inhibiting or preventing intrauterine transmission of the microbial infection.

[0098]   In some embodiments of the disclosed methods, administration is extrauterine. In other embodiments, administration is intrauterine.

[0099]   In some examples, the one or more miRs, or nucleic acid molecule encoding the C19MC or biologically active portion thereof, is administered prophylactically to prevent infection. In other examples, the one or more miRs, or nucleic acid molecule encoding the C19MC or biologically active portion thereof, is administered to treat an existing infection.

[0100]   The one or more miRs administered to the subject can be any single miR or any combination of two or more miRs that are encoded by the C19MC. Similarly, if the subject is administered a nucleic acid molecule comprising the C19MC or biologically active portion thereof, the subject can be administered the entire C19MC or a portion that encodes a single or multiple miRs. The miR genes included in the C19MC are shown in FIG. **8** and listed in Table 1. Table 1 also lists 58 unique mature miR sequences encoded by the miR genes.

[0101]   In some embodiments, the subject is administered a single miR. In other embodiments, the subject is administered at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, or at least 55 miRs.

[0102]   In another embodiment, the subject is administered all miRs encoded by the cluster. In particular examples, the miRs are mature miRs.

[0103]   In other embodiments, the subject is administered a nucleic acid molecule comprising all miR genes of the C19MC (see Table 1). In another embodiment, the subject is administered a nucleic acid molecule encoding a single miR encoded by the C19MC. In yet other embodiments, the subject is administered a nucleic acid molecule encoding at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, or at least 55 miRs of the C19MC. In particular examples, the miRs are mature miRs.

[0104]   In some embodiments, the subject is administered the entire C19MC or a nucleic acid molecule encoding the entire C19MC.

[0105]   In some embodiments, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-517-3p, miR-516b-5p or miR-512-3p. In particular examples, the biologically active portion of the C19MC, or the one or more miRs comprises miR-517-3p, miR-516b-5p, and miR-512-3p. In other particular examples, the biologically active portion of the C19MC, or the one or more miRs comprises miR-517-3p, miR-1323, miR-516b-5p, miR-525-5p, miR-512-3p and miR-515-3p.

[0106]   In some examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p, miR-516b, miR-517-3p, or any combination of two or more thereof. In particular examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p, miR-516b, miR- and 517-3p. In further examples, a single miR selected from miR-512-3p, miR-516b, miR- and 517-3p is administered to the subject.

[0107]   In other examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p, miR-515-3p, miR-516b, miR-517-3p, miR-525-5p and miR-1323. In yet other examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-1323, miR-512-3p, miR-512-5p, miR-515-3p, miR-515-5p, miR-516b, miR-517-3p, miR-517c, miR-518a-5p, miR-518b, miR-518e, miR-519c-3p, miR-519d, miR-520c-3p, miR-520h and miR-525-5p.

[0108]   In some examples, the nucleotide sequence of the one or more miRs is at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to one or more of SEQ ID NOs: 1-59. In non-limiting examples, the nucleotide sequence of the one or more miRs comprises or consists of one or more of SEQ ID NOs: 1-59.

[0109]   Further provided herein is a method of inducing autophagy in a cell. In some embodiments, the method includes contacting the cell with an effective amount of one or more miRs encoded by the C19MC. In some embodiments, the method includes directly contacting the cell with the one or more miR molecules. In other embodiments, contacting the cell with the one or more miRs encoded by the C19MC

comprises contacting the cell with a nucleic acid molecule encoding the C19MC or a biologically active portion thereof. In some examples, the nucleic acid molecule comprises a vector, such as a plasmid vector a viral vector.

[0110] In some embodiments, the method is an in vitro method. In some examples of the in vitro method, the cell is a primary cell. In other examples, the cell is an immortalized cell.

[0111] In other embodiments, the method is an in vivo method and contacting the cell comprises administering to a subject an effective amount of one or more miRs encoded by the C19MC, or a nucleic acid molecule encoding the C19MC or a biologically active portion thereof. In some embodiments, the subject suffers from a disease associated with a deficiency in autophagy and/or a disease that can be ameliorated by stimulating autophagy. In particular examples, the disease is inflammatory bowel disease, Crohn's disease, alcoholic liver disease, Parkinson's disease, Alzheimer's disease, heart disease, diabetes or obesity.

[0112] The one or more miRs contacted with the cell (in vitro or in vivo) can be any single miR or any combination of two or more miRs that are encoded by the C19MC. Similarly, if the cell is contacted with a nucleic acid molecule encoding the C19MC or biologically active portion thereof, the cell can be contacted with the entire C19MC or a portion that encodes a single or multiple miRs. In some embodiments, the cell is contacted with a single miR. In other embodiments, the cell is contacted with at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or at least 55 miRs. In another embodiment, the cell is contacted with all miRs encoded by the C19MC. In particular examples, the miRs are mature miRs.

[0113] In other embodiments, the cell is contacted with a nucleic acid molecule comprising all miR genes of the C19MC (see Table 1). In another embodiment, the cell is contacted with a nucleic acid molecule encoding a single miR of the C19MC. In yet other embodiments, the cell is contacted with a nucleic acid molecule encoding at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or at least 55 miRs of the C19MC. In particular examples, the miRs are mature miRs.

[0114] In some embodiments of the methods of inducing autophagy, the subject is administered the entire C19MC or a nucleic acid molecule encoding the entire C19MC. In some embodiments of the methods of inducing autophagy, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-517-3p, miR-516b-5p or miR-512-3p. In particular examples, the biologically active portion of the C19MC, or the one or more miRs comprises miR-517-3p, miR-516b-5p, and miR-512-3p. In other particular examples, the biologically active portion of the C19MC, or the one or more miRs comprises miR-517-3p, miR-1323, miR-516b-5p, miR-525-5p, miR-512-3p and miR-515-3p. In some examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p, miR-516b, miR-517-3p, or any combination of two or more thereof. In particular examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p,

miR-516b, and miR-517-3p. In further examples, a single miR selected from miR-512-3p, miR-516b, and miR-517-3p is contacted with the cell.

[0115] In other examples of the methods of inducing autophagy, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-512-3p, miR-515-3p, miR-516b, miR-517-3p, miR-525-5p and miR-1323. In yet other examples, the biologically active portion of the C19MC, or the one or more miRs, comprises miR-1323, miR-512-3p, miR-512-5p, miR-515-3p, miR-515-5p, miR-516b, miR-517-3p, miR-517c, miR-518a-5p, miR-518b, miR-518e, miR-519c-3p, miR-519d, miR-520c-3p, miR-520h and miR-525-5p.

[0116] In some examples of the methods of inducing autophagy, the nucleotide sequence of the one or more miRs is at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to one or more of SEQ ID NOs: 1-59. In non-limiting examples, the nucleotide sequence of the one or more miRs comprises or consists of one or more of SEQ ID NOs: 1-59.

[0117] In some embodiments of the methods disclosed herein, the one or more miRs, or the nucleic acid molecule encoding the C19MC or biologically active portion thereof, is administered to the subject or contacted with the cell using a liposomal formulation, a cationic lipid or a polypeptide carrier.

[0118] In some embodiments of the disclosed methods, the nucleic acid molecule encoding the C19MC or biologically active portion thereof comprises a vector. In some examples, the vector is a plasmid vector. In other examples, the vector is a viral vector. Viral vectors can be of, for example, adenovirus, adeno-associated virus, retrovirus, herpes virus or vaccinia virus origin. Viral vectors can include modified versions of the viruses, such as replication deficient viruses. Suitable vectors, such as gene therapy vectors, are well known in the art. In some examples, the miR is expressed from recombinant circular or linear DNA plasmids using any suitable promoter. Suitable promoters for expressing RNA from a plasmid include, for example, the U6 or H1 RNA pol III promoter sequences, or a cytomegalovirus promoter. Selection of other suitable promoters is within the skill in the art. The recombinant plasmids of the present disclosure can also comprise inducible or regulatable promoters for expression of the miR.

[0119] In some embodiments, such as when the miR is administered as a naked nucleic acid molecule, the miR includes modifications, such as nucleotide modifications to increase nuclease resistance, or other modifications to enhance delivery and/or activity of the miR.

[0120] The disclosed methods comprise administering a therapeutically effective amount, or contacting a cell with an effective amount, of at least one miR encoded by the C19MC. In some embodiments, the miR is a variant or biologically-active fragment of the miR encoded by the C19MC. Thus, the miR that is administered to a subject or contacted with a cell can be identical to an endogenous (wild-type) miR (including a pri-miRNA, pre-miRNA or mature miRNA) that is encoded by the C19MC, or it can be a variant or biologically-active fragment thereof. As defined herein, a "variant" of a miR refers to a miRNA that has less than 100% identity to a corresponding wild-type miR and possesses one or more biological activities of the corresponding miR. Examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule (e.g., inhibiting translation of a target RNA molecule, modulating the stability

of a target RNA molecule, or inhibiting processing of a target RNA molecule), promoting viral resistance or inducing autophagy. The miR variants include species variants and variants that are the consequence of one or more mutations (e.g., a substitution, a deletion, an insertion) in a miR gene. In certain embodiments, the variant is at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at about 99% identical to a corresponding wild-type miR (such as one of the miRs listed in Table 1 or set forth herein as SEQ ID NOs: 1-59).

[0121] As used herein, a "biologically-active fragment" of a miR refers to an RNA fragment of a miR that possesses one or more biological activities of a corresponding wild-type miR. As described above, examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule, repressing protein translation, promoting viral resistance or inducing autophagy. In certain embodiments, the biologically-active fragment is at least about 9, at least about 11, at least about 13, at least about 15, at least about 17 or at least about 19 nucleotides in length.

V. Placental miRNAs from Chromosome 19 miRNA Cluster (C19MC)

[0122] Akin to other tissues, trophoblast differentiated functions are controlled by transcription factors, epigenetic modifiers and post-transcriptional influences that ultimately shape mRNA and protein expression. These pathways include small modulatory RNAs that interact with target gene 3'UTRs (or other regions of the genes) and promote RNA degradation and translational repression (Ghildiyal et al., *Nat Rev Genet.* 10:94-108, 2009; Huntzinger and Izaurralde, *Nat Rev Genet.* 12:99-110, 2011; Krol et al., *Nat Rev Genet.* 11:597-610, 2010; Friedman et al., *Genome Res* 19:92-105, 2009; Thomas and Lieberman, *Nat Struct Mol Biol* 17:1169-1174, 2010; Vickers et al., *Nat Cell Biol* 13:423-433, 2011; Herranz and Cohen, *Genes Dev* 24:1339-1344, 2010; Bartel, *Cell* 136:215-233, 2009; Carthew and Sontheimer, *Cell* 136: 642-655, 2009). Among all small RNAs, previous studies have shown that human trophoblasts produce primarily miR-NAs throughout pregnancy, as well as other small RNAs (piRNAs, snRNAs, and snoRNAs) (Mouillet et al., *Placenta* 31:781-784, 2010; Luo et al., *Biol Reprod* 81:717-729, 2009; Mouillet et al., *Birth Defects Res A Clin Mol Teratol* 91:737-

743, 2011; Barad et al., *Genome Res* 14:2486-2494, 2004; Pineles et al., *Am J Obstet Gynecol* 196:261, 2007). Many of these miRNAs are stably released into the maternal circulation, suggesting a miRNA-based mechanism for fetal-maternal communication (Mouillet et al., *Placenta* 31:781-784, 2010; Chim et al., *Clin Chem* 54:482-190, 2008).

[0123] Approximately 30-40% of placental miRNA species are expressed from defined miRNA clusters (Luo et al., *Biol Reprod* 81:717-729, 2009; Liang et al., *Genomics* 8:166, 2007; Bortolin-Cavaille et al., *Nucleic Acids Res* 37:3464-3473, 2009). Unique among these clusters is a primate-specific, large miRNA cluster (~100 kb, 46 highly-related miRNA genes), expressed from chromosomal region 19q13. 41 (Bentwich et al., *Nat Genet.* 37:766-770, 2005). MiRNA members of this chromosome 19 miRNA cluster (C19MC) are expressed throughout human pregnancy, and nearly exclusively in the placenta (Luo et al., *Biol Reprod* 81:717-729, 2009; Liang et al., *Genomics* 8:166, 2007; Bortolin-Cavaille et al., *Nucleic Acids Res* 37:3464-3473, 2009; Chiu et al., *Clin Chem* 52:313-316, 2006). Although the C19MC genomic sequence contains many primate-specific Alu repeats, which may mediate gene rearrangement (Zhang et al., *Mol Biol Evol* 25:1493-1502, 2008; Lehnert et al., *PLoS One* 4:e4456, 2009), secondary structure conservation and low SNP frequency of C19MC suggests that this cluster is evolutionarily stable. Selected placenta-specific miRNA species are found in the maternal blood throughout pregnancy. Their levels are not uniform, and rapidly decline in the first 24 h postpartum (Ng et al., *Proc Natl Acad Sci USA* 100:4748-4753, 2003; Gilad et al., *PLoS One* 3:e3148, 2008).

[0124] A schematic of the genomic organization of C19MC is shown in FIG. 8. A list of the specific miRNA genes included in this cluster is provided in the table below. The names and sequences of the mature forms of each miRNA gene are also shown. Many miR genes encode more than one mature product (the "5p" and "3p" products from the 5' and 3' arms, respectively, of the hairpin precursor). In some instances, two different miR genes encode a mature product with the same sequence (for example, see hsa-miR-512-1 and hsa-miR-512-2). All sequences shown in Table 1 were obtained from miRBase (world wide web at mirbase.org) on Feb. 27, 2012. The present disclosure contemplates the use of any microRNA product (a pri-mRNA, pre-miRNA or mature RNA) encoded by any of the genes listed in Table 1.

TABLE 1

miRNAs of the chromosome 19 miRNA cluster

Gene	Mature miRNA	Sequence of Mature miRNA	SEQ ID NO:
hsa-mir-512-1	hsa-miR-512-5p	CACUCAGCCUUGAGGGCACUUUC	1
	hsa-miR-512-3p	AAGUGCUGUCAUAGCUGAGGUC	2
hsa-mir-512-2	hsa-miR-512-5p	CACUCAGCCUUGAGGGCACUUUC	1
	hsa-miR-512-3p	AAGUGCUGUCAUAGCUGAGGUC	2
hsa-mir-1323	hsa-miR-1323	UCAAAACUGAGGGGCAUUUUCU	3
hsa-mir-498	hsa-miR-498	UUUCAAGCCAGGGGGCGUUUUUC	4
hsa-mir-520e	hsa-miR-520e	AAAGUGCUUCCUUUUUGAGGG	5
hsa-mir-515-1	hsa-miR-515-5p	UUCUCCAAAAGAAAGCACUUUCUG	6
	hsa-miR-515-3p	GAGUGCCUUCUUUUGGAGCGUU	7

TABLE 1-continued

miRNAs of the chromosome 19 miRNA cluster			
Gene	Mature miRNA	Sequence of Mature miRNA	SEQ ID NO:
hsa-mir-519e	hsa-miR-519e-5p	UUCUCCAAAAGGGAGCACUUUC	8
	hsa-miR-519e-3p	AAGUGCCUCCUUUUAGAGUGUU	9
hsa-mir-520f	hsa-miR-520f	AAGUGCUUCCUUUUAGAGGGUU	10
hsa-mir-515-2	hsa-miR-515-5p	UUCUCCAAAAGAAAGCACUUUCUG	6
	hsa-miR-515-3p	GAGUGCCUUCUUUUGGAGCGUU	7
hsa-mir-519c	hsa-miR-519c-5p	CUCUAGAGGGAAGCGCUUUCUG	11
	hsa-miR-519c-3p	AAAGUGCAUCUUUUUAGAGGAU	12
hsa-mir-1283-1	hsa-miR-1283	UCUACAAAGGAAAGCGCUUUCU	13
hsa-mir-520a	hsa-miR-520a-5p	CUCCAGAGGGAAGUACUUUCU	14
	hsa-miR-520a-3p	AAAGUGCUUCCCUUUGGACUGU	15
hsa-mir-526b	hsa-miR-526b-5p	CUCUUGAGGGAAGCACUUUCUGU	16
	hsa-miR-526b-3p	GAAAGUGCUUCCUUUUAGAGGC	17
hsa-mir-519b	hsa-miR-519b-5p	CUCUAGAGGGAAGCGCUUUCUG	18
	hsa-miR-519b-3p	AAAGUGCAUCCUUUUAGAGGUU	19
hsa-mir-525	hsa-miR-525-5p	CUCCAGAGGGAUGCACUUUCU	20
	hsa-miR-525-3p	GAAGGCGCUUCCCUUUAGAGCG	21
hsa-mir-523	hsa-miR-523-5p	CUCUAGAGGGAAGCGCUUUCUG	22
	hsa-miR-523-3p	GAACGCGCUUCCCUAUAGAGGGU	23
hsa-mir-518f	hsa-miR-518f-5p	CUCUAGAGGGAAGCACUUUCUC	24
	hsa-miR-518f-3p	GAAAGCGCUUCUCUUUAGAGG	25
hsa-mir-520b	hsa-miR-520b	AAAGUGCUUCCUUUUAGAGGG	26
hsa-mir-518b	hsa-miR-518b	CAAAGCGCUCCCCUUUAGAGGU	27
hsa-mir-526a-1	hsa-miR-526a	CUCUAGAGGGAAGCACUUUCUG	28
hsa-mir-520c	hsa-miR-520c-5p	CUCUAGAGGGAAGCACUUUCUG	29
	hsa-miR-520c-3p	AAAGUGCUUCCUUUUAGAGGGU	30
hsa-mir-518c	hsa-miR-518c-5p	UCUCUGGAGGGAAGCACUUUCUG	31
	hsa-miR-518c-3p	CAAAGCGCUUCUCUUUAGAGUGU	32
hsa-mir-524	hsa-miR-524-5p	CUACAAAGGGAAGCACUUUCUC	33
	hsa-miR-524-3p	GAAGGCGCUUCCCUUUGGAGU	34
hsa-mir-517-3p	hsa-miR-517-5p	CCUCUAGAUGGAAGCACUGUCU	35
	hsa-miR-517-3p	AUCGUGCAUCCCUUUAGAGUGU	36
hsa-mir-519d	hsa-miR-519d	CAAAGUGCCUCCCUUUAGAGUG	37
hsa-mir-521-2	hsa-miR-521	AACGCACUUCCCUUUAGAGUGU	38
hsa-mir-520d	hsa-miR-520d-5p	CUACAAAGGGAAGCCCUUUC	39
	hsa-miR-520d-3p	AAAGUGCUUCUCUUUGGUGGGU	40

TABLE 1-continued

Gene	Mature miRNA	Sequence of Mature miRNA	SEQ ID NO:
hsa-mir-520g	hsa-miR-520g	ACAAAGUGCUUCCCUUUAGAGUGU	42
hsa-mir-516b-2	hsa-miR-516b-5p	AUCUGGAGGUAAGAAGCACUUU	43
	hsa-miR-516b-3p	UGCUUCCUUUCAGAGGGU	44
hsa-mir-526a-2	hsa-miR-526a	CUCUAGAGGGAAGCACUUUCUG	28
hsa-mir-518e	hsa-miR-518e-5p	CUCUAGAGGGAAGCGCUUUCUG	45
	hsa-miR-518e-3p	AAAGCGCUUCCCUUCAGAGUG	46
hsa-mir-518a-1	hsa-miR-518a-5p	CUGCAAAGGGAAGCCCUUUC	47
	hsa-miR-518a-3p	GAAAGCGCUUCCCUUUGCUGGA	48
hsa-mir-518d	hsa-miR-518d-5p	CUCUAGAGGGAAGCACUUUCUG	49
	hsa-miR-518d-3p	CAAAGCGCUUCCCUUUGGAGC	50
hsa-mir-516b-1	hsa-miR-516b-5p	AUCUGGAGGUAAGAAGCACUUU	43
	hsa-miR-516b-3p	UGCUUCCUUUCAGAGGGU	44
hsa-mir-518a-2	hsa-miR-518a-5p	CUGCAAAGGGAAGCCCUUUC	47
	hsa-miR-518a-3p	GAAAGCGCUUCCCUUUGCUGGA	48
hsa-mir-517c	hsa-miR-517-5p	CCUCUAGAUGGAAGCACUGUCU	35
	hsa-miR-517c-3p	AUCGUGCAUCCUUUUAGAGUGU	51
hsa-mir-520h	hsa-miR-520h	ACAAAGUGCUUCCCUUUAGAGU	52
hsa-mir-521-1	hsa-miR-521	AACGCACUUCCCUUUAGAGUGU	38
hsa-mir-522	hsa-miR-522-5p	CUCUAGAGGGAAGCGCUUUCUG	53
	hsa-miR-522-3p	AAAAUGGUUCCCUUUAGAGUGU	54
hsa-mir-519a-1	hsa-miR-519a-5p	CUCUAGAGGGAAGCGCUUUCUG	55
	hsa-miR-519a-3p	AAAGUGCAUCCUUUUAGAGUGU	56
hsa-mir-527	hsa-miR-527	CUGCAAAGGGAAGCCCUUUC	57
hsa-mir-516a-1	hsa-miR-516a-5p	UUCUCGAGGAAAGAAGCACUUUC	58
	hsa-miR-516a-3p	UGCUUCCUUUCAGAGGGU	59
hsa-mir-1283-2	hsa-miR-1283	UCUACAAAGGAAAGCGCUUUCU	13
hsa-mir-516a-2	hsa-miR-516a-5p	UUCUCGAGGAAAGAAGCACUUUC	58
	hsa-miR-516a-3p	UGCUUCCUUUCAGAGGGU	59
hsa-mir-519a-2	hsa-miR-519a-3p	AAAGUGCAUCCUUUUAGAGUGU	56

Placental Exosomes

[0125] A significant fraction of plasma miRNA is packaged in exosomes. These nanoparticles function as "cargo vehicles" (Valadi et al., *Nat Cell Biol* 9:654-659, 2007; Simpson et al., *Proteomics* 8:4083-4099, 2008; Skog et al., *Nat Cell Biol* 10:1470-1476, 2008) to transfer nucleic acids, proteins, lipids and other biomolecules to proximal and distant tissues (Thery et al., *Nat Rev Immunol* 9:581-593, 2009; Raposo et al., *J Exp Med* 183:1161-1172, 1996; Alvarez-Erviti et al., *Nat Biotechnol* 29:341-345, 2011). Exosomes belong to a large family of intracellular and extracellular microvesicular bodies, ranging in size between >100 nm (apoptotic blebs and microparticles) to approximately 30-120 nm (exosomes). Exosomes can fuse intracellularly with lysosomes to destroy content or fuse with plasma membranes to release exosomal content via exocytosis or ectocytosis (Thery et al., *Nat Rev Immunol* 2:569-579, 2002; Pan and Johnstone, *Cell* 33:967-978, 1983; Keller et al., *Immunol Lett* 107:102-108, 2006). Exosomes are defined by size, cup-shaped form, sucrose gradient buoyancy (1.13-1.19 g/mL), and a detergent-resistant, lipid raft-rich membrane bilayer of proteins,

cholesterol, and sphingolipids. Some of the membrane proteins are common, such as cytoskeletal proteins, chaperones, and tetraspanins, including CD9, CD63, CD81, and others specific to the exosome's cell of origin (Simpson et al., *Proteomics* 8:4083-4099, 2008; Thery et al., *Nat Rev Immunol* 2:569-579, 2002). Surface proteins may determine exosome specificity to target cells, which they enter via endocytosis-based internalization (Morelli et al., *Blood* 104:3257-3266, 2004), cell membrane fusion (Denzer et al., *J Immunol* 165: 1259-1265, 2000), or receptor-ligand interactions (Admyre et al., *Eur J Immunol* 36:1772-1781, 2006).

[0126] Thus, exosomes act as a form of communication among different cell types, with potentially striking consequences to recipient cells (e.g., induction of apoptosis, mediated by the FAS ligand binding to FAS receptors). Relevant to the present disclosure, exosomes were recently found to be enriched for miRNAs (Valadi et al., *Nat Cell Biol* 9:654-659, 2007; Eldh et al., *PLoS One* 5:e15353, 2010), akin to virally-mediated intercellular transfer of genetic material, with potential beneficial or harmful consequences (Eldh et al., *PLoS One* 5:e15353, 2010). The human placenta is known to express microvesicular bodies of diverse sizes, mainly shed as syncytiotrophoblast microparticles, implicated in preeclampsia-related placental apoptosis. Production of exosomes has been studied in first trimester trophoblasts, where exosomes likely contribute to the establishment of maternal immune tolerance, possibly via impaired T-cell signaling, down-regulation of NK cell receptor NKG2D, and enhanced apoptotic pathways through FasL, TRAIL, and PD-L (Luo et al., *Biol Reprod* 81:717-729, 2009; Taylor et al., *J Immunol* 176:1534-1542, 2006; Hedlund et al., *J Immunol* 183:340-351, 2009; Mincheva-Nilsson and Baranov, *Am J Reprod Immunol* 63:520-533, 2010). The production and function of placental exosomes after the first trimester of human pregnancy, and the role of miRNAs packaged in these exosomes, has not been previously studied.

VI. Administration of miRNAs

[0127] A nucleic acid molecule encoding C19MC, or a biologically active portion thereof (including a single miR or multiple miRs), can be administered to a subject in need of treatment using any suitable means known in the art. Nucleic acid-based therapeutic agents can be administered to a subject by any suitable route. In some examples, the nucleic acid molecules are administered using an enteral or parenteral administration route. Suitable enteral administration routes include, for example, oral, rectal, or intranasal delivery. Suitable parenteral administration routes include, for example, intravascular administration (such as intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature); subcutaneous injection or deposition, including subcutaneous infusion (such as by osmotic pumps); direct application to the tissue of interest, for example by a catheter or other placement device (e.g., a suppository or an implant comprising a porous, non-porous, or gelatinous material); and inhalation. In some cases, suitable administration routes are injection, infusion and direct injection into a target tissue.

[0128] In the context of the present disclosure, a miR or a nucleic acid molecule encoding C19MC, or a biologically active portion thereof, can be administered to the subject either as naked RNA or DNA in combination with a delivery reagent, or can be encoded by a recombinant plasmid or viral vector. Recombinant plasmids and viral vectors including

sequences that express the C19MC or biologically active portion thereof, and techniques for delivering such plasmids and vectors to target cells, are well known in the art.

[0129] In some embodiments, liposomes are used to deliver the nucleic acid molecule to a subject. Liposomes can also increase the blood half-life of nucleic acids. Suitable liposomes for use with the present disclosure can be formed from standard vesicle-forming lipids, which generally include neutral or negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of several factors, such as the desired liposome size and half-life of the liposomes in the blood stream. A variety of methods are known in the art for preparing liposomes (see, for example, Szoka et al., *Ann. Rev. Biophys. Bioeng.* 9:467, 1980; and U.S. Pat. Nos. 4,235,871; 4,501, 728; 4,837,028; and 5,019,369). In some embodiments, polymers can be used to deliver a nucleic acid molecule to a subject. Cationic lipids and polymers that can be used to deliver therapeutic nucleic acid molecules have been described (see, for example, Zhang et al., *J Control Release.* 123(1):1-10, 2007; Vorhies et al., *Methods Mol. Biol.* 480:11-29, 2009; and U.S. Patent Application Publication No. 2009/0306194). Polypeptide carriers can also be used to administer nucleic acid molecules, such as miRs, to a subject (see, for example, Rahbek et al., *J. Gene Med.* 10:81-93, 2008).

[0130] Nucleic acid molecules can be administered in any suitable manner, preferably with pharmaceutically acceptable carriers. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present disclosure.

[0131] Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils.

[0132] Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

[0133] Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[0134] Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.

[0135] Administration can be accomplished by single or multiple doses. The dose required will vary from subject to subject depending on the species, age, weight and general condition of the subject, the particular nucleic acid molecule being used and its mode of administration. An appropriate

dose can be determined by one of ordinary skill in the art using only routine experimentation.

[0136] The following examples are provided to illustrate certain particular features and/or embodiments. These examples should not be construed to limit the disclosure to the particular features or embodiments described.

EXAMPLES

Example 1

Materials and Methods

[0137] This example describes the materials and experimental procedures used for the studies described in Example 2.

Cells and PHT Exosome Purification

[0138] Primary human trophoblasts (PHT cells) were isolated from normal singleton term placentas using the trypsin-deoxyribonuclease-dispase/Percoll method as described by Kliman et al., with previously published modifications (Kliman et al., *Endocrinology* 118, 1567-1582, 1986; Nelson et al., *Am J Obstet Gynecol* 180, 896-902, 1999). Cells were maintained in DMEM (Sigma) containing 10% fetal bovine serum (FBS, Hyclone, Logan, Utah, USA) and antibiotics at 37° C. in a 5% carbon dioxide (CO_2)-air atmosphere. Cells were maintained 72 h after plating, with cell quality monitored both morphologically (by microscopy) and by medium human chorionic gonadotropin (hCG) levels, determined by enzyme-linked immunosorbent assay (ELISA, DRG International, Mountainside, N.J.), showing a characteristic increase in medium hCG as cytotrophoblasts differentiate into syncytiotrophoblasts (Nelson et al., *Am J Obstet Gynecol* 180, 896-902, 1999; Chen et al., *J Biol Chem* 281, 2764-2772, 2006).

[0139] For isolation of PHT exosomes, PHT cells were maintained for 48 h in DMEM containing 10% FBS that was ultracentrifuged at 108,000×g for 10 h to deplete pre-existing FBS exosomes. Exosomes were isolated as described previously (Montecalvo et al., *J Immunol* 180, 3081-3090, 2008). Briefly, supernatants from 200 million PHT cells were combined and subsequently centrifuged at 300×g for 5 min, 1,200×g for 10 min, and 10,000×g for 30 min. Exosomes were concentrated by centrifugation at 2,500×g for 25 min using a Vivacell 100 filter (BioExpress, Kaysville, Utah, USA; F-2820-100C), then ultracentrifuged at 108,000×g for 1 h, and the exosome pellet was subsequently ultracentrifuged on top of a 30% sucrose density cushion at 108,000×g for 1 h (Lamparski et al., *J Immunol Methods* 270, 211-226, 2002). The exosomal phase was collected and resuspended in PBS, before ultracentrifugation at 108,000×g for 1 h. The total amount of exosomes was determined by total protein spectrophotometry. Exosome-depleted PHT supernatant was produced by subsequently centrifugation at 300×g for 5 min, 1,200×g for 10 min, 10,000×g for 30 min and 108,000×g for 1.5 h. Exosomes were reconstituted in FBS-exosome depleted complete medium at a ten-fold concentration over conditioned medium.

[0140] Human osteosarcoma U2OS, human foreskin fibroblast (HFF), and Huh7.5 cells were cultured in DMEM-H supplemented with 10% FBS and penicillin/streptomycin. Vero African green monkey kidney cells were maintained in DMEM-H supplemented with 5% FBS and penicillin/streptomycin. Caco-2 (ATCC clone) human intestinal epithelial cells were cultured in MEM supplemented with 10% FBS, non-essential amino acids, sodium pyruvate, and penicillin/streptomycin. Immortalized human first trimester extravillous trophoblast cells, provided by C H Graham, Kingston, Ontario, Canada (Graham et al., *Exp Cell Res* 206, 204-211, 1993) were cultured in RPMI-1640 (Cellgro, Manassas, Va., USA), supplemented with 5% bovine growth serum (Hy-Clone) and antibiotics.

[0141] Conditioned media from PHT or other cells were harvested between 48-72 h post plating. Conditioned medium was subjected to sonication or heat-inactivation for 30 min at 65° C. Recipient cells were exposed to conditioned medium for ~24 h prior to assay.

Viruses

[0142] Experiments were performed with vesicular stomatitis virus (VSV), green fluorescent protein (GFP)-tagged VSV, recombinant yellow fluorescent protein (YFP)-tagged vaccinia virus as described (VV) (Moser et al., *PLoS Pathog* 6, e1000954, 2010), coxsackievirus B3-RD isolate (CVB3-RD) as described (Coyne and Bergelson, *Cell* 124, 119-131, 2006), poliovirus (PV) as described (Coyne et al., *EMBO J.* 26, 4016-4028, 2007), cytomegalovirus (hCMV Towne strain), cell culture grown hepatitis C virus (HCV) expressing firefly luciferase (HCVcc-luc), or GFP-tagged herpes simplex virus-1 (HSV1, strain KOS) as described (Desai and Person, *J Virol* 72, 7563-7568, 1998). VSV was expanded by growth on Vero cells and media was harvested. Viral titers were determined by plaque assays as previously described (Bozym et al., *Cell Host Microbe.* 11:153-166, 2012). Plaque assays were conducted on Vero (VSV and GFP-VSV) or HeLa (CVB) cells. Confluent monolayers were treated with serial dilutions of virus for one hour at 37° C. (VSV) or at room temperature (CVB). Cells were then overlayed with agarose and incubated for 48 h. Plaques were visualized by crystal violet staining and plaques enumerated. HCVcc-luc propagation was performed as described (Liu et al., *J. Virol.* 83:2011-2014, 2009).

[0143] Experiments assessing productive virus infection were performed as follows. PHT cells were infected with CVB, PV, VSV, VV, or HSV-1 for 14-15 h (multiplicity of infection (MOI)=5), or CMV for 24 h. Infections were performed with three individual PHT preparations in duplicate. hCMV infections were performed with two individual PHT preparations in triplicate. For 3-MA experiments assessed by RT-qPCR, PHT cells were infected with GFP-VSV for 15 h at MOI=5. For experiments analyzing immediate early viral gene expression measured by RT-qPCR, PHT cells were infected with CVB, VSV, VV, or HSV-1 for 6-7 h at MOI=1. HeLa cells were infected with CVB or PV at an MOI=5 for 8 h. HFF cells were infected with CMV for 24 h, VSV or CVB (MOI=5) for 15 h. Vero cells were infected with VSV for 6 h (MOI=5). Caco-2 cells were infected with VSV or CVB for 7 h (MOI=5). RL-95 cells were infected with CVB for 15 h (MOI=5). For immunofluorescence, U2OS cells were infected with CVB for 7 h (MOI=5), VSV (MOI=5), VV, or HSV-1 (MOI=1) for 15 h. For RT-qPCR, U2OS cells were infected with CMV, VSV, HSV-1 or VV for 5-6 h (MOI=1). Huh7.5 cells were infected with HCVcc as described previously (Liu et al., *J. Virol.* 83:2011-2014, 2009).

miRNA Mimics, Plasmids, and Transfections

[0144] Mimics for C19MC miRNAs (miRIDIAN) as well as a non-targeting control miRNA mimic were obtained from Thermo-Fisher (Dharmacon, Lafayette, Colo.) as described

14

(Donker et al., *Mol. Hum. Reprod.* 18(8):417-424, 2012). U2OS cells or other cell lines were transfected with one or multiple miRNA mimics or miRNA mimic negative control (final concentration 6 nM for each miRNA mimic) using DharmaFECT-1 transfection reagent (Thermo Fisher Scientific) or HiPerFect™ (Qiagen) according to manufacturer's instructions. Cells were assayed 48 h post-transfection.

[0145] The total concentration of non-targeting control miRNA mimics was adjusted to that of all active miRNA mimics. For siRNA transfections, U2OS cells were reverse transfected using HiPerFect™ transfection reagent (Qiagen). For silencing of beclin-1, 40 nM per well of scrambled non-targeting siRNA (siControl) or beclin-1 siRNA (Cell Signaling, #6222S) were transfected.

[0146] Plasmid transfections were performed using X-tremeGENE 9 (Roche) according to manufacturer's protocol. The mRFP-LC3B expression construct was purchased from Addgene (plasmid 21075) and originally constructed by Tamotsu Yoshimori (Kimura et al., *Autophagy* 3, 452-460, 2007). For experiments with conditioned media and purified exosomes, cells were transfected, exposed to media 24 h later, and fixed 48 h post-transfection. For all other experiments, the cells were assayed 48 h post-transfection.

C19MC BAC Preparation and Transfection

[0147] The BAC RP11-1055O17 containing 160,970 bp of genomic DNA from region q13-42 of chromosome 19 was obtained from the BACPAC Resource Center located at the Children's Hospital Oakland Research Institute (CHORI) in Oakland, Calif. The BAC clone harbors the entire C19MC miRNA cluster spanning around 100 kb and contains an additional 60 kb of flanking sequences. The nucleotide sequence of the genomic insert in BAC RP11-1055O17 is set forth herein as SEQ ID NO: 60. Recombineering of the BAC was performed as described (Warming et al., *Nucleic Acids Res* 33, e36, 2005). A GFP::zeocin cassette from the pSE-LECT-GFPzeo-mcs plasmid (InvivoGen, CA), was PCR amplified and cloned into the Hind III and Bam HI sites of pBluescript II SK(+) (pBS-SK). BAC specific homology arms of ~500 bp each were PCR amplified and cloned into pBS-SK using the restriction sites flanking the GFP::zeocin cassette (5' arm: Xho I and Hind III; 3' arm: Bam HI and Xba I). The whole targeting cassette was then PCR amplified, gel purified, and electroporated into the recombinogenic SW 106 bacterial strain containing the recipient BAC. In addition to the construct that was simply tagged with the GFP::zeocin cassette at the 3' end of the C19MC cluster, a BAC with a deletion of the entire C19MC coding sequence was created and used as a control in transfection experiments. By choosing a 5' homology arm located upstream of the miRNA cluster and keeping the same 3' homology arm, the recombination led to the actual deletion (BAC "trimming") of the entire miRNA locus (~100 kb). The construct contain ~60 kb of genomic DNA flanking the GFP::zeocin cassette. Bacteria harboring the BAC with the desired alteration were selected on selective medium with chloramphenicol (12.5 µg/ml) and zeocin (25 µg/ml). The correct BAC constructs, confirmed by using restriction mapping and PCR, were transformed back into DH10B bacterial cells for propagation. BAC DNA for transfection was prepared using the PhasePrep BAC DNA kit following the recommendations from the manufacturer (Sigma).

RNA Isolation, Microarrays and miRNA RT-qPCR

[0148] For miRNA analysis, total cellular RNA was purified from cells using miRNeasy Mini Kit (Qiagen, Valencia, Calif.), according to the manufacturer's instructions. Prior to RNA isolation, non-exosomal RNA were degraded using 400 ng/µl RNase at 37° C. for 15 min (Valadi et al., *Nat Cell Biol* 9, 654-659, 2007). For miRNA analysis, reverse transcription and quantitative PCR (RT-qPCR) of duplicate samples was performed using the miScript PCR system (Qiagen, Valencia, Calif.), following the manufacturer's instructions. Detection of all miRNAs was performed using respective miScript primers (Qiagen, Valencia, Calif.). Dissociation curves were run on all reactions to ensure amplification of a single product. Control H_2O samples were included in all RT and PCR reactions. Total RNA input was normalized using RNU6B RNA as an endogenous control. The fold increase relative to control samples was determined by the 2-$\Delta\Delta$Ct method (Livak and Schmittgen, *Methods* 25, 402-408, 2001). Microarray analysis of C19MC miRNA expression in PHT cells and in PHT exosomes was performed using Agilent's Human miRNA V3 8×15K arrays.

[0149] For analysis of C19MC miRNA targets, total cellular RNA was purified from U2OS or HTR8/Sv-Neo cells using miRNeasy Mini Kit (Qiagen), according to the manufacturer's instructions (Agilent Technologies, Santa Clara, Calif.). The quality of RNA was confirmed using 2100 Bioanalyzer (Agilent Technologies, Santa Clara, Calif.). A total of 100 ng of RNA was used for labeling, generating cyanine 3-labeled lineary amplified cRNA. Six hundred ng of cRNA was used for microarray hybridization as per Agilent protocol, performed using Agilent's SurePrint G3 Hmn GE 8×60K human arrays. Array data were extracted using a High-Resolution C scanner (Agilent) and a GE1 107 (September 09) feature extraction protocol (Agilent).

[0150] All data were from the three experimental paradigms were log 2 transformed and normalized separately using the cyclic loess normalization method (Wu et al., *BMC Bioinformatics* 6:309, 2005). Identical probes targeting the same mRNA transcripts were averaged by probe set intensity values. A moderated student's t test, which is based on an empirical Bayesian algorithm, as implemented in the R package "limma" (G. K. Smyth, "Linear models and empirical Bayes methods for assessing differential expression in microarray experiments," Statistical Applications in Genetics and Molecular Biology, 3:Article 3, 2004) was applied to test, for each gene, if it was differentially expressed between the cells transfected by the empty BAC or by the C19MC BAC. The Storey's q-value method (Storey and Tibshirani, *Proc Natl Acad Sci USA* 100, 9440-9445, 2003) was used to calculate the adjusted p values for the p values of the moderated t test to control the false discovery rate. Up- or down-regulated genes were subsequently identified that satisfied the following conditions: (1) down (or up) regulation in the C19MC-transfected HTR8 cells with adjusted p values ≤0.05 and log 2 fold change ≤-0.5 (or ≥+0.5), (2) down (or up) regulation in the C19MC-transfected U2OS cells with adjusted p values ≤0.05 and log 2 fold change ≤-0.5 (or ≥+0.5), and (3) down (or up) regulated in the U2OS cells exposed to conditioned medium, with log 2 fold change ≤-0.5 (or ≥+0.5, note that because each group in the U2OS conditioned medium experiment had only one sample, no statistical testing was performed). Finally, the TargetScan miRNA target database (version 6) was searched to identify, among the down regulated genes, those that are predicted targets of at least one of the 4 most abundant C19MC miRNAs: miR-517-

3p, miR-517b, miR-516b, and miR-512-3p. All the analyses were performed using the statistical computing program R and its packages (R Development Core Team, 2011. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0).

[0151] For cellular mRNA analysis, total RNA was extracted using TRIreagent (MRC) or RNeasy (Qiagen) according to manufacturer's protocol. RNA samples were treated with RNAse-free DNAse (Qiagen). Total RNA was reverse transcribed using iScript cDNA synthesis kit (Bio-Rad) or RT^2 First Strand kit (SABiosciences). For each sample, 0.25-1 µg RNA was used for cDNA synthesis. Real-time PCR as performed using iQ SYBR Green Supermix (Bio-Rad) in a Applied Biosystems StepOnePlus real-time PCR machine according to the manufacturer's instructions. Dissociation curves were run on all reactions to ensure amplification of a single product. Gene expression was calculated using the ΔΔCt values with normalization to human actin (ACTGGGACGACATGGAGAAAA, SEQ ID NO: 61; GCCACACGCAGCTC, SEQ ID NO: 62).

[0152] Primers used were as follows: VSV (TGCAAG-GAAAGCATTGAACAA, SEQ ID NO: 63; GAGGAGT-CACCTGGACAATCACT, SEQ ID NO: 64), GFP (CACAT-GAAGCAGCACGACTTCT, SEQ ID NO: 65; AACTCCAGCAGGACCATGTGAT, SEQ ID NO: 66), hCMV Towne strain (GCGGTGGTTGCCCAACAGGA, SEQ ID NO: 67; ACGACCCGTGGTCATCTTTA, SEQ ID NO: 68), ATG4C (TAGAGGATCACGTAATTGCAGGA, SEQ ID NO: 69; GTTGTCAAAGCTGAGCCTTCTAT, SEQ ID NO: 70), UVRAG (ATGCCAGACCGTCTTGATACA, SEQ ID NO: 71; TGACCCAAGTATTTCAGCCCA, SEQ ID NO: 72), PIK3C3 (GAACAACGGTTTCGCTCTTTG, SEQ ID NO: 73; GCTTCTACATTAGGCCAGACTTT, SEQ ID NO: 74), Tk (ACCCGCTTAACAGCGTCAACA, SEQ ID NO: 75; CCAAGAGGTGCGGGAGTTT, SEQ ID NO: 76), VV rpo35 early (GCCAATGAGGGTTCGAGTTC, SEQ ID NO: 77; AACAACATCCCGTCGTTCATC, SEQ ID NO: 78), CVB3 (ACGAATCCCAGTGTGTTTTGG, SEQ ID NO: 79; TGCTCAAAAACGGTATGGACAT, SEQ ID NO: 80), and ISG56 (CAACCAAGCAAATGTGAGGA, SEQ ID NO: 81; GGAGACTTGCCTGGTGAAAA, SEQ ID NO: 82).

[0153] Autophagy and toll-like receptor qPCR arrays (SA-Biosciences) were performed with 1 µg RNA per 96 well plate and subjected to RT-qPCR using SYBR/ROX RT^2 qPCR 2x master mix (SABiosciences) according to manufacturer's protocol. Gene expression was defined from the threshold cycle (Ct), and relative expression levels were calculated using SABiosciences RT^2 Profiler PCR array analysis automated software.

[0154] RNA library construction and miRNA sequencing was performed by Ocean Ridge Biosciences (Palm Beach Gardens, Fla.) using extracted RNA. The small RNA libraries were aligned to the NCBI-37 human reference genome using Bowtie, then intersected with the mature miRNA sequenced annotated by miRBase (v.18) using BEDtools. The miRNA counts in each library were normalized using established algorithms (Anders and Huber, *Genome Biol.* 11:R106, 2010). The C19MC miRNAs and the non-C19MC miRNAs in the six libraries were Laplace smoothed by adding 1 to the normalized counts, log 2 transformed, and clustered respectively by the agglomerative hierarchical clustering, using the complete linkage method. Heat maps were then generated

separately for the clustered C19MC miRNAs and non-C19MC miRNAs. To quantify the differences in miRNA expression between U2OS cells that were exposed to PHT conditioned medium vs. cells that were exposed to fresh medium, the differential expression test was applied, which assumes that the in all libraries were follow negative binomial distributions (Anders and Huber, *Genome Biol.* 11:R106, 2010), and a shrinkage estimator was used for the dispersion parameters of the miRNAs. The p-values of the tests were adjusted using the Benjamini and Hochberg's method (Hochberg and Benjamini, *J. Roy. Statist. Soc. B.* 57:289-300, 1995) to control for false discovery rate. Statistical analyses were performed using statistical computing software R and the DESeq package of R.

Pharmacological Agents

[0155] Cells were pre-treated with 3-methyladenine (3-MA; 5 mM, Sigma) for 30-60 min prior to infection, and cells were incubated with drug throughout the duration of infection. For mRFP-LC3B punctae assays, 3-MA was added for 30 min prior to conditioned or non-conditioned media exposure, and was present throughout. Rapamycin (5 µM, Calbiochem) treatment or serum-starvation with Hank's Balanced salt solution (HBSS) for 4 h was used as a positive control for autophagy.

Immunofluorescence and Confocal Microscopy

[0156] Cell monolayers were cultured in 8-well chamber slides (LabTek) at 37° C. Cells were then washed and fixed as indicated with either ice cold methanol, 3:1 methanol-acetone, or 4% paraformaldehyde in PBS and permeabilized with 0.25% Triton X-100 in PBS. Mouse anti-VSV-G and mouse anti-hCMV gB were obtained from Santa Cruz Biotechnology, and mouse anti-enterovirus VP1 (NCL-Entero) was purchased from Novacastra Laboratories. Mouse-anti clathrin heavy chain (CHC) and mouse anti-caveolin 1 (Cav1) antibodies were obtained from BD Transduction Laboratories. Rabbit anti-Dynamin II (DynII) was purchased from Abcam. Fixed monolayers were incubated with primary antibody, washed, incubated with Alexa Fluor-488 or -594-conjugated secondary antibodies (Invitrogen), washed, and then mounted with Vectashield (Vector Laboratories) containing 4',6-diamidino-2-phenylindole (DAN), Cholera toxin B (CTB) conjugated to Alexa Fluor 488 (8 µg/mL; Invitrogen) and transferrin conjugated to Alexa Fluor 594 (Invitrogen) uptake was performed essentially as previously described (Patel et al., *J Virol* 83, 11064-11077, 2009).

[0157] Images were captured with an IX81 inverted microscope equipped with a motorized stage or with an Olympus Fluoview 1000 laser scanning confocal microscope. Images of infected cells were taken using an Olympus PlanApo 10x/ 0.40 NA dry or Apo 20x/0.75 NA dry objective, whereas all other images were taken with an Olympus PlanApo 60x/1.42 NA oil objective.

[0158] For virus infection assays, cells were fixed and stained for markers of virus infection (CVB and PV (VP 1), VSV (VSV-G), hCMV (gB)) or assessed for GFP-expression (VV-GFP, HSV-1-GFP, VV-YFP). A minimum of three independent fields per condition were counted (at least 600 cells total). Infection levels are reported as the percentage of virus positive cells among the total number of cells, determined by DAPI staining. Quantification of percent virus positive cells was performed using ImageJ (National Institutes of Health)

analysis. For LC3B autophagy assays, at least twenty individual cells from a minimum of four independent fields were captured per condition. The total number of mRFP-LC3B-positive punctae were quantified per cell using ImageJ analysis with identical settings per condition, Analysis of the extent of VSV and mRFP-LC3b punctate co-localization was performed using ImageJ.

Electron Microscopy

[0159] Cells were washed, fixed with 2.5% gluteraldehyde in PBS for 1 h, then processed for electron microscopy as previously described (Gao et al., *J Biol Chem* 285, 1371-1383, 2010), Sections were imaged using a JEOL JEM 1011 transmission electron microscope (Peabody) using an 80 V fitted with a bottom mount AMT 2k digital camera (Advanced Microscopy Techniques). At least five to ten individual cells were captured per condition. The number of autophagosomes (including amphisomes, autophagosomes, autophagic vacuoles, and autolysosomes) were quantified per cell manually.

Immunoblots

[0160] Cells were grown in 6-well plates and lysates were prepared with RIPA buffer (50 mM Tris-HCl [pH 7.4]; 1% NP-40; 0.25% sodium deoxycholate; 150 mM NaCl; 1 mM EDTA; 1 mM phenylmethanesulfonyl fluoride; 1 mg/ml aprotinin, leupeptin, and pepstatin; 1 mM sodium orthovanadate), and insoluble material was precipitated by brief centrifugation. Protein concentration of lysates was determined by BCA protein assay (Thermo Scientific). Lysates containing equal amounts of protein were loaded onto 4-20% Tris-HCl gels (Bio-Rad) and transferred to polyvinylidene difluoride membranes. Membranes were blocked in 5% nonfat dry milk, probed with the indicated antibodies, and developed with horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology), and SuperSignal West Pico or Dura, chemiluminescent substrates (Pierce Biotechnology).

[0161] For beclin-1 immunoblotting, cells were lysed on ice in a 50 mM Tris-HCl, pH 7.5 buffer that contained 150 mM NaCl and 0.5% NP-40. After centrifugation at 12,000×g at 4° C., the supernatant was subjected to 10% SDS-PAGE, transferred to PVDF membrane, and signal detected using monoclonal antibodies as indicated. Densitometry was performed using Image J.

Reporter Gene Assay

[0162] Activation of interferon β (IFNβ) or interferon-stimulated response element (ISRE) promoters was measured by reporter assay. Cells were transfected with 1 μg of DNA/well of a 24 well plate, a 30:1 ratio of IFNβ or ISRE firefly luciferase reporter plasmids to pRL-null (*Renilla* control) as per manufacturer's protocol. Cells were lysed in 100 μL of lysis buffer and the levels of firefly and *Renilla* luciferase levels quantified using the Dual-Luciferase Reporter Assay System (Promega) with a dual injector equipped Synergy 2 SL Luminescence Microplate Reader (BioTek). Levels of firefly luciferase were normalized to control *Renilla* luciferase levels. For poly(I:C) treatment, cells were transfected with 1 μg poly(I:C)/well using XtremeGene-9 for 16 h as per the manufacturer's protocol.

Statistical Analysis

[0163] All experiments were performed at least three times, as indicated in the figure legends. Data are presented as mean±standard deviation. Except where specified, Student's t test was used to determine statistical significance for virus infection and autophagy assays when 2 sets were compared, and one-way analysis of variance (ANOVA) with Bonferroni's correction for multiple comparisons were used to determine statistical significance for reporter gene assays. A $p<0.05$ was determined significant.

Virus Entry Assays

[0164] Virus entry assays in PHT cells were performed with CVB and PV as previously described (Coyne and Bergelson, *Cell* 124, 119-131, 2006; Coyne et al., *EMBO J.* 26, 4016-4028, 2007). VV and HSV-1 internalization assays were performed by incubating PHT cells with virus (MOI 25) at 37° C. until fixation at various time points (30, 60, 90 min). VSV entry assays in U2OS cells exposed to either non-conditioned or conditioned PHT medium for 24 h was performed by incubating cells with virus (MOI=500) for 1 h at 37° C. until fixation in 4% PFA followed by permeabilization in 0.1% Triton X-100. VSV particles were visualized with anti-VSV-G antibody.

Modified TCID50 Virus Titering Assays

[0165] Vero or PHT cells were seeded to confluence in 96 well plates. Cells were incubated with serial dilutions of the indicated viruses for approximately 40-45 h, then stained with 0.05% crystal violet (in 10% ethanol). For experiments performed with conditioned medium, Vero cells were incubated in non-conditioned or conditioned medium 24 h prior to incubation with virus. Serial dilutions of virus were made in either non-conditioned or conditioned medium, and cells were incubated and developed with crystal violet as described above.

Neutralizing Virus Plaque Assays

[0166] VSV virus stock was diluted 1:20 in either non-conditioned or conditioned PHT medium, then incubated at 37° C. for 1 h. Plaques assays were performed on Vero cells. Plaques were visualized after 36 h by staining with crystal violet.

Example 2

Human Placental Trophoblasts Confer Viral
Resistance to Recipient Cells by the Release of
miRNAs and the Induction of Autophagy

[0167] This example describes the finding that PHTs are highly resistant to infection by a number of different types of viruses. This resistance is mediated by exosomes containing miRNAs encoded by the primate-specific chromosome 19 miRNA cluster (C19MC).

PHT-Derived Exosomes Protect Recipient Cells from Viral Infection

[0168] The studies described herein determined that PHT cells were resistant to infection by a panel of viruses, including coxsackievirus B3 (CVB), poliovirus (PV), vesicular stomatitis virus (VSV), vaccinia virus (VV), herpes simplex virus-1 (HSV-1), and human cytomegalovirus (CMV), when compared to non-PHT cells (FIG. **1A**). This lack of viral

replication was not due to inefficient viral binding and/or entry, or to defects in common endocytic pathways utilized by viruses for their entry, such as clathrin- or caveolar-mediated pathways. It was found that exposure of diverse non-PHT recipient cells for 24 h prior to infection to PHT conditioned medium (isolated from naïve PHT cells 48-72 h post-plating) decreased the replication of CVB, VSV, hepatitis C virus (HCV), and VV (FIG. 6A). The antiviral effect of conditioned PHT medium was also observed in several physiologically relevant fetal and/or maternal primary cells, including human umbilical vein endothelial cells (HUVEC), human uterine microvascular endothelial cells, human placental fibroblasts, and human foreskin fibroblasts (HFF; FIG. 1C, right panel). In contrast, conditioned medium from other cell types, such as immortalized trophoblast BeWo cells, had no effect (FIG. 6B). This effect was not the result of direct neutralization of the virus as conditioned medium had no direct effect on viral titers (FIG. 6C). Furthermore, antiviral effects were observed across multiple conditioned medium samples isolated from independent and unrelated PHT preparations (FIGS. 6D-6F). Together, these data indicate that PHT cells release specific components to the medium, which are capable of conferring viral resistance to non-placental recipient cells.

[0169] To better define the component in conditioned medium of PHT cells that is responsible for conferring viral resistance, the conditioned medium was exposed to heat inactivation or RNAse treatment; however, no effect was observed (FIG. 1D). In contrast, repeated freeze-thawing partly attenuated the effect, and sonication completely abolished the antiviral effect of PHT conditioned medium (FIG. 1D). Because exosomes, which function as "cargo nanovesicles" (Valadi et al., *Nat. Cell. Biol.* 9:654-659, 2007; Skog et al., *Nat. Cell. Biol.* 10:1470-1476, 2008), are characteristically released from trophoblasts and are sensitive to sonication (Donker et al., *Mol. Hum. Reprod.* 18(8):417-424, 2012; Taylor et al., *J. Immunol.* 176:1534-1542, 2006; Montecalvo et al., *J. Immunol.* 180:3081-3090, 2008; Luo et al., *Biol. Reprod.* 81:717-729, 2009; Pegtel et al., *Proc. Natl. Acad. Sci. U.S.A.* 107: 6328-6333, 2010), their role in PHT-mediated transfer of viral resistance was examined. It was found that exosomes purified from PHT conditioned medium attenuated VSV infection in recipient cells (FIG. 1E). The antiviral effect was abrogated using exosome-depleted PHT conditioned medium (FIG. 1E). In addition, exosomes isolated from other cell types, such as an immortalized human placental choriocarcinoma cell line (JEG-3) or primary murine dendritic cells, had no effect on viral infection (FIG. 1E). Taken together, these data point to a direct role for PHT-derived exosomes in the transfer of viral resistance to non-placental recipient cells.

C19MC-Associated miRNAs Confer Viral Resistance

[0170] The transfer of RNA and/or miRNAs via exosomes may play an important role in exosome-based intercellular communication (Valadi et al., *Nat. Cell. Biol.* 9:654-659, 2007; Pegtel et al., *Proc. Natl. Acad. Sci. U.S.A.* 107:6328-6333, 2010; Zhang et al., *Mol. Cell.* 39:133-144, 2010). The human C19MC is the largest known miRNA cluster, comprising 46 miRNAs that are highly expressed almost exclusively in the human placenta. Moreover, as a group, C19MC miRNAs are also the most abundant miRNA species in trophoblastic exosomes, with a strong correlation between C19MC miRNA levels in PHT cells and in PHT-derived

exosomes (Noguer-Dance et al., *Hum. Mol. Genet.* 19:3566-3582, 2010; Donker et al., *Mol. Hum. Reprod.* 18(8):417-424, 2012; Taylor et al., *J. Immunol.* 176:1534-1542, 2006; Mouillet et al., *Placenta.* 31:781-784, 2010). To date, the function of these miRNAs has remained elusive. To test whether the expression of C19MC miRNAs could induce viral resistance in non-PHT cells, which do not naturally express these miRNAs, U2OS cells were stably transfected with a BAC that contained the entire human C19MC cluster. When compared to U2OS cells transfected with a control BAC (that is deficient for the C19MC expression sequence), cells stably expressing C19MC-BAC or cells exposed to PHT conditioned media expressed a higher level of C19MC miRNAs, as confirmed by RNAseq (Table 3), and exhibited resistance to VSV infection (FIG. 2A). Likewise, transient transfection of U2OS cells with miRNA mimics of 16 C19MC-associated miRNAs (representing highly expressed miRNAs, or the two subfamilies of the C19MC; Lin et al., *Comput. Biol. Chem.* 34:232-241, 2010) markedly reduced VSV infection (FIG. 2B and Table 2). It was also found that transfection of mimics of the six highest expressed C19MCs (Donker et al., *Mol. Hum. Reprod.* 18(8):417-424, 2012; Taylor et al., *J. Immunol.* 176: 1534-1542, 2006; Mouillet et al., *Placenta.* 31:781-784, 2010) attenuated VSV infection, whereas transfection with mimics of the lowest expressed seven had no significant effect (FIG. 2B). To define the impact of individual miRNAs, individual mimics from among the highest expressed C19MC miRNAs were expressed, and a significant inhibition of VSV infection was detected with mimics of miR-517-3p, -516b-5p, and -512-3p, but not with mimics of several non-C19MC-associated miRNAs (miR-1, -424, -630, and -720; FIGS. 2C-2D). Likewise, a mimic of miR-517-3p also attenuated infection by the DNA viruses VV and HSV-1 (FIG. 2E).

TABLE 2

Groups of mimics to C19MC miRNAs used in the described experiments. The 16 miRNAs are listed in order of expression level (highest to lowest).

16 C19MC miRNAs	Subgroup 1 9 C19MC miRNAs	Subgroup 2 7 C19MC miRNAs	6 highest expressed C19MC miRNAs	7 lowest expressed C19MC miRNAs
miR-517-3p	miR-517-3p		miR-517-3p	
miR-1323		miR-1323	miR-1323	
miR-516b-5p		miR-516b-5p	miR-516b-5p	
miR-525-5p		miR-525-5p	miR-525-5p	
miR-512-3p		miR-512-3p	miR-512-3p	
miR-515-3p	miR-515-3p		miR-515-3p	
miR-518e	miR-518e			
miR-515-5p		miR-515-5p		
miR-517c	miR-517c			
miR-519c-3p	miR-519c-3p			miR-519c-3p
miR-520h	miR-520h			miR-520h
miR-519d	miR-519d			miR-519d
miR-518b	miR-518b			miR-518b
miR-512-5p		miR-512-5p		miR-512-5p
miR-520c-3p	miR-520c-3p			miR-520c-3p
miR-518a-5p		miR-518a-5p		miR-518a-5p

TABLE 3

Differences in miRNA expression between U2OS cells exposed to conditioned or non-conditioned medium, analyzed by RNAseq*.

C19MC miRNA	Conditioned medium	Non-conditioned medium	Fold change (CM/FM)	Log2 fold change	p value	p adjusted (BH)
miR-517-3p	2374.403	765.215	3.103	1.634	2.66E−32	4.68E−30
miR-519a-3p	1738.835	1144.108	1.520	0.604	9.81E−07	4.60E−05
miR-522-3p	1662.638	1245.641	1.335	0.417	0.001083036	0.021856025
miR-1323	1454.781	459.377	3.167	1.663	8.06E−35	3.31E−32
miR-516a-5p	1093.955	635.203	1.722	0.784	7.75E−09	4.34E−07
miR-521	631.942	494.047	1.279	0.355	0.014010033	0.215579384
miR-1283	565.757	341.747	1.655	0.727	4.06E−06	0.000166442
miR-516b-5p	424.862	188.208	2.257	1.175	1.08E−13	9.49E−12
miR-512-3p	337.442	44.576	7.570	2.920	3.44E−38	2.48E−35
miR-524-5p	269.386	37.146	7.252	2.858	2.06E−33	6.34E−31
miR-515-3p	249.009	17.335	14.365	3.844	4.03E−38	2.48E−35
miR-517c-3p	228.786	116.392	1.966	0.975	2.02E−07	1.03E−05
miR-525-5p	216.140	26.002	8.312	3.055	2.73E−30	4.20E−28
miR-520d-3p	200.409	21.050	9.521	3.251	4.39E−30	6.01E−28
miR-520a-3p	141.669	35.908	3.945	1.980	2.43E−14	2.50E−12
miR-518e-3p	122.653	16.097	7.620	2.930	4.67E−19	5.75E−17
miR-519d	113.300	38.385	2.952	1.562	4.05E−09	2.37E−07
miR-518b	105.055	58.196	1.805	0.852	0.000622055	0.013434194
miR-518c-3p	76.726	32.194	2.383	1.253	2.34E−05	0.000823018
miR-518a-5p	70.166	34.670	2.024	1.017	0.002164332	0.040989113
miR-520g	65.535	61.911	1.059	0.082	0.848007306	1
miR-518e-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-519a-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-519b-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-519c-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-522-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-523-5p	65.366	26.002	2.514	1.330	5.44E−05	0.001594773
miR-524-3p	57.113	2.476	23.063	4.527	1.85E−13	1.42E−11
miR-520h	54.554	34.670	1.574	0.654	0.048469819	0.547397683
miR-526b-5p	48.663	28.479	1.709	0.773	0.020670659	0.277189278
miR-515-5p	43.639	34.670	1.259	0.332	0.311332029	1
miR-498	38.128	17.335	2.199	1.137	0.003592299	0.06503118
miR-527	34.719	17.335	2.003	1.002	0.032552612	0.396755106
miR-526a	33.466	8.667	3.861	1.949	0.000139813	0.00374151
miR-519c-3p	32.153	4.953	6.492	2.699	3.16E−06	0.000138861
miR-520a-5p	26.509	11.144	2.379	1.250	0.014724591	0.223777425
miR-518f-5p	25.322	4.953	5.113	2.354	0.000166051	0.004258507
miR-520d-5p	24.485	3.715	6.591	2.721	4.17E−05	0.001426038
miR-518a-3p	24.118	17.335	1.391	0.476	0.300976907	1
miR-525-3p	20.871	14.859	1.405	0.490	0.270466597	1
miR-519e-5p	17.257	4.953	3.484	1.801	0.008673863	0.14013828
miR-518d-5p	16.733	3.715	4.505	2.171	0.005073798	0.086747848
miR-520c-5p	16.733	3.715	4.505	2.171	0.005073798	0.086747848
miR-518c-5p	14.673	7.429	1.975	0.982	0.150512908	1
miR-523-3p	14.119	3.715	3.801	1.926	0.016108611	0.241825612
miR-518d-3p	11.457	1.238	9.252	3.210	0.006515171	0.108380746
miR-517-5p	9.017	1.238	7.282	2.864	0.018394499	0.263298001
miR-512-5p	8.716	8.667	1.006	0.008	1	1
miR-518f-3p	7.288	2.476	2.943	1.557	0.215985658	1
miR-519b-3p	7.132	4.953	1.440	0.526	0.60445537	1
miR-526b-3p	6.258	1.238	5.054	2.338	0.13991013	1
miR-520e	2.789	3.715	0.751	−0.414	0.91188741	1
miR-519e-3p	1.506	0.000	Inf	Inf	0.579448235	1
miR-520b	1.458	1.238	1.177	0.235	1	1
miR-520c-3p	1.157	0.000	Inf	Inf	0.94380054	1
miR-520f	0.428	0.000	Inf	Inf	1	1
miR-516a-3p	0.000	0.000	NA	NA	NA	NA
miR-516b-3p	0.000	0.000	NA	NA	NA	NA

*Counts were normalized by the median of ratio of the observed counts in each library to the geometric mean of the observed counts of all libraries, as described in Methods. Columns of conditioned and non-conditioned medium represent the mean of the normalized miRNAs counts in those samples.

PHT-Derived Exosomes and C19MC-Associated miRNAs Upregulate Autophagy

[0171] Mammalian cells utilize diverse defense mechanisms to combat microbial pathogens. One crucial mechanism is the induction of autophagy, an evolutionarily conserved lysosomal degradation pathway that has been associated with an array of cellular functions. Autophagy also degrades intracellular foreign microbial invaders (a process sometimes referred to as xenophagy) and thus serves as an important cellular response to suppress microbial infections. Exposure of U2OS cells to PHT conditioned medium or to purified PHT-derived exosomes markedly stimulated autoph-

19

agy, as assessed by the formation of mRFP-LC3b-containing punctae and by electron microscopy, whereas conditioned-medium depleted of PHT-exosomes had no effect (FIGS. 3A-3B and FIG. 7A). In contrast, no effect of PHT conditioned medium or C19MC-miRNAs on type I interferon (IFN) signaling was observed in recipient cells, and antiviral activity of conditioned PHT medium was observed in cells that fail to respond to type I IFNs. In addition, PHT cells themselves also do not exhibit enhanced type I IFN signaling.

[0172] Autophagy induction was observed in diverse cell types (FIGS. 3A-3B and FIG. 7B), and was absent in cells exposed to exosome-depleted PHT conditioned medium (FIGS. 3A-3B). In addition, PHT conditioned medium induced the upregulation (>3-fold) of several key pro-autophagy transcripts (e.g., ATG4C, UVRAG, and LC3A) while having no effect on other innate immune pathway components (e.g. toll-like receptors, interferon regulatory factors, cytokine-mediated signaling) in U2OS cells exposed to conditioned PHT medium (FIG. 7C and Table 4), further supporting the induction of autophagy. 3-methyladenine (3-MA), an inhibitor of autophagosome biogenesis, inhibited autophagosome formation in recipient cells exposed to conditioned PHT medium (FIG. 3C). Lastly, incoming VSV particles were trafficked to LC3b-positive punctae formed following exposure of cells to conditioned PHT medium, suggesting that the mislocalization or targeting of incoming viral particles to autophagosomes and/or autolysosome might impact viral replication (FIG. 3D).

TABLE 4

Summary of expression changes in autophagy-related transcripts.

Gene	Fold-change	Gene	Fold-change
ATG4C	3.2861	MAP1LC3B	1.2209
UVRAG	3.2696	CHUK	1.2054
CCL2	3.1764	HSPA1A	1.1822
DAPK1	3.119	ATG12	1.1791
CTSS	3.1154	RIPK2	1.1446
EIF2AK2	2.5184	ATG16L1	1.1417
RB1	2.3295	PTGS2	1.1354
BNIP3	2.3171	TOLLIP	1.124
MAP1LC3A	2.1561	EIF2AK3	1.1192
PIK3C3	2.1554	IL8	1.1002
BID	2.149	UBE2N	1.0968
AMBRA1	1.9193	MAP3K7	1.0954
ARSA	1.849	TLR4	1.0872
BCL2L1	1.7855	APP	1.0846
PRKRA	1.7526	PPARA	1.0624
ATG4D	1.7454	PELI1	1.0265
SQSTM1	1.7187	PRKAA2	1.0185
NFKBIA	1.6335	FAS	1.0149
ATG4A	1.6288	BECN1	1.0139
LY96	1.4979	HSP90AA1	1.0107
NFKB1	1.45885	HSPD1	0.9957
TBK1	1.3469	CSF2	0.9879
TP53	1.3446	HGS	0.9745
MAP3K1	1.3294	REL	0.9743
DRAM1	1.3204	CXCR4	0.9529
ATG3	1.289	MAPK14	0.9497
AKT1	1.2812	IRF3	0.9437
TLR3	1.2655	TICAM2	0.9347
ATG16L2	1.2457	ATG4B	0.9261
TGFB1	1.2354	ATG5	0.9159
ULK2	1.2352	HRAS	0.9159
SNCA	1.2286	CTSB	0.9132
HMGB1	0.9027	ATG10	0.724
TNFRSF1A	0.901	FADD	0.7218
ELK1	0.8971	BAX	0.7145
IL1B	0.8966	PIK3R4	0.7073
UBE2V1	0.8948	MAP2K3	0.6992

TABLE 4-continued

Summary of expression changes in autophagy-related transcripts.

Gene	Fold-change	Gene	Fold-change
GABARAP	0.8913	HSPA8	0.6945
IKBKB	0.8859	MAPK8	0.68385
PTEN	0.8814	ATG7	0.6794
EIF4G1	0.8792	MAPK8IP3	0.6767
GABARAPL2	0.8772	NFRKB	0.6665
MAP4K4	0.8748	TAB1	0.6663
CD180	0.8699	ULK1	0.6621
CLN3	0.8339	TICAM1	0.6597
PRKAA1	0.8324	CDKN1B	0.6285
FAM176A	0.8304	TGM2	0.6192
TRAF6	0.8257	DRAM2	0.6166
MAP2K4	0.8234	RPS6KB1	0.6072
NR2C2	0.8234	RGS19	0.6005
BCL2	0.8218	NFKB2	0.5946
HTT	0.8135	TMEM74	0.576
TLR6	0.809	ATG9A	0.5758
ECSIT	0.804	CASP8	0.57545
BAD	0.8011	JUN	0.5644
BAK1	0.7987	SARM1	0.5564
MYD88	0.7962	NFKBIL1	0.5528
GAA	0.7936	IRAK1	0.5404
IRF1	0.7825	FOS	0.5091
CASP3	0.7749	TP73	0.5061
GABARAPL1	0.7581	TNFSF10	0.4193
HDAC1	0.7541	IRGM	0.2952
RAB24	0.7351	TNF	0.2475
RELA	0.7325	ATG9B	0.2436
		IFNA4	0.1286

[0173] Because a role for C19MC-associated miRNAs was observed in the induction of viral resistance, it was assessed whether these miRNAs could induce autophagy. Transfection of cells with mimics of six of the highest expressed C19MC miRNAs (FIGS. 4A-4B), the entire C19MC (FIG. 7D) or mimics of individual C19MC miRNAs that attenuated viral infection (FIG. 4C), also stimulated autophagy, as observed by mRFP-LC3b punctate formation or by electron microscopy. Furthermore, C19MC-associated induction of autophagy occurred via the upregulation of autophagic flux, as supported by a decrease in p62 levels in cells expressing the entire C19MC (FIG. 4D).

The Antiviral Effects of C19MC-Associated miRNAs Require Autophagy

[0174] An inhibition of viral replication and a pronounced upregulation of autophagy was observed in cells exposed to PHT conditioned medium and in cells expressing C19MC-associated miRNAs. To determine if the antiviral effects of these conditions involved autophagy, autophagy was suppressed by treatment of cells with 3-MA or by RNA interference (RNAi)-mediated silencing of beclin-1, a key factor in autophagic induction (Liang et al., *Nature* 402:672-676, 1999). Inhibition of autophagy using 3-MA or by RNAi-mediated silencing of beclin-1 expression significantly restored the level of VSV infection in U2OS cells expressing the entire C19MC (FIGS. 5A-5B). Furthermore, addition of 3-MA to PHT cells enhanced VSV infection (FIG. 5C). These data show that the induction of autophagy is critical for the antiviral effect of C19MC miRNAs.

Discussion

[0175] The placenta shields the embryo from the spread of a number of diverse pathogens, including viruses. Disclosed herein is the striking finding that placental trophoblasts transfer viral resistance to non-placental cells. Viral resistance is

transferrable via trophoblastic conditioned medium, tropho-blastic exosomes, or miRNA members of the C19MC pri-mate-specific cluster. It is shown that multiple members of the C19MC primate-specific miRNA cluster, which is localized to chromosome 19q13.41 and expressed by a specific RNA Pol-II primarily in the placenta (Noguer-Dance et al., *Hum Mol Genet.* 19, 3566-3582, 2010; Bortolin-Cavaille et al., *Nucleic Acids Res* 37, 3464-3473, 2009; Bentwich et al., *Nat Genet.* 37, 766-770, 2005), are packaged within exosomes, which are capable of carrying their nucleic acids and other types of cargo to neighboring or distal targets (Valadi et al., *Nat Cell Biol* 9, 654-659, 2007). Although the C19MC is the largest known human miRNA cluster, its function remains unknown. Specific members of the C19MC miRNA family are known to be up-regulated in cancers, such as aggressive primitive neuroectodermal brain tumors (miR-517c and miR-520g) (Li et al., *Cancer Cell* 16, 533-546, 2009), hepatocel-lular carcinoma (miR-519d) (Formari et al., *J Pathol*, doi: 10.1002/path.3995, Jan. 19, 2012 [Epub]), breast cancer (miR-516-3p, miR-520c) (Foekens et al., *Proc Natl Acad Sci USA* 105, 13021-13026, 20081; Huang et al., *Nat Cell Biol* 10, 202-210, 2008), prostate cancer (miR-520c) (Yang et al., *Int J Clin Exp Pathol* 2, 361-369, 2009), and thyroid adenomas (Rippe et al., *PLoS One* 5, e9485, 2010). Thus, the data described herein are the first to suggest a unique role of C19MC miRNA members in an antiviral response that is transferrable to either neighboring cells within the placenta such as villous fibroblasts, macrophages or fetal endothelial cells, and to maternal systemic cells, such as maternal endot-helial or immune cells. Whereas the nature of recipient cells and the mechanisms of targeting remain unknown, exosome-mediated delivery of C19MC family members may constitute a powerful evolutionary adaptation by which a developing fetus is protected from viral invaders during pregnancy.

[0176] Primary human trophoblasts produce robust levels of miRNAs throughout pregnancy, as well as other small RNAs (piRNAs, snRNAs, and snoRNAs) (Mouillet et al., *Placenta*. 31:781-784, 2010; Luo et al., *Biol. Reprod.* 81:717-729, 2009; Mouillet et al., *Birth Defects Res. A. Clin. Mol. Teratol.* 91:737-743, 2011; Barad et al., *Genome. Res.* 14:2486-2494, 2004; Pineles et al. *Am. J. Obstet. Gynecol.* 196(3):e261-266, 2007). Many of these miRNAs, including members of the C19MC, are found in the maternal blood throughout pregnancy and rapidly decline in the first 24 h postpartum (Ng et al., *Proc. Natl. Acad. Sci. U.S.A.* 100, 4748-4753, 2003; Gilad et al., *PLoS One.* 3:e3148, 2008), suggesting a miRNA-based mechanism for fetal-maternal communication (Mouillet et al., *Placenta.* 31:781-784, 2010; Chim et al., *Clin. Chem.* 54:482-490, 2008). The data dis-closed herein thus provide evidence for a novel paracrine and/or systemic function of placental trophoblasts—utilizing exosome-mediated transport of a unique set of primate-spe-cific effector miRNAs to directly communicate with maternal cells, and possibly neighboring placental cells, and regulate their immunity to viral infections. It is possible that PHT-derived, C19MC miRNA-containing exosomes specifically target their cargo to a discrete subpopulation of maternal cells, or may aid in the selectively eliciting antiviral responses and upregulating autophagy. Although placental-derived miRNAs are found in low levels in the fetal circulation, it is possible that these miRNAs are sufficient to regulate specific pathways in the developing fetus, such as the induction of autophagy, which is critical for neonatal survival (Kuma et al., *Nature*. 432:1032-1036, 2004).

[0177] The data disclosed herein show that conditioned media from PHT cells, purified PHT-derived exosomes, and miRNA mimics of several members of the C19MC family potently induce autophagy. Autophagy is an important com-ponent of host antimicrobial signaling and often functions to restrict viral replication. Although some of the viruses used in the disclosed study (such as CVB (Schlegel et al., *J Virol* 70, 6576-6588, 1996; Jackson et al., *PLoS Biol* 3, e156, 2005) and HCV (Dreux et al., *Proc Natl Acad Sci USA* 106, 14046-14051, 2009)) are thought to benefit from the formation of autophagic vesicles during their replication, these viruses were also sensitive to the antiviral effects of C19MC miR-NAs. Unlike the induction of autophagy via an innate immune pathway in response to virus replication, recipient cells exposed to C19MC miRNAs exhibit robust levels of autoph-agy prior to their first exposure to viruses. Thus, preexisting C19MC-induced autophagosomes, which fuse with lysos-omes to become autophagolysosomes, could profoundly impact the ability of incoming viral particles to properly traffic or release their genomes. It was found that PHT cells themselves also exhibit a high level of baseline autophagy which indicates that this mechanism plays a role in conferring viral resistance to these cells. Alternatively or in addition, autophagy may underlie other important functions of placen-tal trophoblasts, such as those related to feto-placental nutri-tion or neonatal survival.

[0178] Recipient cells exposed to C19MC miRNAs exhibit robust levels of autophagy when first exposed to these viruses versus a typical setting in which autophagy would be an innate immune pathway that is upregulated in response to virus replication. Thus, C19MC miRNAs would greatly enhance the formation of autophagosomes, which fuse with lysosomes to become autophagolysosomes at a very early stage in the virus life cycle, which could have profound impacts on the ability of incoming viral particles to properly traffic and/or release their genomes. The high level of consti-tutive autophagy in primary human trophoblasts also implies that this mechanism confers viral resistance to these cells. Autophagy may underlie other important functions of placen-tal trophoblasts, related to feto-placental nutrition primarily when resources are scarce. For example, autophagy is criti-cally involved in neonatal survival during the period of star-vation that occurs immediately post-birth, when the mother's milk supply has not yet been established (Kuma et al., *Nature* 432, 1032-1036, 2004).

[0179] Unlike the other viruses tested in the studies dis-closed herein, conditioned PHT medium and expression of C19MC miRNAs significantly enhanced hCMV infection (FIGS. **6G-6H**), indicating that while C19MC miRNAs attenuate the replication of many viruses, they may function in a proviral manner to enhance the infection of CMV, and possibly other viruses. The findings disclosed herein (FIG. **1**A) and the work of others (Chan et al., *Am. J. Pathol.* 161: 1371-1381, 2002) suggest that PHT cells are resistant to CMV infection, and studies of CMV-infected placentas sug-gest that CMV specifically targets invasive and endovascular cytotrophoblasts as a means of entry into the fetal compart-ment (Chan et al., *Am. J. Pathol.* 161:1371-1381, 2002; Maidji et al., *J. Virol.* 81:4701-4712, 2007; Maidji et al., *Virology* 304:53-69, 2002).

[0180] The studies disclosed herein are the first to define an unprecedented role for miRNA members of the C19MC in transferrable autophagy-mediated antiviral responses. The results show that placental-associated C19MC miRNAs are

robust inducers of autophagy, a beneficial pathway in states of nutrient deprivation and a powerful suppresser of microbial infections. C19MC-derived placental miRNAs, released into the maternal circulation by exosomes, communicate an anti-viral signal to maternal host cells, thus providing an unprecedented mechanism to protect the developing embryo.

Example 3

C19MC microRNAs Inhibits HIV Replication

[0181] This example demonstrates that PHT-conditioned media, as well as particular miRs encoded by the C19MC, also are capable of inhibiting infection by human immuno-deficiency virus (HIV).

[0182] TZM-bl cells are HeLa cell derivatives that express high levels of CD4 and the HIV co-receptors CXCR4 and CCR5. These cells are stably transfected with LTR-driven firefly luciferase and LTR-driven β-galactosidase cassettes. Infection of TZM-bl cells with HIV-1 and HIV-2 isolates results in the induction of luciferase and β-galactosidase, allowing for the detection and quantification of infection.

[0183] TZM-bl cells were pre-incubated with PHT conditioned medium or control medium for 24 h prior to infection with HIV-1. Cells were then infected with serial dilutions of HIV (0, 3250, 7500, 15,000 and 30,000 pg/ml) for 48 h, and infection levels were assessed by Tat-induced luciferase reporter gene expression, in triplicate. As shown in FIG. **9**, PHT-conditioned medium inhibited HIV-1 replication, particularly at the higher doses of virus.

[0184] In another experiment, TZM-bl cells were trans-fected with a scrambled control, miR-517-3p, or miR-516-5p mimics for 48 h prior to infection with HIV-1. Cells were then infected with serial dilutions of HIV (1875, 3750, 7500 and 15,000 pg/ml) for 48 h, and infection levels were assessed by Tat-induced luciferase reporter gene expression. As shown in FIG. **10**, both miR-517-3p and miR-516-5p inhibited HIV replication at all dilutions of virus that were tested.

[0185] In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope and spirit of these claims.

SEQUENCE LISTING

```
<160> NUMBER OF SEQ ID NOS: 82

<210> SEQ ID NO 1
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

cacucagccu ugagggcacu uuc                                          23


<210> SEQ ID NO 2
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

aagugcuguc auagcugagg uc                                           22


<210> SEQ ID NO 3
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

ucaaaacuga ggggcauuuu cu                                           22


<210> SEQ ID NO 4
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

uuucaagcca gggggcguuu uuc                                          23


<210> SEQ ID NO 5
<211> LENGTH: 21
<212> TYPE: RNA
```

-continued

```
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

aaagugcuuc cuuuuugagg g                                          21


<210> SEQ ID NO 6
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

uucuccaaaa gaaagcacuu ucug                                       24


<210> SEQ ID NO 7
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

gagugccuuc uuuuggagcg uu                                         22


<210> SEQ ID NO 8
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

uucuccaaaa gggagcacuu uc                                         22


<210> SEQ ID NO 9
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

aagugccucc uuuuagagug uu                                         22


<210> SEQ ID NO 10
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

aagugcuucc uuuuagaggg uu                                         22


<210> SEQ ID NO 11
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

cucuagaggg aagcgcuuuc ug                                         22


<210> SEQ ID NO 12
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

aaagugcauc uuuuuagagg au                                         22
```

-continued

```
<210> SEQ ID NO 13
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

ucuacaaagg aaagcgcuuu cu                                          22


<210> SEQ ID NO 14
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

cuccagaggg aaguacuuuc u                                           21


<210> SEQ ID NO 15
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

aaagugcuuc ccuuuggacu gu                                          22


<210> SEQ ID NO 16
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

cucuugaggg aagcacuuuc ugu                                         23


<210> SEQ ID NO 17
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

gaaagugcuu ccuuuuagag gc                                          22


<210> SEQ ID NO 18
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

cucuagaggg aagcgcuuuc ug                                          22


<210> SEQ ID NO 19
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

aaagugcauc cuuuuagagg uu                                          22


<210> SEQ ID NO 20
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
```

-continued

```
<400> SEQUENCE: 20

cuccagaggg augcacuuuc u                                          21


<210> SEQ ID NO 21
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

gaaggcgcuu cccuuuagag cg                                         22


<210> SEQ ID NO 22
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

cucuagaggg aagcgcuuuc ug                                         22


<210> SEQ ID NO 23
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

gaacgcgcuu cccauagag ggu                                         23


<210> SEQ ID NO 24
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

cucuagaggg aagcacuuuc uc                                         22


<210> SEQ ID NO 25
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

gaaagcgcuu ucuuuagag g                                           21


<210> SEQ ID NO 26
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

aaagugcuuc cuuuuagagg g                                          21


<210> SEQ ID NO 27
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

caaagcgcuc cccuuuagag gu                                         22


<210> SEQ ID NO 28
```

-continued

```
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

cucuagaggg aagcacuuuc ug                                          22


<210> SEQ ID NO 29
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

cucuagaggg aagcacuuuc ug                                          22


<210> SEQ ID NO 30
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

aaagugcuuc cuuuuagagg gu                                          22


<210> SEQ ID NO 31
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

ucucuggagg gaagcacuuu cug                                         23


<210> SEQ ID NO 32
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

caaagcgcuu cucuuuagag ugu                                         23


<210> SEQ ID NO 33
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

cuacaaaggg aagcacuuuc uc                                          22


<210> SEQ ID NO 34
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

gaaggcgcuu cccuuuggag u                                           21


<210> SEQ ID NO 35
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35
```

-continued

```
ccucuagaug gaagcacugu cu                                        22


<210> SEQ ID NO 36
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

aucgugcauc ccuuuagagu gu                                        22


<210> SEQ ID NO 37
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

caaagugccu cccuuuagag ug                                        22


<210> SEQ ID NO 38
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

aacgcacuuc ccuuuagagu gu                                        22


<210> SEQ ID NO 39
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

cuacaaaggg aagcccuuuc                                           20


<210> SEQ ID NO 40
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

aaagugcuuc ucuuuggugg gu                                        22


<210> SEQ ID NO 41
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

aucgugcauc ccuuuagagu gu                                        22


<210> SEQ ID NO 42
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

acaaagugcu ucccuuuaga gugu                                      24


<210> SEQ ID NO 43
<211> LENGTH: 22
<212> TYPE: RNA
```

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

aucuggaggu aagaagcacu uu   22

<210> SEQ ID NO 44
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

ugcuuccuuu cagagggu   18

<210> SEQ ID NO 45
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

cucuagaggg aagcgcuuuc ug   22

<210> SEQ ID NO 46
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

aaagcgcuuc ccuucagagu g   21

<210> SEQ ID NO 47
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

cugcaaaggg aagcccuuuc   20

<210> SEQ ID NO 48
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

gaaagcgcuu cccuuugcug ga   22

<210> SEQ ID NO 49
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

cucuagaggg aagcacuuuc ug   22

<210> SEQ ID NO 50
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

caaagcgcuu cccuuuggag c   21

-continued

```
<210> SEQ ID NO 51
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

aucgugcauc cuuuuagagu gu                                              22


<210> SEQ ID NO 52
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

acaaagugcu ucccuuuaga gu                                              22


<210> SEQ ID NO 53
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

cucuagaggg aagcgcuuuc ug                                              22


<210> SEQ ID NO 54
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

aaaaugguuc ccuuuagagu gu                                              22


<210> SEQ ID NO 55
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

cucuagaggg aagcgcuuuc ug                                              22


<210> SEQ ID NO 56
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

aaagugcauc cuuuuagagu gu                                              22


<210> SEQ ID NO 57
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

cugcaaaggg aagcccuuuc                                                 20


<210> SEQ ID NO 58
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens
```

-continued

```
<400> SEQUENCE: 58

uucucgagga aagaagcacu uuc                                         23


<210> SEQ ID NO 59
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

ugcuuccuuu cagagggu                                              18


<210> SEQ ID NO 60
<211> LENGTH: 160970
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

cctttatggt cagtgtttac agggaagatg gagggaaaat tagagtcaga gattttaggt    60

tttatggcag gatttgggga aaagggattc tggtgtctat ggctcacttt gggaaagaca    120

gtttctagtt tctatggcta gccttggggg agaaggaggg tcaggaagaa acttccgctt    180

ctgaagctgc ttcggaagcc tttgtttttga ggttatcggt ttctgagccc caatattagc    240

ctgccacagt ctaagctttc aaagcgcctg tcaaactctt gtggatctat gtatttcaaa    300

gaccaaaatc aacagctcac atatggggtc caagaggagg gggaggtca ctgcacgttg    360

tcacgtgtga gatctttgtt gttgttgttg agatggaatc tcgctctgtc acccaggctg    420

gagtgcagtg gcaccatctc agctcgactg taaccttcac ctcccaggtt ctagcaatta    480

tcctgcctca gcctcccaag tatctggaat tacgggtgcg tgccatcatg ccccgctaat    540

tttttttttt tttttgtatt tttagtagag acggggtttt caccatgttg gccaggccag    600

tctcaaactc ctgaccccaa gggatctgcc cacctcggcc tcccaaagtg ctgggactac    660

aggcatgagc caccgcgcct ggcctcttgt gagatctgat aagaagtcac gcactagaag    720

gaagggaaga gtgtactcca caaccccaaa cgatgcgttt ggaatcattt caaacccaca    780

taacaagagt ttcatacgga attgggacag aacatggccc ctaatgagcc cccctaaata    840

attctcaagg accacttctc caatgacgaa ggagattgag gatttttttt tcctacgttt    900

attggccgtg tggatatttt gcctttgtaa aatatgtgtc caagcctttt gcccatttct    960

ccagtgggta gtatttcctt tgttttttttt ttttgagaca aagtctcact ctgttgccca    1020

ggctggagtg cagtggcctg atctcggctc actgcaaacc ctgcctcctg ggttcatgcc    1080

agtcttctgc ctcagcctcc caagtgctgg gactacaggt gcaccacc acgccctgct     1140

aattttttgt attttttagta gagatggggt ttcaccatgt tagctaggat ggtctcaatt    1200

tcctgacctc gtaatctgcc cgcctcggcc tcccaaagtg ctgggattac aggcgtgagc    1260

cactgcacct ggcctaaaag aatctttaaa ttgtccatga gcgatggtgc gtgcctgtgg    1320

tcccagctac ttggaggctg agaaggaagg atcccttgag cctgggagtt tgaggcagca    1380

atgagctatg ctcttaccac tgcactccag cctgggtgaa agaggaagaa gacccttaat    1440

aggcggacca cggtggctca cgcctgtaat ctcaatactt tcagaggcct aggtggaaga    1500

attacttgag accaggagtt caagaccaac ctggcaacaa tagcgagacc ctcatctctc    1560

caaaagtttg aaaaagaaaa aaaaaatttt taatgaaaca gaagtcgtta attttatttt    1620
```

-continued

```
attttctaag acatcttgtt atagcaaaaa gtccttaatt ttaatatagt ctaatttata    1680

tattttcttc attgtaaaaa tttttgggtc ctatctagca aatgttagct tacctctatg    1740

taataaagac attcttctgt gttgtcttct aaaacaaaac attgttttat tttctgattt    1800

taggtctgca gttcatttgt agattttttgt gtctaggatt aggtagggtt aagatcattt    1860

gtggccaggc atggtggctc acaccagtaa tcctaacact ttgggaggct aaggcaggag    1920

gatctcttga gcccaggagt ttcagaccag cctggggaac atagaaagac cctgtctctc    1980

tatttttttt ttcagttaaa tatatacttt taaaaagatc atttgtggtg ctatagttgt    2040

gggtgtttaa tttgtaattt actttgttct gttgatctat ctaatttttt ttttagacgg    2100

attcttcctc tgtcacccag gctggagtgc ttcagcctct caatgccatc atgcccagct    2160

aatttttttgg acttgtagta gagacagagt ttcaccatat tgaccaggct ggtctcgaac    2220

tcctggcctt aggtgacccg cccacctcag cctcccaaaa tgctgggatt ataggcatga    2280

gctactgtgt ccagccagat ctgtctaatt ttttttttttc tttgagacgc agtctcactc    2340

tgtcactcag gctggagtgc agtggcgtga tcttggctca atgtaacctc cacctcctgg    2400

gttcaagtga ttttcctacc tcagcctcct gagtagctgg gattacaggt gcgtgccacc    2460

acgcctggct aatttttgta tttttagcag agacggggtt ttgccatgtt ggccaggctg    2520

gtctcaaact cctgacttcc agtgatccgc ccaccttggc ctcccaaaat gctaggatta    2580

caggtgcgag ccactgtgcc tggcccagag ctgtctaatt ttaaagaatg tatgaagatt    2640

cagatttagg ttcctgctat tatgttatgg gaaatctttt cctagtttct tctgattaat    2700

ataaatcctt aatttatttt ttatttattt ttttactaca gtcctctttt attactttt    2760

attttctta atttaatat aatgaaaagt tcgattttc ctgttatggt tagcattttt    2820

ttcttctgtt taagaggtgt ttcctggctg ggtgtggtgg ctcacacctg caatcctagc    2880

actttgggag gccaaggtgg gaggatcact tgaacccagg agttcaagac cagcttgggc    2940

aacatagtga aacccttgtc tccaattttt ttaaattaaa aattaaaaaa ggcggggctg    3000

ggtgtggtgg ctcacccctg taatcccagc actttgggac gccgaggcgg gtggatcacc    3060

taaggtcagc agttcgagac cagcctgacc aacatggaga aaccctgtct ctactaaaag    3120

tacaaaatta gctgggcgtg gtggtgcatg tctgtaatcc cagctattcg ggaggctgag    3180

gcaggagaat cgcttgaatc caggaggcgg aggttgcagt gacccgagat tgcgccattg    3240

cactccagcc tgggcaacaa gagtgaaact ctgtctcaaa aaaataaat aaataaaaaa    3300

taaaataaaa aagaagtgtt tccctagcgt gaagacatga agctcttctg taaacttcat    3360

tgttctgcct ttacaattca atctacaacc cactagaatt aatcttccgt atatatagca    3420

tggggtggag gtcaaacacc tttttttccat atggatgttc agctgtccca gtgtcattta    3480

tttaaaagac tgtactggac ctggcatggt ggctcacgcc tgtaatccca gcactttggg    3540

aggctgaggc gggtggatca cttgaggtca ggagttcgag accagcctaa ccaacatggc    3600

aaaaccccat ctctgctaaa aatacaaaat tagccaggtt tggtggtgca tgcctgtaat    3660

tccggctact tgggaaactg aggcgggaga tcccttgaa cctcataggc agaggttgca    3720

atgagccaag atcgcaccat tgcattccag cctgggcaac aagagcgaaa ctctgtctca    3780

aaaaataaga aaaatagag gccgagaatg gccttgctg ccaccaacat ggagactttg    3840

taccgtgtcc cgttcttagc gcttgaatgt cccaacctga agctgaagaa gccgccctgg    3900
```

-continued

```
ctgcacatgc cgttggccat gactatgtat gctctggtgg tggtgtctta cttcctcatc     3960

accagaggaa tcgtttatga tgttacggtt gaaccgccag gtgttggctc tatgactgat     4020

gaacaagggc atcagaggcc agtagctttc ttggcctaca gagtaagtgg acaatattat     4080

tatggaagga cttggatcca gcttcctgtt tacaatggga ggtttaggtt tcataatcct     4140

ggaccgatcg aatgcaccaa atatcccaaa actcaataga tttcttcttc tattcgttgg     4200

attcgtctgt gtcctattga gtttttttca cggctagagt attcgtgaga atgaaactac     4260

cgggctctct gatgggttag agtgccttta agaagaaatc aggctgggtg cagtggctca     4320

cgcctgtaat cccagcactt tgggaggccg aggcgagcgg attatctgag gtcaggagtt     4380

cgagatcagc ctgggcaaca tggtaaaacc ccatccctac tacaaataca aaattagcca     4440

ggcgtggtga cacatgtctg taatcccagc tactcgggag gctgaggcag gagaattgct     4500

tgaacccggg aggcagagga tgcggtgagc cgagatcgca ccattgcact ccagcctgga     4560

caacaagagt aaatctccgt ctcaccaaaa aaaaaaaaa gaaaaaaaa aagaaatcag     4620

tgcatactgg atttgctcct gtcaatgaag ttttaaaggc tgtccaatcc tctaatatga     4680

gatgtagaaa agaaggaaga gcagcagtaa aagaaatatc tagtgaaaaa ccaggaagtg     4740

tattgaagct tggactagaa tttcttcttt attaaagaga caaatttatc acagtatttt     4800

ctttttcctgc tgaccacatt gctataccaa tgatgatgag tggcattttc ttcttagttt     4860

tttatttctt taagaaaata caagccaggc gcggtggctc acttctgtag tcccagcact     4920

ttgggaggcc aaggtgggca gatcacgagg tcaggagttc cagaccagcc tggccaccat     4980

gttgaaaccc catctctact aaaaatacaa aaattagccg ggcgtggtgg tggcggggca     5040

cctgtaatcc cagctacttg gaaggctgag gcaggagaat cacgtgaacc tgggaggcgg     5100

aggctgcagt gagcctagat cgctgccact gcactccagc ctgggcgaca gagcgagact     5160

ctgtttcaaa aaaaaaaaa gaaagaaaga aagaaaagaa aatatactgc atacctacaa     5220

ctataatagc aaatatagtg attatttttt acaacccccct taacactttt tggagatgac     5280

atttctgact ttcagaaatt aacataaaat caagaagcaa gattccatga gctgagaact     5340

ctggacagct ggtcagcttt acctacggag ctttggcttt aactagagtg tgtgatggta     5400

gattatttca gataggtatg taagactgct gcctgaacaa taacatgtat gaaaggaaca     5460

gaaataaata ctaattaaaa aacaaaataa gaaaaaataa aaaataaaca ctactatgga     5520

catggtagct catgcctgta atcctagcac tttgggatgc caaggtgggt ggatcgcttg     5580

aaccaaggag ttcaaggagt tgggagacca gtctgggcaa catagcaaga ccccatctct     5640

aaaaaaaaaa aaaaaaaaag agtactaaag actcagagat agaaaaatgg aaattattca     5700

tattgtctcc agatttttt ttttttggac ggagacttgc tctgtcaccc aggctggagt     5760

gcagtggcac tatcttggct cactgcaacc tccacctccc aggttcaagc aattctcctg     5820

cctcagcctc ccaagtagct gggattacag gcatacgcca ccaaacccgg ctaattttgt     5880

acttttagca gagacagggt tttgccatgt ttgtcaggct ggtcttgaac ccctgacctc     5940

aggtgatcca cccgcctcgg cctcccaaag tgctgggatt acaggtgtga gccaccgcgc     6000

ccagccagta gtctttttatc cttgtaacag attaatcttt tctagggaaa tggagacctt     6060

tcattttcat gtcctttta catccctgtt gattgtatct ctgcctccat tctgttgatc     6120

ggaatgacac taacttaatt tgggttctct aaagcagaca ctgatacaaa ggcttcagtt     6180
```

-continued

```
ccagaggttt atttagaatg tgatcctaaa ccaagaggga ggtagcaggg agagtaagac    6240

aggaaaggat ggggagccaa caccttatct aaggacatgt tgaggccagg cgtggtggct    6300

catgcctgta atcccagcac tttgggaatc cgaggcgagc agatcacaag gtcgggagtt    6360

tgagaccagc ctggccaaca tagtgaaact ctgtctctac taaaaatgca gaaaacaggc    6420

cgggtgcggt ggctcacgcc tgtaatccta gcactttgtg aggccgagac gggcggatca    6480

cctgaggttg ggagttagag accagcctga gcaacatgga gaaaccctgt ctctactaaa    6540

aatacaaaaa ttagccttgc gtggtggtgc atgcttgtaa tcccagctac ttgggaggct    6600

gaggcaggag aatcacttga acctgggagg cggaggttgc gatgagccga gatcgtgcca    6660

ttgcactcca gcctgggcga caagagtgaa acttcatctc aaaaaaaaaa aaaacaaaaa    6720

acagaaaaaa ttagctgggc ctggtggcag acgcctgtgg tcctagctac tcaggaggca    6780

aaggcaggag aattgcttga acctgggagg tggagattgc agtgagccga gatcatgcca    6840

ctgcactcca gcctgggtga cagagtgaga ctctatctca aaaaaaaaaa aaaaaaagga    6900

taagttgctg aagtctgtga agtggacaat gagggcttga ttcctttgaa gcctgttgaa    6960

gactgtttac gcttcctctt atcatcccct gcctcatccc ctgtcacaga gatgaaagac    7020

tgggacattt ctgtgccaaa tttcatccca cattgggtga ggctttccct gagacatgtt    7080

gacttcctgc agttcaaagc tactttcttc tttagacagg gtctcgctct gtcccccagg    7140

ctagagtgct atagcgtgat ctcgcctcac tgcaagctcc gcctcccggg ttcaagccat    7200

tctcctgcct cagcctcccc agtagctggg actacaggca cctgccacct tgcccggctg    7260

ttttttttgta tttttagtag agacagggtt tcaccatgtt agccaggatg gtctcgatct    7320

cctgacctca tgatccgccc accttggcct cccaaagtgc tgacattaca ggtgtgagcc    7380

accgtacccg gcctattttc ttctttagac agggtcttcc tctgtcccct aggctggagt    7440

gcagtggtgt gatcttggct cactgcaacc tctgcccct gggttcaaga gattctcctg    7500

cctcagcctc ctgagcagct gggattacag acatgcgtca ctatgcccgg ctaatttttt    7560

gcatttttg gtagagatgg ggtttcacca tgttggtcag gctggtctcg aactcctggc    7620

ctcaagtgat ctgtctgcct tggcctccca aagtgctggg attacaggtg tgagccaccc    7680

cgcccggggc aaagctattt ccatttttaa attttttgtt attgttgttt tgagaccaag    7740

tctcactctg ttgcccaggc tggagtgcag tggcatgatc tctaaatttt gtattttttag    7800

tagagacggg tttttcacctt gttgcccagg ctggtctcga attcctgacc tcaggtgatc    7860

cacttgcctc agccgcccaa agtgctggga ttacaggcgt gggccaccat gcccagcctg    7920

ccaaagctat tttctatggg ataaatgaca gcagaaagga ccccagagca aaatactaca    7980

aagatgtatg gcacgtgcat gaggtgagag tatggtagaa tcaagtgagt ctctgctttc    8040

atgagactga acagtgaggc tcaggttaaa attagaggtg tacaagagag tatgatatgg    8100

acatctgcta ctgaacaatc cttgtgcttc ttgaaaatgc tcatttccat attttttatt    8160

ttttattttt tttcagatac aaggtctcac tgtgtcaccc aggctagatt gcaggggcac    8220

aattaaggtt cactaaagtc ccaacccccc gggttcaagc aatcctcctg cctcagcctc    8280

tggagtagct gggactgcag ttgcatgcca cagtgcccgg ctaatttttt tattttttgt    8340

agaggcaagg gcttgctctg ttgcccagat tggtcttgaa ctcctggcct caaatgatcc    8400

tcccacccgt gcctcccaaa gtgctgggat tacaggcata agccactgca cccagcctca    8460
```

-continued

```
tttctatatg taagttcatt tagtcattaa gtcttgaagc aaagatccag ccacgatcta    8520

tataaaattt tcaatacagg ccaggcatgg tggctcacgt ctataatccc ggcactttgg    8580

gaggctgagg cagactgatc actttaggtc aggagttcca gaccagcctg gccaacatgg    8640

tgaaacgcta atacaaaaaa ttagctgggc atggtggtca gcacctgtaa tcccagctgc    8700

tagggaggtt gaggcaggag aatcggttga acctggaggt agaggttgca gtaagtcaag    8760

atcacgccac tgcactccac cctgggaaac agagcaagac tctgttccaa aaaaaaacaa    8820

aaggcaatct ttcctagaaa aaaatagttt ctgcacattc ttaggcacgc atttgtaggc    8880

tgctatagct atttaaaatt ttcaatacaa tatgtttacc agagcaaact acaatcctca    8940

ttgttatgtg ggccccaaac cattactgat actcatctgt ttcccccacg tcgtctacat    9000

ttcctcatgg tgggccagta cttcattttt tgtaactcat ttgcctgcta gggtgactca    9060

ggcctttgtt tctgagagat ctgagtctgg tgttgctagg aaggaaaagg ttaactagtc    9120

tataatccat tctttctccc aacctggtga tgtctgagga ggcatccctt ggtcaaactt    9180

ctttgtaaac atgctaatca gatctcatgg tatttattag aggaaaacaa ccagagattc    9240

ttatctgtga gatgctttca gcaggacata cttgttcttt cttgatgtct tgcagtaaac    9300

aaggaattta ggggtttatg ggcatgagcc actggaaaat gtcagcgtca catatttagt    9360

taagagagag agagagaggg gctgggcgtg gtggttcatg cctacaatcc cagcattttg    9420

ggagactgag gcaggaagat cacttgagcc cagaagcgta agatcagcct aggtaacata    9480

atgagacctc gtcttattaa gagtctgatt ctaccctccc ttggtgttat ctcagttact    9540

gtacttttac agggctgtgg ttgtgcaact tcctgctggg catggggaat tctctgagtt    9600

ccagacaaga accttcctgc ccaatatgca gcagcaaccc agtctcttca taatgctcgt    9660

ggttgattat ccatgcccgc caactacctc atttctctgc ccagtgcttt atcagcctga    9720

agagcccaca gtcaccaggc agaaaacctt actgtgcttc ttggtgaaag tgttccctct    9780

tcaaaaatga agacatcacg ccagataagg tttggggact agaagcacaa tttcttcaag    9840

tgggtcccta gacaggatat tgataaaatgc caattctgtt tcactccctg gtagctacac    9900

ctgtatattc taactactag ggtcacagcc ccttatattg actgttggtt atatgcagat    9960

attgcatctt agaggacagc accccaaacc catgggatgt tatacctggg ctgacacttt   10020

agttgagccc tttaaaaagc cattcctggg ccaagcccgg tggctcacac ctgtaatccc   10080

agcactttgg gaggctgagg cgggcggatc acgaggtcag gagatcgaga ccatcctggc   10140

taacatggtg gaaccctgta tctaccaaaa atacaaaaaa aattagctgg gcctggtggc   10200

aggcgcctgt agtcccagct attcagaagg ctgaggcagg agaatggcgt gaacccagga   10260

ggtggaggtt gcagtgagct gagactgtgc cactgcactc cagcctgggc gacagagtga   10320

gactctgtct caaaaaaata aataaataaa taaataaata aataaataaa aggccattcc   10380

tggctgggca tggtggctca cgcctgtaat cccagcactt gggaggccg aggagggcgg   10440

atcacctgag gttgggagtt tgagaccagc ctgaccaaca tggagaaacc ctatttctac   10500

taaaaataca aaattagcct ggcatggtgg cacatgccta taatcccagc tacttgggag   10560

gctgaggaag gagaatcgct tgaatccggg aggcagaggt tgcagtgagc agagattgca   10620

ccattgcact ccaacctggg caacgagagt gaaactccat ctcaaaaaaa acaaaaagcc   10680

attcctggcc tggcgcaatg gctcacgcct gtaatcccaa cactttggga ttacgcttgc   10740
```

-continued

```
caaagtaagt gaattacctg aggtcaggag tttgacacca gcctggccaa catggtgaaa    10800

ccccgtctct actaaaaata cacaattagc tggacatgat ggcaggcgcc tgtaatccca    10860

gttactcagg aggctgaggg aggagaacct cttgaaccca ggaggcaggg gttgcagtga    10920

gccaagattg cgccattgca ctccagccag ggcaacaaga gtgaaactcc gtctcaaaaa    10980

ataaataaat aaataaataa ataataacca ttatgttatc ccatgatggc agctctttct    11040

gtataaggta ataaatatgc gatgtaaaga gtgtatttca tattaatgca ctgattgttg    11100

tacctttttt tttttttttt tttttttttt gagacaggt cttgctctgt cacccaggct    11160

ggagtgcagt ggcgcaatct cgactcactt caacctctgc ctcccaggtt caagcaatcc    11220

ttctgcctca gcctcctgag tagctgggat cacaggtgcc cgccaccacg cccagctaat    11280

ttttgtactt ttttagtaga cacggggttt tgcctgttgc ccaggctggt ctcaaactcc    11340

tgacctcagg tgatctgccc tccctggcct cccaaagggc tgggattaca ggcacaggga    11400

gccaccatgc ccagctgttt ttttgttttg ttttttgttt tttttgagac agagtctcac    11460

tctgtcgccc aggctagagt gcagtggctt gatcttggct cactgcaacc tcggttcact    11520

gaagcctccc agtttcaagc cgtactctta cctcagcctt ctgagtagtt gggattacag    11580

gcgtgagcca ctgtgcccag cctttgtgtt tgtattttta gtagagatgg ggtttcacca    11640

tgttggccag gctggtcttg aactcctggc acaagtgat ccacctgcct tggcctccca    11700

aagtgctggg attacaagga tgttagaaaa tggctgggcc tggtggctta cacctactcg    11760

ggaaactgag gcacgagaat cgcttgaacc cgggagacgg gcattgcagt gagctgagat    11820

caggccattg cactccagcc tgggcgacag tcacaaaaaa aaaaaaaaag aaagaaagaa    11880

agaaagaaaa cacatcaatt ccaggaaata caaatcagat gagatcgggc gtgttcccgg    11940

tggtatggtc acagaaacag gaagcacaaa tcaatcacct ccaccactgc cctctccggg    12000

ggaaaggatg aaatgtaatc aacttaccac taactagtca gtcattcccc ttaaaggaca    12060

atagcagatc aaggtgtcat catgggcttt tttttttttt tttttgagac agggtctcgc    12120

tctgtcgccc agcctagagt gcagtggcac caccatagct caaccttctg ggctcaagcg    12180

atcctcctgc cttagcctct ggagtactag gactataggt gcatgcctcc atgcctggct    12240

aattgaaaaa ttttttttgt agagacagga tttggctttt ttacccagac tcatctcaaa    12300

ctcctggcct caagcgatcc tcccgcctcg gcctctcact ggtactctta tcacaggcat    12360

gagccagcgt gtctggccct gatcacagcc agaaactccc aggctgtgat aatgagctca    12420

gctttcatga gagacagctc atgctattag gcacatcctt cgtctcttct cctgctaccc    12480

tgctaccgcg tctctgttca tgggtgcatt atacaagcag tggtctgagg atagagcctc    12540

agtgatgccc actgcacaag gcaccctctc ttcctggttg ctcaggatct tctctgtggt    12600

gagcactccc tggagaacat taacatgaga cacagagatc tcatgcctct gcctcttctc    12660

ataattcctt tttttttttt gagagggagt ctcaccgtgt tgcccaggct ggagggcaat    12720

ggtgtgatct cagctcactg caaccttcac cttccaggtt caagtgattc tcctgcctca    12780

gcctcccagg tagctggggc tacaagtgtg tgtcaccgca cccggctaat ttttgtgtct    12840

ttagtagaga cggggtttca ccatgttggc caggctggtc tggaactcct gacctcaggt    12900

gatctgcctg cctcagcctc ccatagtgct gggattacag gtgtgagcca ctgtgcccag    12960

tgcccccccct tttttgtgtg tgtcagggtc tcactctgtc acccaggcta gagtgcaggg    13020
```

-continued

```
gcataatctc ggctcactgc aacatctgcc tccaaggctc aagtggtcct cccacctcag   13080

cctcctgagt aacagggact acaggcacgt gccaccaaac ccagctaatt ttttgtattt   13140

ttggtacaga cgagacttca ccatgttgcc caggctggtc acaaactcct gacctcaagc   13200

gatccaccag ccttggcttc ccaaaatgct gggaatacag acgtgagcca ccgtgactgg   13260

ccccagctaa tttttgtatt tttagtagag atgggttttc accatgttgg ctaggctggt   13320

ctcacactcc tcacctcagg tgatccacct gcctctgcct cccacagtgc tgggattaca   13380

ggcataagcc accacgcccc accgtgagac ccccatctct acaaaaaaag ttttaattag   13440

ctgtgcatgg tggcaggcac cctagtccca gctacctact gaggaggctg atcgcttgag   13500

cccaggaggt caaggctgca gtgagctggg atcacagcac tgcactccag cctgggagac   13560

agagggagac tctatctcca aaaagaaaaa aagactagag attgtgcccc aggcacagat   13620

catattaatc ccagtgatat ctgggagtg gtggccagac tccttcccag gactggtctt    13680

ccggtttggc aatgagtgtt agtcaaggcg tgaggttctc atgggccgtc tcaagcactc   13740

tgttcgacat cttttttactc tctcccaggc tggggtgcag tggcgtcatc ttggcttact   13800

gtagcctccg cctccagggt tcaagcaatt ctggtgcctc agcctcccga gtagctggga   13860

ttataggcgc ctgccatcac gcctggctaa tttttttttgt atttctagta gagtcagggt   13920

ttcactatgt tgcccaggct ggtcttgaac tcctgacctc aggtgatctg cctgcctcga   13980

cctcccaaag tgctggggtt gactgctcgt ggccctctg ttgcacatct tgacttctca    14040

gcctccaagg tgattcttta ggacaccaat ttaatccctc taaacatggc aacagagcca   14100

gcggtttcca gccctatttg cgcagtagaa ggattattta caaatcctcg tacttagact   14160

ccacccgcag agattcaagt ggactgagcc tggagtgaag ccgaaggcat tttcttataa   14220

tcctgagaat gataatatac agctgtcttt gaaaaccacc actaagactt gtaaactttg   14280

ttcattcaag tcttctttttc tccccttaaa agcaggctta tccttgaggt gtgcttttttc   14340

agactccagt aagcatcact gagaacactt aattaatata ctgaggcctc tcacaagagg   14400

gaaggagtgg aagaactcct ggagaaggac ttggaaggga gagatgtttt tctttctttc   14460

tttcttttttt ttttttttgg agacagagtt cactcttatt gcccaggctg gagtgcaatg   14520

gcgtgatctt ggctcactgc aacctctgcc tcccaggttc aagcaattct cctgcctcag   14580

cctccccagt agctgggatc acaggcgcct accaccatgc ccagctaatt tttgtacttt   14640

tttagcagag acgggctgtc gccacgttgg cctggctggt ctcgaactcc tgacctcagg   14700

tgatccgccc acctcggcct cccaaagtgc tgggagtaca gacatgagcc accgtgccca   14760

gccaagatgt ttttcttaac acaaaaagtt tttgtctggg tgtggtggct cacgcctgta   14820

ctcccagcac tttgggaggc cgaggcgggg agatcacttg caatcaggag ttcgagacca   14880

gcctggccaa cgtggcaaat acaaaaatta cctgggcatg gtggcgcttg cctgtaatcc   14940

cagttatttta ggaggctgag gcaggagaat tgcttgaatc cgggaggcgg aggttgcagt   15000

gagctgagat caagccactg aactccagcc tgggcgacag agtaagactc catctcaaaa   15060

ataaaaaaaa atttctaaag caagcgcttg ggctgttctg atgtcaacat acagtagctg   15120

gccctacctt taacccagga taaggggcaa aagtataccc aaagatacat gtaatcaaag   15180

ttgctgggtg cagtggccca cgcctataat cccagtgatt tggaggctg aggtgggagg    15240

attacttgat cctggaggtt gagaccagcc tgggtaacac agtgagacct tgtctctgaa   15300
```

-continued

```
acctaaaata aaataaaata aaataccact gtgctctatc ctgagcaaca gagcaagacc  15360

ctgtctcaaa tataataaaa ataaaaataa tcagtccttg ggtttagcat ctttggacta  15420

atggtaccag catgagggaa agcaggtctt tgtagctctg ataagtgaac tttgacactt  15480

cttagtgttt ttctctaact gtggtgacat acgaataaca tataattaac catttaaaaa  15540

taagcggttc ggtggcattt agtacatcac agtgttgtgc aaccaccacc tctaggtagt  15600

tccaaaactt tttctttctg tttttttttt tgagacagag tttcgctctt cttgcccggg  15660

caggagggca atgacacgat ctccactcac cgccacctct gcctcccagg ttcaaatgat  15720

tgtcctgcct cagcttcccg agtagctggg attacaggca tgtgccaccg cacccggcta  15780

attttgtatt tttagtagag atgaggtttc tccatgttgg ccaggctggt ctcaaattcc  15840

tgacctcagg tgatccaccc gcctcggcct ctcaagtgct gggattacag atgtgagcca  15900

ccatgcctgg ccccaaaaca ctttcctaac tctaaaataa agtcccataa gcaggtattc  15960

cccactccct cctcctcccg gcctgtccat ccacaaatga atggattaaa caatatggtt  16020

tatccataca atggagtata attcagctgt aaaaggggct tggcgcagtg gctcacacca  16080

gtaatctcag cactttggga ggccgaggcg ggcagatcac ttgaggccag gagtttgaga  16140

ccagcctggc caacatggtg aaaccaggtc tctactaaaa atacgaaaat tagccaggcg  16200

tgttagtgca cacctgtaat cccacctact caggagactg aggcatgaga atcacttgaa  16260

tttaggaggc agagaagttg cagtgagctg agatcctgcc actgcactcc agcctgggca  16320

acagagcaag actctgtctc aaaaaaaaaa aaaaaaaga ggaatgagat accgacacat  16380

tataccatga ggataaacct tgaaacaac atgctcagta aaagaagcca gcacacaaaa  16440

ggttacatat tatataatgt aattttattt tagtttttga aaagctggtc tcctgggctc  16500

aagcgatcct cccttcttgg cctcccaaac tgctgggatt acaggtgtga gccactgtgt  16560

ccggcctatg atttttttt tttaatgaaa tacctggaaa agataaatcc agagaaacag  16620

acggcagatt acaggctctt tttaaattgg tttctgacac tatcacaaga taaaaatgtg  16680

gtttaaaatt gttgcttggt atgtcttatt cacctctaaa gatatactgt tcatcaggcc  16740

gggtgcagtg gctcacacct gtaatcccag cactttggga ggctgaggcg ggaggatggc  16800

ttgaacccag gagttctagg ctgtaatgtg ctctgccaat tgggcatcca cactaagttc  16860

ggcatcaata tggtgacctc ccaccaggtt gcctaagaag tggggaaatg gtctaggttg  16920

aaaatggagc aggtcaaaat tttcatgctg gctgggcaca gtggctcaca catgtaatcc  16980

cagcactttg ggaggccaag gcagatggat cacctgaggt caggagtttg agaccagtct  17040

ggccaacatg gtgaaaccct gtctctacta aaaatacaaa aaaaaaatt agctgggcat  17100

ggtggcatgt gcctataatc ccagctattt gggaggctga ggcaggagag ttgcttgaac  17160

ccaggaggca gaggttgcag tgagccggga tcacgccact gcactctaac ctgggcgaca  17220

gagtgagact ccatctcaaa aaaaaaaaa aaaactttca tgctgatcag tagtggaatc  17280

agcttgtgaa ttccctcca gcctgagcaa cacagactgc ctcttactaa tcccagcact  17340

ttgggaggct gaggtgggag gatggcttgt gcctaagact ttgagactag cctagccaaa  17400

atcccttctc tacaaaaaat gcaaaaatta gctgggtatg gtagtgtgca cctgtagtcc  17460

cagttactca ggaggcttag gtgagaggct cacctaggcc caggaggtta aggctgcatt  17520

gagctatgat tttgccactg cactccaggc tgggcctagg cctttgtagt cacagctact  17580
```

-continued

```
tgggggcaaa tgtaggagga tcacttgagc ccagtaggtc gaggctgcag tcagctgtgt   17640

tttttgagac atagcaagac cctgtctcaa aaagaaaaaa aaaagtagct acaagctcat   17700

ttatgcaaag gctaaccact gtcacaagta gagatgtgca gaactgagat tcaaatggat   17760

ggaatggcaa gaaaaactgc cacttctgtg aacctgaagt caaactgccc ttgtcgtcaa   17820

gataaaaggt atacatggtg tgagcctggg catctgaaag gtgttgcagc ttttttctttt   17880

attttttttga gatggagtct cactcctgtc acccaggctg gagtgcagtg gtgcgatctc   17940

agctcactgc aacctctgcc tcctgggttc aagcaattct cctgcctcag cctcctgagt   18000

agctgggatt acaggtgccc accaccacac ccagctaatt ttcgtatttt tagtagagat   18060

ggggtttcgc catgttggcc aggctggtct cgaactcctg acctcaggtg atccgcctgc   18120

ctcagcctcc caaagtgctg ggattacagg tgtgagccac ctgtaattag ccaggcttgg   18180

tggtgggtgc ctgtaatccc agctactggg aaggctgagg caggagaatt gcttgaacct   18240

gagaggcgga ggttgctgtg agccgagatc gtgccactgc actccagcct gggtgacaga   18300

gtgagactcc atctctaaat aaataaataa ataaataaaa tgagatgatt tctgagtgag   18360

ttaactaaat caggatatgc agaacaatgc caagcatata ttagccacta aagaatatat   18420

aagttgcctg aaagcccctt tagggtttaa acctggactt cattattcac aatcacattc   18480

ccggtcccca ttacggagcc tggtcacctg ggtgcttgtt agatatggaa atcatcagat   18540

cccacccag accgagtcag aaacgttgag ggcaggagtt caagaccagc ctggccaaca   18600

tggcggaaac tccgtctcta ctaaaaatac aaaaattagt caggagtggt ggcacaggcc   18660

tgtgatctca gctactcggg aggctgagac atgagaatcc cttgaacctg ggaggcagag   18720

gctgcagtga gccaagatgg tgtcattgcg ctccagcctg ggtgacagag tgggactctg   18780

tctcaaagaa aaagaaaaaa agaaaagaaa ttgcagcttc tgctcaggaa gtctggagtg   18840

ggccaggatt ctgcatttta acaactccca ggagtgttag tggggctggt ttgtggactc   18900

gcctttgagt cgttggtctc cgctcaatca atattagata aaatgacagt attgggagaa   18960

atccaggggg ctctggagga ccgagggatc atattggagg cagataggc agagaaaggt   19020

ggaggaggtg ggagtcgggt gtggctgtgg aggaagctac ttaaatccgg atttgatctt   19080

tgctagttct tatccctgga cctgaaccca ggcgcacatc tggattagaa gatgccaggc   19140

tcagaggatc ttcgtaaagg taagccagaa aaaatgagaa ccgaagcaaa gacacgtgaa   19200

gaagtggaaa gcagctggcg gcgggaaaag gcagagggac caggcggccg aagctggtgc   19260

ttcgtccacg tgggtggcag ggacttccca cagaggctgt catcgttttt gttgttgttg   19320

ttttgttttg ttttgtttgt cttttgagac agtctcactc tgtcgctcag gctggagtgc   19380

agtggcacga tttcggctca ctgcaacctc cacctccag gttcaagcaa ttctcctgcc   19440

tcagcctccc gagtagctgg gatgacaggc acacgccacc acacctggct aatttttttt   19500

tttttttgtat ttttagtaga ccgggggggtt tcaccatatt gaccaggctg gtctcgaact   19560

cctgaccttg tgatccgtct ggctcagcct cccaaagtgc tggggtgaca ggcgtgagcc   19620

actgcacccg gccaagtttt tgtatcttta tagagatggg gtttcaccat gttagctagg   19680

ttggtctcaa gcccctgacc tcatgtgatt ggctggcctc ggcctcccaa agtgctggga   19740

ttacaggcat gagcctcggt gcccggccgc ggctgtcatc tgcagcacac ggcaaatgca   19800

gggaagcctg tttctgcctt caaatccgaa atcttctccc tcgtagttgt gtcctaattc   19860
```

-continued

```
ttcccacccc gatgcttgtt cttgagcaca ggggaatctg attcctatga ggatgattag    19920

gtcctagata gaatataggc ttagccaagc tggaaatctc atgttcatga gcacttacta    19980

gactctggag ctgctgccaa accattttca ggcatgatgc gattcagatc ttttagagcg    20040

aggcatgcgg tggctcatgc ctgtaatccc agcactttgg gaggccgagg tgggcagatc    20100

gcttcagccc aggagttcaa gaccagcctg gcaacaaaa caagacgttg tctctacaaa    20160

aaatacaaaa attagccggg catgtcagtg ttgtgtagtt ccagctactc gggaggctga    20220

ggtgagagga tcgcttgagc ctggggaggt tgaggctgaa gtgagctgtg atcatgccac    20280

tgggcaacac agcagtacac tgtctcaaga aaaagaaagt aaaaggtgac atccgtgaca    20340

gcagtgatgt tattttttctg cttatttcct tgctatattc ctaaaagaat atacttaatg    20400

aacattgaat aaatgataag aataaaacca tgtccatcca tttcaccttg gattgagttg    20460

cctatttcta cacaaagaaa atagaaccca agaggtaagg cacaagcgat cccttattta    20520

cgtatttatt tatttattta tttattattt tcttgagaca gggtctccct ctgtctcagg    20580

ctggagtgca gtggcataat ctcggctcac cacagcctct gcctctgagg ttcaagcgat    20640

tctcctgcct cagcctcccg agtagctggg actacaggcg tgcaccatca cgcccagcta    20700

attttttgtac ttttagtaga gacagggttt caccatgtta gccagaatgg tcttgatctc    20760

ttgacctcat gatccgcccg ccttggcctc ccaaagtgct gggattacag gcatgagcca    20820

ctgtgcccgg ccaaattttt gtgttttaa tagagatggg gtttcaccat gctggccagg    20880

ctggtctcaa actcatgacc tgatatgatc tgcccgccct ggcctcccaa agtgctggga    20940

ttacaggcgt gagcaaggga tcccatattt aaatgataac agaaaaaag gatggaggaa    21000

ccaggggga aggaacaac cttttcctat gaaaatgaca aatgaggctt ggaaaaacaa    21060

ggacaaaagg cagatcaagt tgtcctcccg cttcagcctc ccacagtact gggactgcag    21120

cctgaggcac gaccccggcc agcagtgtct ccatatctaa gaacctcagt cacggccggg    21180

cacagtggct cacgcatgta atcccaacac tttgggaggc cgaggcgggt ggatcacctg    21240

aggtcaggag ttcgagacca gcctagccaa catggtgaaa ccctgtctct gctagaaata    21300

caaaaattat ccgggcatgg tggcgtgcgc ctgtaatccc agctactcgg gaggctgagg    21360

caggagaatc gcttgaactc aggaggtgga ggttgcagtg agctgagatt gtgccactgc    21420

actccagcct cggtgacaga acctcagtca cttgatcatc acgttgtacc tcagtggaaa    21480

ggaaaggaaa gctcaggctt ttgagaatgg agttgttagc atttcccatt tgtgtctttt    21540

tcctcctctt tcaaggcaag gaccagatgc attcacacag gaaacgaacc atgttcacta    21600

agaagcaact ggaagatctg aacatcttgt tcaatgagaa cccatacccca aaccccagcc    21660

ttcagaaaga aatggcctcg aaaatagaca tacacccaac agtactgcag gttggaaaat    21720

gatccctctt ctcactaaac tgccttcctg atctaatcta aattcagagt ccctctagga    21780

taattcctga ggtctcattc caatcgccaa tattccccaa acccacactc tcctactcac    21840

gtccccgtaa acctttcttc aacccccctag agcaagaatg ggaaaatttt tccagtaaag    21900

gaccaggtag taaataattg aagctttgtg gccataccg tctctctagc aactatttta    21960

actatgccac cacagtgcga aggcagccac agacaacgta aacaagaggc ccatctgtgt    22020

tcccagaaac tcttttactc aggttggagc acggtggtgc aatcacagct cactgcagcc    22080

tcgacctccc gggctcaagc aatcctacca cctcagcacc ccaagtagct gggactacag    22140
```

-continued

```
gtctacaggt gcacactacg cctcccaaag tgttgggatt acaagcatga gcccggctgt    22200

attttatttt ttgtagagat ggggtttcgc tatattgccc aggaggctga tcttgaactc    22260

ctggtctcaa gtgattcacc tgccttggcc tcccaaagtg tcaggattat aggcataagc    22320

cactgcgcct ggcctgaagt ttatacaatt ttcacattac aaaatagtgt tgttttgttt    22380

tgttttaaga cagggtgttg ctcttgccca cattggagtg cagtggcacg atcatagctc    22440

actgcagctt tgaattcctg ggctgaagcc atcctcccac tcagattccc aagtaggtgg    22500

gactacaggt gtgtggtact acagcctccc gagcagctga tactactggt gtgtaccacc    22560

aggcccagcc aatttgtgtg ttttttgtag agatggggtt tcgtcatgtt gcccaggctg    22620

gactcaaact cctgaaatca agtgatccac ccacctcagc ctcccagagt cctgggatta    22680

taggcatgag ccactgtgcc tggccagtag tattctttta ttttctctct tttttctttc    22740

agtcccaaca cacatacaac acaaaatagt actcttattg tgtttgtttt ttctcaacca    22800

ttttaaaacg taaagcctat tcttagtgca tgggtgatac aaagacaggg ggtggtcaga    22860

tttggccacc agccttagct ggctggcctg agccccagag cagccctgc gactgatccc    22920

cttgctctcc tatccctgc tctgggtttt ctgacccctg tctcaatttc tgtccccaaa    22980

atctctcatt tctgctcctt cctgggagta gattgagtag ggttcacaa agaggatgta    23040

agtggccaag ctgtggcact agctgttctc acctagaagt actcatatta tcaactaaaa    23100

ggaaaacttg ggtggggtat ggtggctcat gcctgtaatc ccagcagttt gggaggccga    23160

ggtgggcgga tcatgaggtc aggagttcga gaccagcctg gccaatatgg tgaaaccctg    23220

tctgtactaa aaatacaaaa attagccagg catagtggtg tgagcctgta gtccccgcta    23280

ctcaggaggc tgaggcagaa gcatcgcttg aacctgggag gcggaggttg cagtgagccg    23340

agatggtgcc actgaactcc agcctgggcg acaaggtgag actccatctc aaaaataaaa    23400

taaaataaaa taaaaataaa taaataaata aatattagga gagtttaagg gccaaaaaaa    23460

ggaaaaaaaa agaaaagtta aaaacttaaa ggttaaaaaa aagaatataa ataaataaaa    23520

tacgtttaac aaaataaaaa ttaaaaagta aaaatttttt aaaaatagaa tgacaagtca    23580

tctgaattcc acccccattct cttctctctc ttcccttcag gtctggttca agaatcacag    23640

agcaaaactc aagaaagcga aatgcaagca tattcatcaa aaacaagaaa ctccacaacc    23700

gccaatacca gagggtgggg tctccaccag tgtcggcctg agaaatgcag acacactacc    23760

cagattgccc aacgctgctc acccgatcgg cctggtgtac acgggtcatc gagtcccctc    23820

attccagctc atcctgtacc ccaacctcaa ggtccctgca aatgacttca ttggccacag    23880

aatagtccat tttggctgct gccgagatcc taatatatac tgcctctacc ccattttgga    23940

atcccaagtt tgcgctccaa gcttccattc tggctctcct gcctgttcat ctaaccaaag    24000

tcgagagaga tgataaatac aaaaagtcac atgttgtaat gatgtgtgtg tggtactgtg    24060

acatttgcgt ttggtcttcg tgcctgtttc ctggaaagca gctccagagt tccatggagt    24120

ctccaaagtg ccatcttttt gtattttgtg tgctaatgtt gaccgatagc ttcaggatgg    24180

ggactggtct ctgaaaagac cccagtagga ttagagggca aacttctggg aggggaagga    24240

agctgagggt gaggctgatc accattggcc agtggtttca tcagtcatgt ctgggtaagg    24300

aagcatccat caaaacccag gaggacaggg tttgaagaga tccctgacag ctaagcatgc    24360

ggacgtacct ggagggtggc atatccgggg agggcatgga agctccgggc ccctcgtcat    24420
```

-continued

```
acgcctcatc ctagcagggt gcggtggctc atgcctctaa tcccagcacg ttgggaggcc   24480

aaggcaggcg gatcacctga ggtcaggagt ttgggaccag cctggccagc atggcgaagc   24540

ccatctctac taaaagtaca aaaattagcc gggcgtggtg gcttgtgcct gtaatcccag   24600

ctactcggga ggctgaggca ggagatggc gtgaacccgg gaggcagagg ttgcagtgag   24660

ctgagggat tgtgccactg cattccagcc tgggtgacag agcaagaatc tgtctcaaaa   24720

aaaagaaaca agaaagcaca gaggaccagc tggaatattt ggaagaccag aaaatgtcct   24780

taaaactcaa aatgcctggg catataggtc aggtccacct agcctttga atcaatgcga   24840

acccttcctc aaggcctgga ggttggcaac acaaaatcac cctgtggaga acctaaagca   24900

ttccctctct gagagttgag tcaattggga ttccacccc aaaattccta aaaatctcaa   24960

gttcctagaa aattctcaga aaaagcaagc tctcctatac ctccctggct gtactctgat   25020

gcaacttggc aaccatcaga gaatctccat ccccttgaac cttggtcctc tgccaatgtt   25080

cctcacgcct gtaatcccag cactttggga ggctgaggcg ggcggatggc ttgagcccag   25140

gagttcgaga ccagcctggc cagcatggta aaacctcatc tctaccaaaa acatcaaaat   25200

tagccagtct catatactgg tctcaaaata aataaataga ttaaaattta aacataaaat   25260

aaacatgagt gtgttagaaa gaacctactg gcccggcgtg gtggctcaca cctgtaatcc   25320

cagcactttg ggaggcagag gcaggcggat catctgaggt tgggagttcg agaccagccc   25380

gaccaacatg gagaaacccc gtctttacta aaaatacaaa attagccagg catggtggcg   25440

catgcctgta atcccagcta ctggggaggc tgaggcagga gaattgcttg aacccgggaa   25500

ggggaggttg ccatgagccg agattgcgcc attgcactcc aagcctcctg ggcaagaaga   25560

gcaaaactcc atctcaaaaa aaaaaaaaa aaaaggaac ctactgtagg atttggagtt   25620

gagtaatttc agatagaatc aaaggaagag aaaggtctgg attgggtggt gccagcggca   25680

gcttctatga ctgagtatct caatacatct tatctatagg acggctgact agaaagagga   25740

caaacctata atagataaat gggcggcagc cattgcttag ccataggcga atatttgatg   25800

ggttggggct caggacaaat gttaaaaaca atcttaataa cagcatgccg gcccggcggc   25860

ccacacctgt aatcccaggg gatttcagag gtggaggggg aggcggaagg attgcttgag   25920

cccaggaggt tgaggctgca gtgagctgtg attgcaccgc tgcactccag cctgggtggc   25980

agagcgagcc cctatatcaa aacaaacatt atcaagaaaa attattaaat gaataacaaa   26040

aacaggctgg gcacggtggc tcacgcctgt aatccaagta ctttgggagg ctgaggcagg   26100

tggattgctt caactcagga gtttgagacc agcctaggca acacggtgaa accctgtccc   26160

tacaaaaaca caaagaagga gtctcgcttt gtcgcccagg ctggagtaca gtggtgtgat   26220

ctcggctcac tgcaacctcc tccatctcct gggttcaagt gattctcctg cctcagcctc   26280

ccaagtagct gggactacag gcatgcacca gcacacctgg ctaattttg tattttagt   26340

agagatgggg tttcatcatg ttggccaggc tggtctcaaa ctcctgacct caggtgatcc   26400

acctgcttca gcctcccaaa gtgctggaat tacaggcttg agccaccatg cccagcctct   26460

acaattaatt aaaaaagaac cataacccca aaacttgtac aaccaccagt ccaagaaacc   26520

aagtcacaat ttctgcagca atcagcccca aatgcccagg gcttgatcca tcactcgtag   26580

cttccctagt ttttgtgccc atcccccaac cttgatttca atttaggacc aaccagagaa   26640

acccaatgtt tggctaaaca atcccacagg atcctacttc tggttagctc cctggcggcc   26700
```

-continued

```
tcccaacgtc agcagccttt ggtcaggaca tatctgaaga cttcgttttt tttctgctat    26760

aaagctttct ttcctttttt ttttttctcc tgaggtgaag tctaactctg tctcccaggc    26820

tggaatgtag tggcatgatc tcggctcact gcaacctccg cctccctggt tcaagcgagt    26880

ctcacacctc agcctcctga gtagctgaga ttacaggcat gcaccaccac acctggctaa    26940

tttttatggt gttttttttt gtttgttttt ttgtttcttt ttgtagagac ggggtttcac    27000

catgttgccc aggctggtct cgaactccta acctcaaatg ttctgcccaa ctcggcctcc    27060

caaagtgctg ggataacagg cgtgagccac tgcgcctggc catggaacct cactctttaa    27120

agtgtgcagg accccagtc attccccact gtgtcgcggt tcccataaca gtgcctgtca     27180

ccaagtatgt tttcaaaata catttttgga agagagagag aaacagaagg ggaggggta     27240

ggaagagaaa gtaggggaag aggaaagtga gagagggaga caggaaggga gagggaaggg    27300

agacacagag atgaagacaa agggaaagag acagaggccg ggtacagtgg ctcatgcctg    27360

taatcccagc actttgggag gccgaggtgg cggatcacct gaggtcagca gttccagacc    27420

agcctggcca acatggtgaa accccgtct ctaccaaaaa tacaaaaatt atctgggagt      27480

gatggtgtgt gcctgtaatc ccagctactc gggaggctga ggcaagagaa tcacttgaac    27540

ctgggaggtg gaggttgtgg tgagccgaga tcgcacccctt gaactccatc ctgggcaaca    27600

gaacgaggct ctatctcaaa aaaaaaaaaa aaaacagaaa gaaaagaaaa gaaaaggaac    27660

agcttccaag catctttgga gaagggcttc actaacatca aatcctgtct tcctctcatc    27720

accttctagc ccagtatttc cccaacgtga gaataataag aatcatctgg ggagctgtta    27780

aaacccagac tctgagacca gacaggggca tgcttcccag gtgtgggcat gattttttccc    27840

tggggttgta tttaacaaag ttcaaaaccc aggaggtaca atcaaaacct gagccgtctg    27900

gagactcaag acttcttagg gaagacgaaa aagagaaatt ccggccaggt gcagtggctc    27960

tcgcccgtaa tcccagcact ttgggagtcc aaggcaggag gatcgcgtga tcccaggagt    28020

tggagaccag cctggccaac atggtgagac cctcatctct acaaaaaaaa aaaaaaaaaa    28080

agagagagag agagaaagaa gttcccagag aaagttccca gaggaaacag gagggaaaag    28140

ggcgaggact gcacccagcc agctagggta tgagtgtgaa ccatagtcta gggggctggg    28200

tgtgaattcc cagtccaggg gctgtgaata cgtggagaca ccgatgctgg ccctgcaccc    28260

agcctcctcc ctgggcgaac tattgactga agccacccct cgtgtcccca ctgttcctgg    28320

tctcaacttc ctcacctgat gaatgggcgg ggagggtaat tccctacgg tggggctttt     28380

ctcactctgt tatgtgttct tacaaaatgt gctctctgat atcatctata tctccctaga    28440

aggaatcatt agtttatctt tttttttttt tgtgggacag ggtttcactc tggtcgccca    28500

ggccggagtg cagtggtgcg atctcggctc actgtaacct ccacctcctg ggttcaagcg    28560

attctcccac ctcagtctcc caaggcctgg tgcggtggct tacgcctgta atcccagcac    28620

tttgggaggc caaggtgggc ggatcacttg gggtcaggag tttgagacca gcctggccaa    28680

tatggtgaaa ctccctcttt actaataata caaaaattgg ccaggcgtgg tggcgggcag    28740

gtgtaatccc agctactcgg aaggctgagg caggagaatt gcttgaaccc agaaggcgga    28800

ggttgcagtg agccgagatc gtgccactgc actccagcct ggggacagag tgaaactgtg    28860

tctcaaataa taataataat aataataata ataatttagg ccaggtgcag tggctcacgc    28920

ctgtaaaccc agcactttgg gaggccgagg cgggtggatc acgaggtcag gagttcaaga    28980
```

-continued

```
ccagcctggc taacatggtg aaaccccatc tcaactaaat atacaaaaaa attagccggg   29040

cgtggtggca catgcctgta atcccagcta cttgggaggc tgaagcagga gaatcgcttg   29100

aacccaggag gggagggttg cagtgagcca agaccgtgct actgcactcc agcctggcaa   29160

cagagcaaga ctccgtctca ataataata ataataataa tttaaaaaaa aaataaaaaa   29220

taagaaataa aagaatgaac cacaatgtcc ctttgttcta caggccactc ttgtgctatc   29280

cacagttgcc aaaaacccccc acctgccttg tctatggacg cccatcgggt gataccacaa   29340

acacctttga tcctacagat accagggtaa attcagcatc caagtccttg aattcttccc   29400

gtgagtataa gctgccctgg ctcagccctc ttctttgcca ggaacccaat ccttcaaact   29460

tccctcaaag actgggtact tttagcatga ctgctctaga gattctgggt ggggctcaaa   29520

gtttaacctt cagggtcagc aacattttat ggaaagagcc acagagtaaa tatttgaaac   29580

attctcgtac actgacactc agctggactg gcaaagcaga atatctgtgt gtcagtgtgc   29640

gttttattca gccgttgttt gggtcagggt ctgtgggcgg cccctggcag ctaatgccct   29700

cctgtgagga acaatacctc accatcaagc acagtccgtc acatattctt gccctggtcg   29760

ctcgctcttt ctttcttttc tttctcttct ttctttcctt tctttctcat tttcgtttct   29820

ttctttcttt ccttcttttc ttttttcttt tgtctctctt tatctatttc tgtttctttc   29880

tctctctctc acctttcttt cttttccttcc ttccttcttt ctcttccttt ctttctctat   29940

ctctcttct ttctttcctt ccttcttcc ttgtttcctt cttctcttttc ttttcttctt   30000

ttttcttct ttcttttctt tctttctctc tctctctttc cttttctttc tctctctc   30060

tctctcttc tctctttctt tcttctgac agggtcttgc tgtgtcaccc aggctggaat   30120

gccaagatgc actcataggt cactgcagcc caaataaatt tccccaggct caggtgatcc   30180

tcccacctca cccttccaag tagctaggac caacaggtac atgccaccat gcacgtctaa   30240

tttttatttt tattttttga gactggtctt gctctgtcac ccaggctgga atgcagtggc   30300

acgatcacag ctcactgcag cctcgacaac ccggcccctc caagcaatct ccccctcac   30360

cctcccaagt agctgggacc tcaggcatgt accaccatgc cctgctaatt ttttattgtt   30420

tgtagaggcg gggtctccct atgttgcgca gggtggtctt gaacacctgg cctcaagcaa   30480

tcctcctgcc ttggccaccc aaaatgctgg gatcatgggc gtgagccact gtgcctggtc   30540

tggtcttcct cctttcatcc tcttagtcct tgacctgtcc ctcttctaga gtcctccctc   30600

ttcatgaccc tctccccctt gttggggctc agaaactgat acctctaaat acagcatgtt   30660

aaaggtgcct caagggccgg gtgcagtggc tcatgcctgt aatcccagca ctttgggagg   30720

ccgaggcagg cagatcactt gaggtcagga gttcaaggcc agaccgacca acatgcaaaa   30780

ccctgtctct actaaaaata tggaaaaaga aaattagttg ggtgctgtga cacacgcctg   30840

taatcccagc tacttgggag gctgaggcag gagaatctgg gaggcggagg ttgcagtgag   30900

ccgaggtcac accactgcac tccagcctgg gcaacagagc gagactctgt ctcaaaaaat   30960

aataagaaat aaataaatga gcctcaaggt ctctgacctc ccccgatcat ctcttccaaa   31020

gcacaggcct ttatctgtgt aagatccaga cctgccaaga ggaataattg ttttttcttc   31080

tcctccctgt gagacaaaga atgtaaccac acctgaacag atcccatcac tgtcaatagg   31140

aatgatttcc aggacccatt catgctctct agtaatcctt tattgccctc aatggaattc   31200

ctctagcccc ctcccataat cagtttgcca ggagaacata taagcttctg aacccccttg   31260
```

-continued

```
ggggatgggc gatcactggc tctccccatg ctcaggttaa agacatttgt aagccttttc   31320

tcctgctaat ctgcttccta tcagttcttt tcagccaacc ttcagagagc caaaggcagc   31380

cttcaccttg gcctcaacac cttccatgcc ttttgcttct cctcctcccc tgcaaagcat   31440

tccccactcc ttgggttccc cactttcaag catcccaccc tccctgttat atgtcatcct   31500

cctcattctc tgctttttata accctttttaa aattatgggc ccagccaggt gcagtgatgc   31560

atgcctgtaa tcccagctct ttgggaggct gaggcaggca gttcacttga gctcaggagt   31620

cctacacagc tgggggcaaca tggtgagacc cccatctcta ccaaattgca aatattagcc   31680

gggtgtggtg gtgtgagcct gtattcccag ctactcagga ggctgaggta ggagaatggt   31740

ttgaccccag gagatggaag atgtagtgag ccaagatcac gacactgcac tccagcctgg   31800

gcaacagagc aagatcgagc ctaaaaaaaa aaaaattagg tggggtgcgg tggctcacac   31860

ctgtaatccc agcactttgg gaggtcgagg caggtggaac acctgaggtc aggagtttga   31920

gaccagcctg gccaacatgg caaaacccca tctctactaa aaatacaaaa aaattagctg   31980

agtgtggtgg cgggtgcctg taatcctggc tacttgggag gctgaggcag gagaatcact   32040

tcaacctggg agccagaagt tgcagtgatc tgagataatg ccattgcact ccagcctggg   32100

tgatagagtg agactctatg tcaaaaaaaa aatacataaa aaaattaaaa attaaaaatc   32160

aatttaaaaa atgccagcta gtatactttt cctctctccc ttccttttttc tatctctctc   32220

tcttttttttt tttttttttt tttttttttt tttttttgag acagtttcac tcttgtcgcc   32280

caggctggag tgcaatggcg tggggatctt ggctcactgc aacctccacc tcctacactc   32340

aaatgatcct tctgccttag cctcctaagt agctgggatt acagatacaa gcaacaaatc   32400

ctaattcttg tattttttcgt agaggcaggg ttttgccatg ttctccaggc tggtctcaaa   32460

gcgaatgctg gccaggctca ttttttttaat ttgaattgtg ggaaaactga ggctggatcg   32520

aatggtcctg gacatgccct ggaacaaaca acatttagct gtgcaaggca cagtgtcagt   32580

gtctggtatt ggggtgcccc agtctcaagt cccaagaaaa agacaaggca gaccatgaat   32640

tttgtgtggc tccaactcag ttttcttcat ctgttgcttc acttgcagtg ccagaccaga   32700

atcactttga cctaaaacta gctacgataa ttaacattca gtatgactca ttacctaaca   32760

aattcaaaat gtaaggaact gtctttagaa cttgttctat ataaacatgt tattaaggtc   32820

tgctgcggct gttctatgca gctcttttttt tttttttttct ggcgatagga tctcactcta   32880

tcgcccaagc tggagagcag tggcatgatc acagctcact gcagcctcaa cctcctgggc   32940

tcaagcaatc ctcccacctc agcctcccaa agtgctggga ctacaggcgt gcaccctgc   33000

acccaactag ttttgtattt tttgtagaga tggagtgtca ctatgttgcc caggctggtc   33060

tccaactcct ggcctcaagc aatccaccaa ctcggcctcc caagtgctgg gattacaggc   33120

ggacgccact gctcccagcc ccagattttt ttctcattta tatttccgca aacctcaaaa   33180

aaaccccccaa aggtccctag gtcagtcact tcccactagt aaataagtca gcatctttgc   33240

aaagatcaaa ggaaaagcaa ttttccttac cacagagcct cttacaggaa agagagctct   33300

gattttccat atgttcccca accatgctag gatgttcctg tgccctgatg gcattcttac   33360

taacccattg ttccattcct ttccagccct ccttcctgta acgtaagtgc aggtgggagt   33420

tggggattgg tccgctaact gggtatagag aaaacagatg ggtatgctat tctcagtaag   33480

ggagcttctg tcctgggaaa aatgtggcct ctcctaagga accctatccc attgaatcac   33540
```

-continued

```
cctgattcac tttttttttt tttttttttt tttttttttg agatggagtc ttgctctgtt   33600

gcctaggctg gagtgcaatg gtgtgatctc ggctcactgc aacctctgtc tcccggttct   33660

agtgattctc ctgcctcagc ctcccaagta gctgggacta taggcataca ccaccaagcc   33720

tggctaattt tttttttttt tttttttttt tttgagacgg agtcttactc tgtgccaggc   33780

tggagtatag tggcgtgatc ccggcccgct ggctcactgt aacctccgcc tcctggattc   33840

aagtgatttt cttgcctcag cctcttgaat agctgggact ataggcgccc accaccacac   33900

ccagctaatt tttgtatttt tagtagaaac aggttttcac catgttggcc aggatggtct   33960

cgatctcttg acctcgtgat ccacacgcct tggcctccca aagttctggg attacaggcg   34020

tgagccactg cgcccggccc taattttttgt gttttttagta gagatggggt tttgccatgt   34080

tggccaggct ggtctggaac tcctggcctt aggtgatctg cccacattgg tcttccaaag   34140

tggcgagatt acaggcaaga gccactgtgc cctgcctctc acattttctc tcttcccaga   34200

tttggttcaa gaacttaaga gctaggccat gtgcggtggc tcacgcctgt aatcctagca   34260

ctttgagagg ccaaggcagg cagatcgctt gaactcaaga gttccagacc accctgggca   34320

acatggtgag atccctgact acaaaaaattc gccaggtgtg gtggcatgtg tctgtagtcc   34380

ctgctattca ggaagctgag gcaggcggat cgcttcagcc tgggaggtca agactgcagt   34440

gagctgagat ggagacacag cactccagcc tgagcgacag agccagaccc tgcctcaaga   34500

aaacaaaaca aaacgataac actggagagc cagagcagga accagtctcc tctccaatct   34560

ccaaacctga gagagacatg agtcacactg acggctttgc ctgcctgcga tctctctatg   34620

tgtgttgatt cttgcggaac aaggcgcttc gagcatctcc tctgccccta cgcccgtgac   34680

cctgtccctc ttcttgtctc cattgccccc caagcgggta catttgccca ccttctcacc   34740

tgggacaccc tgggcgtgga tctcctcacc tgcagcgcta ggtgtgctcc cagggtctcc   34800

acatccctaa ccccccgcaag gctggcctct ttacctgcaa agccccccgc cgcggcctcc   34860

tccctctacc ataccccaat gccaggctca cttcctgccg cctgcctgga acggggctgc   34920

tcatgcatcc cccacgccct ctgaagcccc cccggcgcac tccacgccct ctcgcctgac   34980

ccctgtttcc gctgccggcg tctccacacc ccctgacgcc gccacgccct ggaccgaggt   35040

ctctagagct gcgcgccggc tgcacgtccc ttaggagttt ccgtgcgcca cgaggcgctg   35100

gcgcgcgtct cccggcccat ccaccccggg cccggcgaca cctttctttg ccacctggaa   35160

ccaacatctt ggttcccttt tgagggatca gaacttgttt aattggaata cggcaaaatt   35220

ctgaattttt ctgccgtctc tattccaact tcagagttct gccgtccagc cctgcgacaa   35280

tcttccggtg ccaacgcggc aggtcagtat gtatccccca cgatgccccc cgggccacgg   35340

gcccctagtt aacaggtttc cctttcgccc gctgcctgga agtatcgcca cctcgccccg   35400

cccaaccccc caccagacag ctctgcagcc acagccctc atccaaccag gaagtccagg   35460

gcccatctgg cccgctagac ctcgggaaac cacggcgtca gagcacccat taagaggggt   35520

ccaggccggg cgcggtggtt cgcatcaggg cgcccattaa gaggggtcca ggctgggcac   35580

ggtggttccc atcagggcgc ccattaagag gggtccaggc cgggcgcggt ggttcgcatc   35640

agggcgccca ttaagagggg tccaggctgg gcacggtggt tcccatcagg gcgcccatta   35700

agaggggtcc aggctgggca cggtggttcc catcagggca cccattaaga ggggtccagg   35760

ccgggcgcgg tcgttcgcat tagagcaccc attaagaggg gtccaggctg gcacggtgg    35820
```

-continued

```
ttcccatcag ggcgcccatt aagaggggtc caggccgggc gcggtggttc gcatcagggc    35880

gcccattaag aggggtccag gctgggcacg gtggttccca tcagggcgcc cattaagagg    35940

ggtccaggct gggcacggtg gttcccatca gggcacccat taagagggt ccaggccggg     36000

cgcggtcgtt cgcattagag cacccattaa gaggggtcca ggctgggcac ggtggttccc    36060

atcagggcgc ccattaagag gggtccaggc tgggcacggt ggttcgcatc agagcacccg    36120

ttaagagggg tccaggctgg gcacggtagt tcgcatcgga gcaccagtta agagggatgc    36180

aggccgggca cggtggctct aatccgagca ctttgggagg atcacccgag gtgaggagtt    36240

cgagaacagc ctggccaacg tggtgaaacc ccgtctttac ggaaaaatac aaaatttatc    36300

agggcgtggt ggcgggcgcc tgtaatccca gctattcggg aggctgaggt gggagaatcg    36360

gttgaacgcg ggaggcggag gttgcagtga ccagtgagc cgagattgtg ccgctgcact     36420

tccagcctgg gcgcagagt gggactccgt cttgggaaa aaaagggtag tccaggccgg      36480

gcgtggtggc tcaggcctgc aattccagca ctggaggagg ccgcggcagg aggatcgctt    36540

gagaccagga gttaagagac ctgcctgggc aatatagtga gacccctgtg tttgtttgtt    36600

tgttgagacc cttgtgttaa agcaaactaa atatggcctg agaaggactc cgtaattcta    36660

tatttgagtc cttgtggatg aactgcaacc taacttaata ggtacaaaag attgaaaacc    36720

taagttaggc cctgcgtggt ggctcacgcc tgtaatccca gcactttggg aggccgaggc    36780

gcgcgaatca cctgaggtcg ggactttgag actagcctga ccaacatgga gaaacccgt     36840

ctcttctaaa aatacgaaat tagccagacg tggtgactca tgcctgtaat cccagctact    36900

cgggaggccg aggcgggagg atagcttgaa cccggaaggc ggaggttgca atgagccgag    36960

attgcgccat tgcacactct agcctggtca acaagagcgg gaaactccat atcaaaaaaa    37020

aaaaaaagga agcctaactt acgttttatg cgcctgtaac cgccactgag tgttggccaa    37080

tcccagcagc ccagcagctg tacttcatcc actcacaggc tgctgagcat tcaaactgtg    37140

ttcaaataag gcaaacgctg agcggtaacc aatccagctc tttctgtacc tcacttccga    37200

tttctgtatg tcactttcct tttcttgtcc ataaatttgt tctgaccacg aggcacccct    37260

ggagtccgtc tgaatctgcc gtgactttcg gagctgcccg atttgcaaga ggttcattgt    37320

tcagttgaac tcctttacat ttatttattt tatgtatttt attttattta ttttatgtat    37380

tttattttat tttatgtatt ttgttatttt attttatttt atttatttta ttttattttt   37440

gtttcatttt tatttttatt ttattttatt tttattttca tttttttgag acggagtctc    37500

gctctgtggc ccaggcggga gtgcaatggc accatctctg cgcactgcaa cctccgcctc    37560

ctaattcaag tgattctccc gcctcagcct tacgagtagc tggtattaca ggtgcccacc    37620

accacacctg gttaattttt tctgttttta gtagagatgg ggattcacca cgttggcccg    37680

gctggtcttg aactcctgac ctcaagtgat ctgcccacct cagcctccca aagtgctggg    37740

attacaggtg tgagccactg tacctggccc cctttaaatt taattcggct gaagttttc     37800

ttttaacaga tggtgtcaga agcggagtcc agagtagagc ttctaggaac cttcgggagt    37860

gctgagtgaa cacgcaaggt gcctgcggaa cccacttgtg tccattgacc tctccgagtg    37920

gccggggatc gtgggtaagt tccctctcgg atttcagagc tccacagatt tgtgtttttga   37980

gctctccgag tttcattgag caaatatctg atccaaactg ggtttggaag ctgtgacaga    38040

aactggactg ttctgggaa tggatctgat gtggtaatta ctggcttgg acccagttag      38100
```

-continued

```
aggcctctta catgtgactg ggtcagaaag aaactggtag caaatggtaa tattgcagga   38160

ggtgtaaaat ttggcttta aaaattaaca gggatgtttg tgttctaccc ctttgtttca   38220

tttttcttgt gcacttaggt attaaaaaaa aaattactgg gtaagttaat caagggaacc   38280

tgagagtaat gaatgccaat attttaggta aaaatgggat cttttttttt ttttttttga   38340

gatgaagtct cgtttggtcg cccaggctag agtgcagtgg cgcgatctcg gctcactgca   38400

agctccacct cccaggttca cgccattcta ctgcctcagc ctccccagta gctgggacta   38460

caggcgcccg ccaccacgcc cggctaattt tttttttttg tattttcagt agagacgggg   38520

tttcactgtg atggccagga tggtcttgat ctcctgacct cgtgatctgc ccgcctcggc   38580

ctcccaaagt gctgggatta caggcatgag ccaccacgcc ctgccaaaaa tgggatcctt   38640

aaattctgaa aaactgagtt ccttctggct tatacattag gcacgggaag gagcaaagac   38700

ttacagaaat ggcaaaatct gcctgagcgt ggtggctcac gcctgtaatc ccagcacttt   38760

gggaggctaa ggtgggtgga tcacctgagc tcaggagttc gaaaccagcc tggccaacat   38820

ggtgaaaccc atctctacta aaaagacaaa aattagtggg gcgtggtagc ttgtgcctgt   38880

agtcccagct acttatgagg ctgaggcacg agaattgctt gaacccagga ggcggagttt   38940

gcagtgagtg gagattgcac cactgtactc caacctgggt gacagagcga gactctgtct   39000

caaaaaataa aaatggctgg gcgcagtggc tcacgcctat aatcccagca ctttagaagg   39060

ccaaggcagg tggatcacct gaggtcggga gtttgagacc agcctggcca acatggtgaa   39120

actctgtctc tactaaaaat acaaaaaatt agccaggtgt ggtggcatgc acctgtaatc   39180

ccagctactt gggaggctga ggcgggagaa tcttgaaccc aggaggctga ggttgcagtg   39240

agccaaggtt gctccattgc actccagcct gggcaacagg agcgaaacac tgtctcgaaa   39300

ataaataaat aaataaataa aaattaaaaa attaaaatga gggctcccga aagttaaatc   39360

tgctaatctt tcagcttcgt tactatcctg atccaaagga agcagactgc agcaccagtt   39420

ggctgacttt ggataagtaa tggggtccat tttacctgag taaagtatgg gatgggtca    39480

gaggccctcc cctcagtaaa gtcccccttg gttaaaaatg ggttaaagat gacagggccc   39540

agctggggtc aagtttgagc cttgcgagtt cagtattggg tgctaagcac agtggccagt   39600

gtctgtgttt tgtcacgtat tttgctttgg cgccatgatg aaaaaatgtt aattggctta   39660

ccccacgcaa ccccttcggc cacacttgca aaactaagag gcttttgctt aaggttccat   39720

aaaacagaaa aagaatttcc tttgtgatgc cgcaggcttg gccctcagga ctatagtgtg   39780

gcaagcagag tcactaggac cacctgggca aagggaacct agaagcctgg catgctggca   39840

aaaggtaaag tatttcttac caattagact gtggcccctc tgtgcaaact ggttagatga   39900

acggtaaaaa tcactgttta tctcctctgt aatgctttga ttaatacaaa aaagaattct   39960

gaggttggtc ttaggaagct gtaataaatc tggtatgctt tgtgtctttc tgtattctgt   40020

cacgaagagg ggtaccttcg gatgaaatgc gtgcccaggg ccgcataagc ccgctgttca   40080

agacggccca gcaaactggt caatcatgtc cttggaagct taacctccta ataccatgtg   40140

gccctgcttt ctcttttcac aacggcaggc caggttcagg gttccattcc cggcttactc   40200

agcgagtact ttctggtgtc acctttacca tgtgttgatt ctcttccctc tgtttcttat   40260

agaacacaga aatattagct gtttggccta gccaaggttg ggtaataaaa gatttaaaag   40320

gacttttta aacaagcgct atagttaaaa ctcaggtaca ttaaaagtgg atatttggcc   40380
```

-continued

```
aggcatcgtg gctcatgctt gtaatcccag tacttgggga ggctgaggca ggtggatcac   40440

ttgaggtcag gaattcaaga caagcctggg caacatggca taactctatc tctactaaaa   40500

aaaaaaaatt agctgggcat gttggtgcac gcctgtaatc ccagctattc aggaaggcgg   40560

gaaaattgct tgaacccggc aggcggagct tgcagtgagc caagatttca ccactgcgct   40620

ccggcctggg tgacagagcg agactccgtc tcaaaaaata aaaataaaat aaaaataaaa   40680

taaaataaaa taaataaaat aaaagtgtag tgctcgcttc agcagcacat atactaaaat   40740

tggaatgcta cagagaagat tagcatggcc cctgcacaag gatgacatgc aaattcatga   40800

agcgttccat attttgtgca tcctggcaag atcatttctg tatctgctaa ctagcactaa   40860

agaaatagtg tgaatctaag caaaaatgag tggcacccaa aaacaaaatt gtggttttca   40920

ttaaaaaata taaatattta taataaaaa tatatatgat atataaaaaa taaaatatgt   40980

ataataaaat acataata tatataaaat aaaaaagtat ataaaaaata tatatgtgtg   41040

tgtatattca aattcttttt ttttttttg agacggagtt tcactcttgt cacccaggct   41100

ggagtccaat ggcacgatct cggcttaccg caacctccac ctcctgggtt caagtgactc   41160

tcctgcctca gcctcccgag tagttgggat tacaggcacc tgccaccacg cccagctaat   41220

ttttgtatcc ttagtagaga cagggtctcg ccatgtaggc caggctggtc tgaactcctg   41280

accttgggtg atccacccgc ctcggcctcc caaagtgctg ggattacagg tatgagccac   41340

cgtgcccggc aatgtatata ttcaaattct aacagcctgg gactccttgg gaaaaacagg   41400

aggcaccaga gacgccattt tggaaaaaaa cctgttttcc tcatggaacc acaggaattg   41460

gaaatggata gattcccctt cagaaatcta aggctctgtt cttttttggga ttcaggatct   41520

ggtataaaaa tgggacccctt aatttttgga gacctgtgtt gctttctgct gtgcccactt   41580

attatattgg gccctagaaa ctgcatgctt tcctggtcct tttgtccaa ggactccacc   41640

ctaaagccag taatctcaaa taaataaata aacacctaaa tcaaatattt tgaaagaaca   41700

ataaaaacta atgcctttta gttcacataa ctttagtaat cttttgggaaa taaaaagttt   41760

taaagattat tgggaaaaat gaagacattt agtctaaatt aggcaggtca gatattaggt   41820

ttgttcgatg ctttaaggtc atcaactgct tcttaggctt ttgaaaattg ttcagtttac   41880

ctacttggga gcattagatt ctagataagg cctgggaaca tgtggaatta gccatgcact   41940

ctatctatgc aaaggttata aagaaaagag attttttttt taattaacaa aaaccacagg   42000

tggttgtgct ccgcctaccc agcacagcag gtgagatggt gcaccctcag tggactgaag   42060

aggccatggg atcccacctc agccggatag cacgctggcc ttcaccttca ttgtgccatg   42120

gcagctttcg tgtgagccac tgactcgtgt acatgttaga ctccttggtc tataagaaag   42180

catcttgtat ggtaaattgt tgttctaaag taaaataact ggtttgttca aaaaggggat   42240

gctaaggaga agtcagaaag tcaaagcatg ttgtagatgg tctgggaaag tcgtgaaagg   42300

gttcgtgaaa ggaaatttaa gccaccaaaa gtaaaagttg ctagttacca ttataacata   42360

tgattgaaac tactgaaaaa atagttttac atggaaagtg tgtgagaaga gtgaaacatg   42420

tttttggtaa aatattttta aaaggcagga gaatgtcaaa tttcacctag ttgagagggt   42480

tatgtgattt ttaaattaga taagaataag ctcacggttt gaacaagttg tggaaggttt   42540

gtaaaaacta atcttgcaaa aaaaattctg tgtgcaaaca cgttgactaa atttaaaggg   42600

gtattttcca gttttccata aattaaacat tgaaatgaaa ggacaaacag ggtttctttt   42660
```

-continued

```
tttgttttttt tgttgcccag gctatgggca actatgtagc taggcatgtt ggtgcatgcc   42720

tgtaatccca gctactcagg aagctgaggc aggaaaattg cttgaaccca agaggcagag   42780

gttgcagtga gccaagatcg caccactgca ttccagcctg ggtgacagag caagaccta    42840

tctcgaaaaa aaagaaaaaa gaaaagcaat agctccctgg gtgtcaggta tcagtgagaa   42900

tgggaagtca ggtcttctct gactcctagg acattcctct ctctgtcttt gggggttgaa   42960

ttccttgtta gaactccatc ttgttaaagg ggcctcgcac ctgcccttgc cttctgcagc   43020

agccctcctt aatcctctcc aaacttccat ctccagacca ccggattctc ctcatgagtg   43080

ccctgggtgg acattggtga aaggtcactg ccttcaggac acaccatagg tacagtcacc   43140

gaggtaaccc agttcaaaga agagcaggat gttcagtatt tacaaaggga tctagcaatt   43200

ggtccaaacc agtcagtgct ggcatgcacc gttcatcgtg ccatcagtgg caagatggag   43260

atctggcaat gcatggctca cagtaagata cacgccctgt gccattccac cctatcatta   43320

gaaaaggagt cttctttttc tttctttctt tcttttttt tttttttgg agacagggtc      43380

tcactctgtt gcccaggttg tagtgtaatg gtgcaatctt ggctcactgc agcctctgcc   43440

tcctggggtc aagtgatcct ctcacctcag cctcctgagt ggctgagatc acagatgcca   43500

gccaccacgc ctggctaata ttttttgtttg tttgtgttat gttttttttgag actgagtctt    43560

gctctgttgc acaggctgga gtgcaatggc gcaatctcgg ctcactgcaa cctccacctc    43620

cctggtacaa gcaattctcc tgtctcagcc tctcaagtag ctgggattac aggcgcctgc    43680

cactacgccc gcctaatttt tgtatttta gtagagacga ggttttgcca tgttggccag     43740

gaatggccag acctcaaatg atctgcccgc ctaggcttcc caaagcgctg ggattacagg    43800

tgtgagccac tgcacccagc caatttttgt atttttttttt tttttttttt ttgtagagac   43860

agggttttgc cgtgttgccc aggctgatct cgaactcctg acctcaggtg atcaccttcc    43920

ttggcctccc aaagtgttgg gattacaggt gggagccacc atgtccagcc gcttttttctt    43980

tttaaaaaaa attttttttg acataacaga caacaccact ctctttttatt ttttttataga   44040

gacggggtct cattatgttg accagtctgg tctttttaaa ttttatttttt ttgagatgga   44100

gtctcactct gttgcccagg ctggagtgta gtggcgggat cttggctcac tgcaacgtct   44160

gtaccccaga ttcaagtgag tctcctgcct caggcttcca agtagctggg attacaggct    44220

catgccacat cgctggctaa tttttttttt ttgtatgttt ttaaatttta tcttttaagt    44280

agagacaggg tttccccatg ttggccaggc tggtcctgaa ctcctgactt caggtgatcc   44340

accctcctca acctcccaaa gtgctgggat tacaggcatg agccaccata cccagccttc   44400

ctgctatttt tgaactacct gtaccaggct ggtttctctg ggtgagggga gtggtcaggc   44460

agaggcaggc cccgtcatgg taagcagcta ggagactgct agagattgac agggcactca   44520

tgagtgccct gggtggacac tggtgaaagg tcactgcctt caggacacac cataggtaca   44580

gtcaccaagg taacccagtt caaagtagag caggatgttg ggtatttaca aaggagatct    44640

agcaattggt ccaaaccagt cagtgctggc atgtaccgtt catcgtgcca tcagtggcaa    44700

gatggagatc tggcaatgca tgggctcaca gtaagataca cgccctgtgc cattccgtag    44760

acgtagatca agcgattatt actgcagaaa tctccgtgga cgtagagcaa gcaattatta    44820

ctgcagaaat tgcaggagca ggttctgcag catgtcacat ccaaagaagc ttcccttgca    44880

agttggtaac cttgagggct tcaataccac acagagttgg tctaggtgat ggctgaccat     44940
```

49

-continued

```
ccaggcataa taatttgggg aacaattcca ggatggaggt tatgttgcta gacttgtttg      45000

tccgggaaag tggtagacag gaagttcctg tctgcacacg tctcctggct ccagcccttt      45060

cccctgtcca tctgtcctac agactccgcc tcaggcatgt tgtcttggag gacgtgcaga      45120

aaggcagcca tgcactttct aggtttcgat gccgtcttag agtcactggt caccaggtct      45180

gggtcaaacg ggagtctctg gctgtcaaga ctggactggg aggaatcaca tcgcttcttc      45240

accatcagct ttatctgctt tgccttttcc gacttcagct ttctctgcag ggggtatcag      45300

tggggttgac aaagattgac atcttttttgt tatcctcatc cctaatcttg ccactgacat      45360

tcttcagtgc ctaggcgatg ctggcattct ccacaaagat gtgggcctgc attttctcat      45420

agcgaaactg aatcaggagg aaggggcatt gcattgactc tgaatcaaat tcagcagcca      45480

cttctcattt tatgcagatc ttgaactagc agctccctaa ggtccgatct ggcctgtttc      45540

cctctgttct tttctctgga ggttttttggc gctttctctg tgttaacatg ggtttggtct      45600

tgtttatggc aagtgcctct ccatggctgg gtgcggtggc tcacgcctgt aatcgcagca      45660

ctttgggagg ccaaggctgg cgaatcacca gaggtcagtt cgagaccagc ctagccaaca      45720

tggcgaaacc ccgtctctac taaaaatata aaaaaattag ccaggtatgg tggcgggcgc      45780

ctgtggtccc agctactcag gaggctgagg caggagaatc gcttgaaccc gggaggcgga      45840

ggttgcagtg agctgaaatt gtgccattgc actccagctt gggtgacaga gtgagactct      45900

gtttaaaaaa aaaaaaagta agtaaataaa taaatgttga tattatgtag ccatgttatg      45960

tagtttttgca tagcctttct ctgtcttata gctatgaaag acaatttcca aaacatagcc      46020

tagaatggag aattgaagat aaagtgagaa ctgttgggca tagtaaccta aaaagggatc      46080

ccctctggtg tggaaagatt gttccaacgc aaaagggact gagatccaga gatggcagtt      46140

gtttgagatc tggaatcttc agaagaggta gatcagactt gctcaggaaa taatgggtcc      46200

taccatcaca gcgggtacgg atggggctac aagatgagag aggctggata ggagagtatt      46260

taaggaaaaa aaaaagacag aaaaggacca aaggacagtc tgtgagaccc cagagaatgc      46320

attaaacctg aagaatttct gaacaatgac gtctgatatt caggcttccg ttgtttcttt      46380

ttgtgctgta atcttccgtg ttttctctgc acatagctca gtaaagctct attcaccagt      46440

taacctagag tctgtcttga gataagcagg gagggctgtg acggctgcac aagggcggag      46500

tggtttgtag acctgaaaag gaacttgtaa gagctggcag atcttaacca ggagagggag      46560

cccctttcca cagcctagaa gcttctgaag tcatttaaat ggaactgaat tatatgaagt      46620

caaatgtcag ttggggaaaa agtcaaactt tattatttat ttatttattt gtaattgtgc      46680

gtatacatat atatatatat atatatatat atatatatat atatatatat aatttttttt      46740

aaattatgat ctccgtgata gtaccaaatc aaactttttt tggagacaga gtcttgctct      46800

gtcacccagg ctgagtgca gtggcgtgat ctcggctcac tgcaacctcc gcctcccagg      46860

ttcaagcaat tctcctgcct cagcctcctg aagagctggg attacaggcg cgtgccacca      46920

tgcccggcta attttttgtat ttttagtaga gatagggttt caccatgttg gccaggctgg      46980

tcttgaactc ctgacctcag gtgatccacc cgccttggcc tcctaaagtg ttggaattac      47040

tggcatgagc gaccacgctg gcccaaaccc tgcttttttac tggagagacg aggtagccct      47100

aagttaaaaa aaaaaaaaaa aagacccgt ttcacttctt ttggatatac ccggggtgac      47160

attgctagat cattctgcaa ttcctccttt tttttttttt tttttttgct gggggtggga      47220
```

-continued

```
tagagtctca ctcccaggct ggagtgcaat ggtgtgatct tggctcactg caacctccgc    47280

ctcctgggct caaacgactc tcctgcagtg aggagctggg attacaggtg cctgccacca    47340

caacctgcta atttttttttt tattttttgt attttttagta cagacggggt ttcactatgt    47400

tggccaggct ggtcttgaac tcctgacccc gtgatccgcc cgccacagcc tctcaaagtg    47460

ctgggatgac aggcatgagc ctccgcgccc agtagatcat tctgtaattc tgtgtttaac    47520

ttttttccccc ctaaacttaa ctgaagtgat atttaacttt ctgaggaatc accaaatcaa    47580

aggtgacttt tgagacaaat acaggaagtg gaggtggttt tcctcatgta gatgaagaca    47640

ttctaaaccc agaactgaaa acacacatgg aatccttta agtatcagga tgccttggtg    47700

gacaaaatgg atacatccaa cttctcaagg agcttaatat tcagtattaa agctgaggtg    47760

agctcaggtg attcacgcct gtaatcccaa cattttggga ggccaaggca ggcggatcac    47820

ttgagcccag gagtttaaga ccagcctggg caacatagtg agacccctcc cccctgcccc    47880

cgtctctaca aaaaataaaa aaattacaga cgcatggtgt agtcccagct acttggcagt    47940

caaaggtaga aggactgttt gaacccagga gtgggttgaa gctgcagtga gccttgattg    48000

taccagtaaa ctttagcttg ggaggcagtt gagaccctgt ctcaaaaaaa aaaagaaagg    48060

aagaatttct ctctcccaac ttcccttggt ttctcctcgc cccccggcta aaaagtgatt    48120

ggggaccttt taaaaaactt cctgctctcc acagaatggg attacagccc cgagatgatc    48180

cataaaagat tttcaggaag aatgaagagt ttagggagtg aaggttctaa aacagtaaat    48240

agagtgtcac aaagaaatcc attcatctct ttgaaggctg ggtatttgga aaaagagaga    48300

aagaaagctt cattcagaga gcgctcgcct gtatttaggg gtgtttggag ggggcggggt    48360

gactatagaa ttagggtaaa gttcagtgtc ttgcaaatca gccctgaaat agccctgatc    48420

cctgcaggcc tgtctggttt cccaaaccct ccactagctt tcaaatttgc attaaaaagc    48480

ttttggcttg ttcattctgt tctttctttc ttttctttct tttatttatt tattttttt    48540

gagacggagt ctggcactgt cacccagact ggagtgcaat ggcgcgatct ccgctcactg    48600

cagcctctac ctcccgggtt caagcaattc tcctgcctca gcctcccgag tagctgggat    48660

tacaggcgcc caccgccaca cctggcttat ttttttttaatt tttaatagag atggggtttc    48720

tccatgttgg ccaagctgtt ctcaaacttc tgacctggtg atccacctgc ctcagcctcc    48780

caaagtgctg ggattacagg cgtgagccac tgcgccaggc cctcattctg ttacttcttt    48840

ctttctttttt tcattaattt aagttctggg atacacatgc gggatgtgca ggtttgctac    48900

ataggtaaat gcgtgccgtg gtggtttgct gaacctattg acctaggtat taagcctcac    48960

agccattagc tatttgtcct gatgcccttc tgcctcctgc ccattctttg ttatttcttc    49020

atattccaat taatgttcat tttgaggacc tggctctggc caggcaaggt tccagtctgg    49080

agtcaaactg aggaaagtat tacctttcac aaacacttag accacgttgg gagggggagaa    49140

tgattgtcct ccacatgcgt atgggtgtgt tataaacccc aggaaggtaa atactaagca    49200

aaggcgtgca cagataatta ttgcaactga tgattccacg tcaattgtac tgtactgtga    49260

gtaggttat aggctgccgt gacaggggcc atcacctggg tacgagggtg ctggcttcct    49320

cttgaagacg tgactttaaa attgtgagtt gaatagatgc aaggatattg gcccagtgga    49380

ggaactttga ggggaggggg cagggtatcc tggttgggag gaaattacat acagaaattg    49440

gggagtggtg acaacattga ctcttccagt aattgtctgg gtgtggtaac tcaggactgt    49500
```

-continued

```
aatcccagca ctttgggagg ctgagatggg aggattgctt gagcttggga gttccagatc   49560

agcctaggta acacgaggag atctaaaatt gaaaaaaaac gtagctgggt gtggtggctc   49620

attcctataa tcccaacaac tttgactcag gaggctgaag tgggaggatc ccttaaggtc   49680

aggaggttga ggctgaagtg agctagcact ttgggaggcc gaggtatgtg gattacttga   49740

ggccaggagt tcgagaccag gctggctaac atggtgaaac cccatctcta ctaaaaataa   49800

aaaaattagc caggcatggt ggtgcgcgcc tgtaatccca gtgactcggg aggctgaggc   49860

aggtgaatca cttgacccct ggaggcagag gctgcagtga gccagatca taccactgca   49920

ctctagcctg gacaaccaga gtgaaactct gtctcaaaaa aacaataata atttttaaaa   49980

aattttttaa ataaaaaaat taacaaatga cccgcacatc tggggtgaag taagacgagg   50040

ctggcagcat agctctgtca cctgtggtta ggattaatta agctcagctt taaaggctgg   50100

atcttggcct cctgggtttt aattttgact tctccacttc tcagccatgt tttgtttgt   50160

tttgtttgct tgaggaggga caaatcaggc cagcattgag cctctttccc ccgtgtgtca   50220

actgagattg ataattacaa gattaaatga tgcttgtctg tgattttagc atctgttcag   50280

cccatcattc atttcaagag tattgactgg gcttcagggt aggttccatg ttagtactgg   50340

ggacgccgtg ggtgggaggg agactgggtc tccaccctcc tagagttata gtctaggcct   50400

gcggttaagc agattttgt gcaggaatca aacccactac actacctgtc agaaatcaag   50460

ccctgttcca ggcactggga aactcagaat ttaaagggga tgtaccaggt ctctgtcctt   50520

gcggagcatt atcgatcagt agaagagaga aaataaacaa gcaaacacct gagacaattg   50580

taatagcaat aatgtgatat caataaaatg aaacagagca acagaaatag ggtagatggg   50640

ccgggcgcgg tggctcaccc ctgtaatccc agcactttgg gaggccgagg tgggcggatc   50700

acgaggtcag gagatcgaga ccatcctggc taacacggtg aaaccccgtc tctactaaaa   50760

atacaaaaca ttagccgggc gtggtggcgg gcgcccgtag tcccagctac tcgggaggct   50820

gaggcaggag aatggcgtga agccgggagg cggagcttgc agtgagccga gatggcgcca   50880

ctgcactcaa gcctgggcaa cagagtgaga ctgtctcaac aaaaaaagaa aagaaaagaa   50940

acagagtaga tggtcttaga aatgacaagg aatcccaatg agaggttcta cctgggacaa   51000

aatagaaaaa tgggaaatca taataagctc tggaattggg gcagtggtat tgtttatttc   51060

ctagttgtgg caaatctaat gtaaaatatg gacattaaag aaaactgggt ggagaacata   51120

gagaactttc tgtacttttt gcaacttttc tgtaagtcta aatttattcg aaggccgggc   51180

gcagaggctc ctgcctgtaa tcccaaaacg ttaggaggct gaagcaggta gatcacttga   51240

gcttggtagt ttgagaccag cctgggcaaa aaagtgagac ttcatctcca ttaaaaattt   51300

aaaaaattag ctggctttgc tggtgagcac ctgcaccaga ctggttagcc tgggcagcat   51360

agtgagaccc cgtttctata aataagataa aaatcagctg ggtgccaggc gtgatggctc   51420

atgcctgtaa tcccagtgct tcgggaggcc gagggggcg gatcacctga ggtcgagagt   51480

ttgagaccag cctgaccaac atggagaaac cccgtctcta ctaaaagtac aaaaattagc   51540

tgggcgtggt ggcacgcgcc tgtaattcca ggtactaggg aggctgaggc aggagaatca   51600

cttgaacctg ggaggcggag gttgcagtga gctgagatca ctccactgcc ccccagcatg   51660

gctacagagc aagactccgt agcgggatat tgcatgcatg taatcccagc tactctggag   51720

actgaggcag gagaatcatt tgaacctggg gggcggaggt cacagtgagc caagatcatg   51780
```

-continued

```
ctattccagc ctgggtgaca gagtgagact acctctcaaa aaaaaaaaaa agaaaaagaa    51840

aaagaaaaag aaatgcattt acagaagcta ggaaaatcaa attcagggag gaggctggag    51900

ggcaaagagt gggtgtggcc agactttaat ccattctcca tctgtggggt ggtccctagg    51960

gtataaaaga gctccagggc ccctgccctg cctttcatcc tcaggatggg aagtcctcac    52020

agagttcagt aagtattggc ttcccatggt gtttctgcac ttcccccggg gtcatatgag    52080

cctcacattt aggttgtaag actcccccta aaatctccaa cactgagtcc tctctatttg    52140

tagtcatgac tccgacacct tgattctctg cccctaatac tctttttttt tttttgagac    52200

ggagtttcac tcttgttgcc caggctgcag tgcagtggtg tgatcttggc tcactgcaac    52260

ctctgcctcc cggattcaag caattctcct gcctcagcct cccgagtagc tgggattaca    52320

ggcatgcacc accatgccca gttgattgtt tttgtatttt tagtagaggt ggggtttcac    52380

catgttggcc aggtctcaga ctccaagcct cgagtcatcc gccctcttca gcctcccaaa    52440

gtgctgggtt tacaggtgtg agccaccatt cctggaccgc attattgatt ttttaaaatt    52500

tttggatttt gttcaattag tgattgagtc tcactgtgtt gcccagatgg gcttgtctcc    52560

caggctggag tgcagtggtg agatcgtgac tcacagtagc ctcaacctcc ctcaccccag    52620

cgtcccgtgt agttgggatg gcaggcatac aggaccatgc ttagctaatt tttttttttt    52680

tttgtagggt tggggtctcc caccattgtc taggctggtc atcaacacct gggcacaaac    52740

atcctctcac cccggcctct gagccactgc acccagtagg ttttaggttc attttatttt    52800

ttatttaggt gtccacaaag gcagcttttt ccttttcttt attttttaaa gagacagggt    52860

ctcactctgt tgcccagggt gggagtgcagt ggccagatct tggctctctg caacctctgc    52920

cttccagact caagtgatcc accttcgtct ccagagtagc tgggactata ggtgtgcaca    52980

aacacaccca gctgagtttt aaatcttttg tagagaaggg ggcctcagta tgtttcccag    53040

gctggttttg aagtcctgtg ctcaagcaat ccttctgcct tggcttccca aactgctagg    53100

attacaggtg agccaccaca ccgggcctgt ccacgtaatt taaaaggtgc tggacgtgtg    53160

cggtggctca cgtctgtaat cccagcactt tgggaggctg aggtgggcgg atcacgaggt    53220

caggagttcg agaccagcct ggccaatatg gtgaaaccct gtctctacta aaaatacaaa    53280

aattagccag gtgtggtggc aggcgcctgt aatcccagct tctcaggagg ctgaggcagg    53340

agaattgctt gaacccagga ggcggaggct gcagtgagct gatgatcgct ccatggcact    53400

ccagcctggg caacagagca agactaagaa aaaaaaagaa agaaaaagaa aaagaaaaca    53460

aagtaatgta aaaggtgtta ttcaggctgg gaccccccaa agtgctggga ttacaggcat    53520

gagccccagg gcaggcctag gatttgcatt acaaggctct gcattgttcc tgagaactgg    53580

agagagtgct caatctacct ttcgctattg agcaacattc agaagtcagt tttaaatctc    53640

ttatcttctg catagaggat gtgcctgcag tttccaggta ctggacaata cagggagggt    53700

acttctcagt ctgtggcact cagccttgag ggcactttct ggtgccagaa tgaaagtgct    53760

gtcatagctg aggtccaatg actgaggcga gcaccgaaga aacaccatgg gggggagggg    53820

gggcgggggg ctccaggagc cactgcaggt aaaagctaaa ccgtggtgct tgttctgcgc    53880

cataaactgg acttcagccc agctttaagg aaatgaccac ggtctctggg ttgtgaggct    53940

gggttccgta gcagctataa tgcttggatt caggatagc ctgggtcaca ccattgccag    54000

agaagaggca accaatccag accccaaaag cgggttcttg gatctcttgc tggaaagaat    54060
```

-continued

```
ttcgaggcaa gtcacaacac agcgaaagaa gcaagctgag gcctgggctc aatcctcctg    54120

cttcgtcctc ccaaagtgct gggattacac gcatgatccc ctgtgccctg ccaatatttg    54180

gtaattataa ctggtggtca gcttacaatg tggctatttc cagaccataa gtaccaactc    54240

tataggtgcc ttgtgagtga gtgccttgct acttcaagca gttactttcg tgtgttatta    54300

aaccagaggc ctgctaagcc tctgtgccta gtaaagatta caatttggaa tgtcagcccc    54360

cagctgtcct gtgtgattgg caggttaggt ccttgttgaa ccagaagcaa ctggccagtc    54420

gtacagatgc aactttcgga ccagtagaaa atttctatgt caacctggag acatagggat    54480

tgtacctttc tgatacccta ttagtaaata aatagtattt atttataaat tatgtataat    54540

agtatttatc tgaatatatc ccaagcagcc caagtgtgtt ccagacataa catttttatt    54600

tacatttaaa tatcactaag attagagata cacatctaac tcaggttttc aactagtctt    54660

accattgaaa gaactattgt ggcaggacgc agtggcgcac gcctattatc ctagcacttt    54720

gggaggccga ggagggcgga tcacaaggcc aggagttcga gaccagcctg gccagcatgg    54780

tgaaacccca tctctactaa aaatacaaaa aaattagctg ggcatgatgg cacaggcttg    54840

cagtcccagc tactcggtag gctgaggcag gagaactgct tgaacccggc agacggaggt    54900

tgcagtgagc cgagatcgcg ccaccgaact ccagtctggg caacagagca agacgcttgt    54960

cttaaaaaag agagagaaag aactacttgt tctctgtaag ccatgctggt ttagccaaaa    55020

tgctgcagtt gtgtatggcc agggacgttg aggctgcagt gagccgacgg ctgtgttgcc    55080

gctctgcagt ctgggggaca gagcaagaac ctgtctcaaa aaacaagaa gttagtgaga    55140

cagacatgcc gttctgttac ttttcccctt gctggttcaa agctaggtag ttgccaatta    55200

aatgtaatct tgtagagcaa aaatgttttt cattttttga dacaggatct cactctattg    55260

cccagcctgg agtgcagttg tgggaactca gcaacctc cacctcctgg gtttaggcag    55320

ttcttctgca tcagtctccc gagtagctga gactacaccg gtgcccagag ggcagtggcc    55380

agatcttggc tctctgcaac ctctgccttc cagattcaag tgagccacct ccgcctcctg    55440

agtagctggg actataagta cgtaccacca tacccagtta attttttgcat ttttttgtaga    55500

taaggggggct aagtatgttt cccaggctgg tttcgaagtc ctgtgctcaa gcaatccttc    55560

tgccttggct tcccaaactg ctaggattac aggtgagcca ccacaccggg cctgtccacg    55620

taatttaaaa ggtgctggac gtgtgcggtg gctcacgtct gtaatcccag cactttggga    55680

ggctgaggtg gcggatcat gaggtcggga gttcgagacc agcctggcca atatggtgaa    55740

accctgtctc tactaaaaat acaaaaatta gccaggtgtg gtggcaggcg cctgtaatcc    55800

cagtttctca ggaggctgag gcaggagaat tgcttgaacc caggaggcgg aggctgcagt    55860

gagctgatga tcgcgccatg gcactccagc ctgggcaaca gagcaagact aagaaaaaaa    55920

aaagagaaaa agaaaaagaa aacaaagtaa tttaaaaggt gttattcagg ctggggatcc    55980

ccaaagtgct gggattacag gcatgagccc cagggcaggc ctaggatttg cattacaagg    56040

ctctgcattg ttcctgagaa ctggagagaa tgctcaatct acctttcact attgagcaac    56100

attcagaagt cagtttttaaa tctcttatct tctgcataga ggatgtgcct gcagtttcca    56160

ggtactggac aatacaggga gggtacttct cagtctgtgg cactcagcct tgagggcact    56220

ttctggtgcc agaatgaaag tgctgtcata gctgaggtcc aatgactgag gcgagcaccg    56280

aaaaaacacc atggggggga ggggggcgg ggggctccag gagccactgc aggtaaaagc    56340
```

-continued

```
taaaccgtgg tgcttgttct gcgccataaa ctggacttca gcccagcttt aaggaaatga    56400

ccagggtctc tgggttgtga ggctgggttc cgtagcagct ataatgcttg gattcaggga    56460

tagcctgggt cacaccattg ccagagaaga ggcaaccaat ccagacccca aaagcgggtt    56520

cttggatctc ttgctggaaa gaatttcgag gcaagtcaca acacaatgaa agaagcaagc    56580

tgaggccggg cgcggtggct cacgcctgta atcccagcac tttgggaggc tgaggtggat    56640

ggatcacctg agatcactat ttttcttttt attttctgag atggagtttc actcttgttg    56700

cccaggctag agtgcaatgg cacgatctcg gctcacagca acctctgcct cccgggttca    56760

agccattctc ctgcctcagc ctccggagta gctgggatta ctggcatgcg ccaccacgcc    56820

cagctaattt tgtattttta gtagagacgg ggtttctcca tgttggtcag actggtctcc    56880

aactcccaac ctcaggtgat ccgcccgtct cggcctcaca aagtgctagg attacaggcg    56940

tgagccaccg cacccagcct gttttctgca ttttttagtag agacagagtt tcactatgtt    57000

ggccaggctg gtctcaaact cccgaccttg tgatctgccc gcctcggatt cccaaagtgc    57060

tgggattaca ggcgtgagcc accgcgcccg gccttatttt tctttttttt tttttgagac    57120

aggatcccac tctattgccc agcctggagt gcagtgcagt gatctcagct cactgcaacc    57180

tctgcctccc gggttcaagc aattctcctg catcagccgc ccaagtagct gagattacag    57240

ccgtgcctgg cttatgtttt gtgtttttag tggagatggg gtgccaccat gctggccagg    57300

ctggtcttaa actcctgacc tcagttgatc ctcccacctc agtctcccaa agtgctggga    57360

ttacaggtgt gagccaccgc gcccagcaag cataagattt tttgacacat ggaggatcac    57420

ttgctggatg tgcactgaga agtaatgtgc ccatttccca gccacactct cccaaaggct    57480

tttacaggcg ctgtccccgt gaggtggtag aacagaatgt cagaattcaa cacattccaa    57540

cactgtcttc tgttgagctg taggaggact gcctgtggag ggacatgggt tctatgctac    57600

cttgcaggtt ttccctgggg cttgtgatca ctgtctcctt ggtgacatgc aatctgggag    57660

tgctttctgg agtctgataa gaacatactg gcacattgcc tgtgacgtgt gggacccagg    57720

cattttcagt gctgaggtga gtccttgatt gtaactgatg gggactggta tcttaactcc    57780

aggttactga agactaggaa tttcttgcct tacagtaaaa ttgcaaagaa gagtagcata    57840

agaggtagat cagaagactg cagaatagat taacaaatga atgcccaaat gaggatgcta    57900

aacttggatt tgcatcaaga agacagatat tggtcgggcg tggtggctca cgcctgtaat    57960

cccagcactt tgggaggctg aggcgggtgg atcatcctgg ctaacacggt gaaacccccgt    58020

ctctactaaa aaaatacaaa aaaattagcc gggcgtggtg gcaggcgcct gtagtcccag    58080

ctgctgggga ggctgaggca ggagaatggc atgaacccag gaggcggagc ttgtagtgag    58140

ccgagatcgt gccactgcac ttcaccctgg gcgacagagc gagactctgt ctcaaaaaaa    58200

aaaaggacag gtattaggat agttttgaag cccacttgct cctatcatgg cattgaagca    58260

tcagtttgct gccaatcact ccttcttctg tgttcataga caggactgtg gaaatgtaca    58320

cttggattct ttcacaggta atgctgagaa atttaaaacc aaaaacggcc gggtgccgtg    58380

gctcctgcct gtaattctag cactttggga ggctgaggcg gcggatcac aaggtcagga    58440

gttcgagagc agcctggcca atatggtgaa accccatctc cactaaaaat acaaaaatta    58500

gcctggcata gtggcgggcc cctgaagtcc cagctactca ggagactgag tagacgagga    58560

gaatggcttg aacatggggt gcagaggttg cagtgagctg agatcgcacc gctgcactcc    58620
```

-continued

```
agcctgggca acaagagtga aactctgtct caaaaaaaaa aaaaaatttg aaattaaagt    58680

gtatgattag agtgcatgat tggttctgac tggatgtgta acatgtgcat agccttctca    58740

taaatcaaag gttttatgt gaaacctacc actagtgatg taactgaatt tgtgtaaatg     58800

ctggtgtgtc tgccttttcc tagcaactcc ctgggcagcc tgaggattct ttgaggttat    58860

tttttttcaa gatctggctg ggagcttctg catgagtgct gtgtgaacgt cctccatctg    58920

cagtgtgagg acagcgaacc ctagtgtgag ttaaccacgt aggaagagtt tgaagtcaga    58980

catgacattc agactgaggt cctcaaaact gaggggcatt ttctgtggtt tgaaaggaaa    59040

gtgcacccag ttttggggat gtcaattgtg aatcctcatc ataacccatc cccagtcccc    59100

catcgcattg caccacatgg atgcacccag tggactggcc tttgcttttc tattgtttct    59160

ttttctctcc actgcaatca gctttctcac gttgaatgca ttccattttc taagcgctct    59220

cctaggcaaa aatccctcta atgcaaagca aaaatgtctg ttatgcaaca ttgttctgag    59280

accccaggaa ttgcagttaa cttggctcct tagtatgtgc ttcctaaggc gggtggggtg    59340

gctcgcgcct gtagtcccag cactttggga ggcaggcgag gcacttgaaa ccctgtctct    59400

actaaaaata caaaaattag ctggacatgg tggcatgtgc ctgtaatccc agctacttgg    59460

gaggtgcaga caggagcatc gcttgaaccc aggaggcaga ggttgcagtg agccaagata    59520

atggcactgt actgcaacct gggtgacaga gcgagactca aaaaaaaaaa aaagtgcttc    59580

ctgtgaaggt ttcctttccc ttctgccccc cataccagtc catctattta gtagatgtcc    59640

tggtttctac ccaggatatc atggaccagg ggttctgtct tccagccttg agtacaatgg    59700

tgcgactata gctcactgca gtctcaacct cctgggctca agtgatcatc ctgcctcagc    59760

ctccaagtag ctggtattac agatgcacgt gcccccattc ccagaggttc ttaaatttat    59820

gacaaaaacc cagaagcttg gctgaagcag cttgttgggg cccacccaca gattttgttt    59880

ggtgccatag acctgggttg ggatctgggg agccattttt cttagtctca atgtaaatgt    59940

ctaagcattt tctttttttc tttctttttt tttttttgag acagggtttc gctcttgttg    60000

cctaaactgg agtgcagtgg cacaatctcg gctcactgca acctctgcct cctgggttca    60060

agtgattctc ctgcctcagc ctcccaagta gctgggatta caggtgtgca ccaccatgcc    60120

cggctaattt tttttattt ttttattttt tttatttttt gagatggagt cttgctctgt    60180

tgcccaggct ggagtgcagt ggtgtgatct cggatcactg caagctccgc ctccttgatt    60240

catgccattc tcctgcctca gcctcccgac tagctgggac tacaggtgcc cgccaccacg    60300

cccagctaat ttttttgtat ttttagtaga gacggggttt cactgtgtta gccagggtgg    60360

tctcggtctc ctgatctcgt gatctgcctg cctcggcctc ccaaagtgct gggattacag    60420

gcttgagtca ctgcccctgg ccaattttt gtatttttag tagaaatgga gtttcaccat    60480

gtttcctgcc tatctctcta tgtatttaga caggtctca ctatgttgcc caggttggtc    60540

tcaaactcct ggactcaagc aatcctcctg cctccacctt ccaaagtgct gggactacag    60600

gcttgagcca tcctgcctga ccatttgaga gtttttttttt tttgagatgg agtctctctc    60660

tgtcacccat gctgtagtgc agtagtgtga tcttgcctcc ctgcgacctc tgcctcccgg    60720

gttcaagcaa ttctcctgcc tcagcatccc cagtagctgg gattacaggc gcccgccact    60780

acacccagct aatttttgta tttttagtag agacagggtt tcaccatgtt ggccaggctg    60840

gtctcgaact cctgacctca ggtggtctgc ccacctccgc ctcgcaaagt gctgggataa    60900
```

56

-continued

```
gaggcgtgag ccaccgtgcc tgtcttcaac aatgatttct aattgcattt tatggtggtg   60960

attgaacata atgtactttg gtccttctcc attgtatgcc tcgtgtatta tgtgtctcat   61020

aacgtctgtc ccgtcctatg ctatgtgtgc atttgaatgt tggggagggt tcagtagatg   61080

tccattgagt tggtttgcaa acttatttga aacttctact tacttctgcc taattctgct   61140

tattattgag agtggactgc tctgggatgc cttttgtttg cactctgatt tcagatggac   61200

cctgagaatg ctcaagcccc aaaccctcct tgggaagtga agctcaggct gtgatttcaa   61260

gccagggggc gttttctat aactggatga aaagcacctc cagagcttga agctcacagt   61320

ttgagagcaa tcgtctaagg aagttgatgg caatgttaat agtttttaa acaagcatga   61380

aatcagattc ctgtgtttac ttctggatgc tgttgatcca ggaaatgtac ttagaaaatt   61440

cattttaacg gaaatagtca taagcgtctt ggtaatttca tgaagctaca gtgagtaaat   61500

tgcctgagaa tttccctgcc tgaaaggtct tcaggagtgt aattttttt taatatagct   61560

tatttaatac aaatagagat gcggtctcac tcttgcctag actggtgtgc agtgtcatgt   61620

tcacagctca ctgcagcctc tcaacctccg gggctcaagc atcctcctgc ctcagcctcc   61680

caaagtgctg gaattacagg tgtcagccac cactccctac tcatacttgt atatttctct   61740

ttaaattctg ttgaggtttt atggcctagc ctgtggtcta tcctggagaa tatttgtgtg   61800

catgacaatg tgtatatata tatatata tatattttt ttttttttc ttttttttga   61860

gatggagttt cactcttgtt gcccctagctg gagtacagtg gcatgaatct cagctcactg   61920

caacctccgc ctcccgggtt caagcgattt tcctgcctca gcctcccgag tagccgggat   61980

taccctccac cacacccggc taattttttgt attttttagta gaggtggggt ttcgccatat   62040

tgaccaaggt ggtcttgaac tcctgacctc aggagtcccg cctcggcctc tcaaagtgct   62100

gagattacag gcgtgagcta ccctgcccag gctgaccatg tatattccta atttttgtac   62160

ttttttttt ttgagacgga gattcactct tgtggcccaa gctggagtgc aatggcatga   62220

tctcggctca ctgcaacctc tgcctcctgg gttcaagcaa ttctcctgcc tcggcctccc   62280

gagtagctgg gattacaggt gtgcaccacc acgcctgact gacaatatat attcttaaac   62340

agctcagatt ccattttgga tcctcccatc aggactggaa cttaggtgta ctggaactta   62400

ggtgaacact tggctcaaaa ttcattgctg ttctctataa atctagccag ttctcttggt   62460

taaatttaag gtatgtatag tagtcgctgc ttttctttc gggggacaaa actcaggagg   62520

attgcttctt gattcataag ggcaacctgt tgagattttc acgcaaggaa cccgagatgt   62580

tcatttaatg ggcttataat ttgggattcc agaacacatg caaacagggc aaatgaatgt   62640

ttggctgtat ctttattttt gtgttcattt cagcctggtc aaggttttag aatccaagga   62700

aaccaataaa cacccagagt gctggagcaa gactgtctcc tgctgtgacc ctcaagatgg   62760

aagcagtttc tgttgtctga aaggaaagaa agtgcttcct ttttgagggt tactgtttga   62820

gaaaagcaac cttgaggttg atgctgatgt ttgtaacaca cctgcagagt atacttataa   62880

tcagacttgg gtgatgtgag gttttgtttt tactccaaga tgagggtctc cacccaggct   62940

ggaatgcagt tgcccttcca acctagaact cctgggatga actggtcctc tatgcctcag   63000

cctgccgagt agctgggact ataatatagg ggtgtgccgc catatttggt agattttttca   63060

atttttgta gagatggggc ctcaccctgg ccaggatggt ctcaactcct gagctcaagc   63120

aatcctacag gtgtgagcca ccgtgcccat tttaaagata gttgacatga tcaagcatag   63180
```

-continued

```
tgggacacac agccccagct actgcagagg ctggggtggg agagtctctt gatttcaatg    63240

ctataccgtg cactaatgac acctttgaat agccactgca ctccagcctg ggccaacata    63300

gcaagatccc atctcttaaa aaaaaataca ttacatggca cctggttcca gagacaccat    63360

ttgtgttggt caaacaatgg cctcctataa atttagttta atgaatccaa accatgtttc    63420

cttcattaag agagtaaata agcctccaag tctatccagt cttttttgaga cagagcttgg    63480

ctcttgtcac tcaggctaga gtgcaatggt gcaatctcag ctcactgcaa cctctgcctc    63540

ctgagttcaa ggagttctct cacctcagcc tcccaagtag ctagaatgac aggcgcctgc    63600

caccatgacc agctaatttt tgtgttttta ctagagatgg ggtttcacca tgtcggtcag    63660

gctggtctcg aactcctgac ctccgtgatc caccccacctc agcctcccaa agtgccggga    63720

ttacagacga gagccaccac gcccggcctg tccagtcttg ttctgcagtc cccaatgggg    63780

attttttttt tcctgttcat ttgtcttttt attttaatct acttgtccct gacactgaaa    63840

attttttcctt cctaacagct taccatcatt tctcagaata gacctgcttc ctctgtgaga    63900

agcttatagt tgattcaacc ctcaaccact aatgccaaca accctagtga gttcttttga    63960

ctacagctgg accatttatc ctgtttcctg tgggtagcgg ttccaatgta ccattccaac    64020

aggcaaaacc tcgcctctga atacaggttg cttggcaaga tctaaaatgt ttgctgtgcc    64080

taatataaac tattgtaaag aaaatccatc tcaatcacag tgacaaatgt cacatgagac    64140

aaaaccacag atattttcgc aaaaataggg tcctttagaa ccctagaagg gtctctctag    64200

taacaggtgg gatgttcagc agctcttgtt gttgccacag tgagcgatgc ctgttcgtcc    64260

agcccttaac acctcttact ccatggaagt tctgcctgca ctgctttata gaacacctct    64320

tgggttgagg tagagttgga ggggacctca gtgtcccttg ctgatgggat gtgcactgct    64380

tagcaagcgc acggaggtgg agtgcatggg ctctgagttt ttattgggta aatgcagccg    64440

aaatgtagtg tgcatgaaca ggtcaaaaaa ttgcacattt gatttaattt ttaaatttta    64500

gagatggggg tctcactgtg tcacccagac taaactgggc tgtgctccta tgcgtaccct    64560

agtagctggg acttcaggtg aatattaacc catgcatagg caaggagaga ggaaggctct    64620

gacagtctgt gatctcccct cactgcaacc tccaccctct ggactgggaa cgtcagggca    64680

ctgcaccgat gcaggcagga tgagccgagg ggaaaggaga gccaggcatc actggctggg    64740

gacattttgg gtttgatctg gatggagcag gtgtctcctg gagagagagc ccctgggatt    64800

ttcactctgc tccctggctg tcttagtcat ggaatctgac aacagagact cctgcccagg    64860

gccacttcat ttggtttctg gaccccagtg gtccttcctg cctggactta ggatcttttg    64920

gggaagtttg ggatctggca gggcatctgc ataatccata gaaatccctg agagtcactt    64980

cccttggctg acatctccat gttcctaccc attaccttcc aaaggagacc cttaactgaa    65040

ttaccaaagg gggcttccca gagcagggaa acccggttaa ctttctattt caggtcaaca    65100

gtatacttga gatgtacttg aactagaaat gattggttgt ttaggtgtgg gcatttgttt    65160

ttcctaactt agtctccaag aaaaaaaatt attgaggttt tacagcctag cctgtggtct    65220

atcctgaaga atgttcgtgt gtgtgacaat gtacattctt ttttttcccccc cagctctgtc    65280

aaatcttact gaggagcttt tacggcctag cctgtggtct gtcctggagg gtatttgtgt    65340

gtacaacaat gtatattctt aaacattatc ttagattcca ttttggatgt tcccatcagg    65400

actgtgtgtt tctgtgctgg aactcaagtg aacactggct caacatcctt agaaatccag    65460
```

-continued

```
cccaattctc ttggttaaag ataaggtatg tgtggtaggc attgcttttt ctctttgggg    65520

acaaaactca ggaggattgc cccttgatga acaaggctaa cctgctaagc ctttgaagca    65580

aggaactgga gatggtcctt tcaggggttt atgttctgga ttccataaaa catgcaaaca    65640

ggggcaatga atgcaccttt tttattttta tttttatttt tttttgagat ggagtcttac    65700

tcttgccagt ctggagtgca gtggcacgat ctcggctcac tgcaacttct gcctcctggt    65760

tcaagtaatt cccctgcctc agcctcccga gtagctggga ctacaggtac atgccaccac    65820

aggcggcaaa tggttgtatt tttagtagag acggagtttc accatgttgg ccaggatggt    65880

cgtggtctct tgaccagcct cccaaagtgt tgggattcca ggcgtgagcc accgcgcctg    65940

gccaatgaat gcatctttat ttttgtgttc attttaatct ggtaaggtaa attccaacaa    66000

aaaacccaga gttttggagt gagaagatct catgcagtca ttctccaaaa gaaagcactt    66060

tctgttgtct gaaagcagag tgccttcttt tggagcgtta ctgtttgaga aaaaccacgt    66120

tgaagttgat gctgatcttg gtaacacatt tgcagagcgt gcttatcatc agacttgcat    66180

gatgttgggg ttctgttttt gtttagtttt tttgcaacac agggtctctt gcccaggctg    66240

gagtgcggtg acacttccaa cctagacctc ttgggctcag ttggtccctg cccccaccccc    66300

ctcccccttt tttttctctt gagacagtct ctctctgtgg cccaggctgg agtgcagtgg    66360

tatgttctct gctcactgca acctctgcct cccgagtagc tggtattaca ggcacatgcc    66420

accacgcctg gctaattttt gtattttag cagagacgga gtttcatcat gatggccaga    66480

ttagtcttga actcctgacc ttaggtgatc cacctgcctc ggcctcgcaa agtgctggga    66540

ttacaggcat gagccactgt gcctggccca aacgtatat tcttaaatat catcttagat    66600

tccattttgg ttgctcccat cgggactgtg tgtccctgtg ctggaactca agtgaacaca    66660

tggctcaaaa tccattgctg ttctctagaa atccagccca attctcttgg ttaaatataa    66720

ggtatgtgtg gtaggctttg cttttttctct ttggagacaa tactcaggag ggttgcccct    66780

tcgtgaacaa ggctaacctg ctgagccttt gaagcaagga actggagatg gtccttttag    66840

gggtttatgt tctggattcc agaaaacatg caaacaggga caatgaatgc atctttattt    66900

ttgtgtccat tttaacctgg taaggaaaat tccaacaaaa acccagagtt ttggagcgag    66960

aagatctcat gcagtcattc tccaaaaggg agcactttct gtttgaaaga aaacaaagtg    67020

cctccttta gagtgttact gtttgagaaa aaccacgttg aagttgatgc tgatcttggt    67080

aacgcatttg cagagcgtgc ttatcatcag acttgcatga tgttggggtt ctgttttgt    67140

ttagttttt tgcaacacag ggtttctgtt gcccgggcag gagtgcggtg gcgcttccaa    67200

cctagacctc ttaggctagt tggtcccccc tactttttt gttgttttg ttcttgagac    67260

agagtctcac tatgtgggcc aggcgggcag gcagtgacac attctctgct cactgcaacc    67320

tcggcctccc aagtagctgg tattataggc acgtgccacc acgcctggct aattttttgta    67380

tttttagcag agatggagtt tcaccacatt ggccaggtta gtcttgaact cctgacctca    67440

ggtgatctgc ccgcctctgc tttccaaagt ggtgggatta caggcatgag ccaccctgct    67500

cggactgcag ggtgtttttt ttttttttt taattattat ttgtatttt ttgtgctgcc    67560

aaagcaagca cttgtgtgta ggaattttgt ttgtttgttt gtttgtttgt ttgagatgga    67620

gtctcattct tgtcgcccag gctggagtgc agtggcatga tctcggctca ctgcaaccta    67680

cgccttccgg gttcaagcga ttctcctgcc tcagcctcct gagtagctgg gatttcaggt    67740
```

-continued

```
gcatgccgcc accccggcta attttttgtcc ttttggtaga atcggggttt tgccatgttg   67800

gtccggctgg tctcaaactc ctgacctcaa ctaatccacc tgcctcggcc tcccaaactg   67860

ctgggattac aggcatgagc caccgcaccc ggtgaggagt tattttttaat gtgagcaaac   67920

agtatattct tttttttttt tttcatagac agggtctcaa caatatatga tgtatattta   67980

atcatatagt cttatcatgt atataatgta gtcatatgta caccaaaccc tgttctacac   68040

acggagaata ctcttgtatc actttgggta tttatttact tgtttctttc tgtgtttttc   68100

ttgtttgttt gtttgttttg ttttgagaca aggtctagct ttatcaccca ggctggagtg   68160

cagtggtgcc atgtcgactt actgcaacct ccacctgcca cctcagcctc ctgagtactt   68220

gtctacaggt gcgcaccacc acacccagct aactttttcta ttttttgtgc ataaggtttc   68280

accatattac ccatgctggt tgagctcgaa ctcctgagct caagtgatcc tcctgccttg   68340

ccctctttaa gtgctgggtt tattggtgtg agccaccacg ccccacccat acttgtgtat   68400

ttctgtattt attgaggagc ttatacagca taccctgtgg tctatcctgc aggatgtttg   68460

tgtgtgagac agtgtatatt cttgaacata gtagattcca ttttggatgc tcccatcggg   68520

actgtgtgtc cctgtgctgg aactcgagtg aacacttggc tcaaaatcca ttgctgttct   68580

ctagaaatcc agctcaattc tcatggttaa atataaggta tatgtggtag gcattgcttt   68640

ttctctttgg ggacagaact caggaggatt gccccttgat gaacaaggct aacctgctga   68700

ttctttgaag caaaggactg gagatggtcc ttttaggggt ttatgttctg gattccagaa   68760

aacatgcaaa cagggccaat aaatgcatct ttttgttttg ttttgttttg tttttgagat   68820

ggagtctcgt tctgtcaccc aggctggagt gcagtggcac aatcttggct cactgcaagc   68880

tcagcctcct gggttcacgc cattctcctg cctcagcttt ccaagtagct ggggctacag   68940

gtgcccacca ccacgctagg ctaatttttt gtatttttag tagaggcggg gtttcacccct   69000

gttagccagg atggtcttga tctcctgacc tcgtgatctg cccgcctcgg cctcccaaag   69060

tgctgggatt acaggcatga gccactgcgc ccggccccaa taaatgcatc tttatttttg   69120

tgtccattta aacctggtca aggaagattc ccacaaaaaa tccacggtgc tggagcaaga   69180

ggatctcagg ctgtgaccct ctaaagggaa gcgctttctg tggtcagaaa gaaaagcaag   69240

tgcttccttt tagagggtta ccgtttggga aaagcaatgt tgaagttgat gctgatcttg   69300

gtaaaatatt tgcagagcgt gcttatcatc agacttggat gatggtgggg ttttgctttt   69360

gttttgttgt attccaagac aaggtccctg ttgcccaggc tggagtgcgg tgacacttca   69420

acctacattt cttgggctcc ggtcgttttt gtttgtttgt ttgtttgttt gacagggagt   69480

ctcactgtgt gtctcagcaa tgcagtggca ctatcttggc tcactgaaac ctcagcctcc   69540

tgagtagctg ggatcacagg tgcgtgcaac cacgcccatc taattttttgt atttttttgca   69600

ttttcagtag agacggggtt tcaccgtgtt agccaggatg gtctcgatct tctaacctcg   69660

tgatccgccc gcctcggcct cccaaagtgc tgggattata ggcgtgagcc accgcgcccg   69720

gccgagaaac taatcttttg agatgaactc tgagatgtgg attttagctt gtttgcagcc   69780

accaccactc tagttttgga agattttcat caccccgaag aggcttatac tcatttgcag   69840

tcagtaccca cccacctctt ccacccagac cgtggcaacg actccccatc tctctagctc   69900

tggatctgcc tcttgtaggc cggtcacgta gaccaatctt gtatgggtgt ccagttgagg   69960

ataatgggtt ggtcctggtt gtctgcaatg tgaatcttac cactgaaggg tggtccctgg   70020
```

-continued

```
agggaagcag gaggctggga gaactgggcg gaacatcctt tgggaatgga gtggggcggg    70080

cagaccctga tgtctgggaa gctcacaagg gtggaagacc ccatcttcct ccctgagaac    70140

tgcaaggtga ccctcctggg gcactggaag gagtgaaggc ctctgggctg ggaacgtcag    70200

ggcactgcac cgatgcaggc aggatgagcc gaggggaaag gagaagcagg catcattctc    70260

tggggacatt ttgggtttga tctggatgga gcaggtgtct tctgggagag agagccctg     70320

ggattttcac tctgctccct ggctgtctta gtcatggaat ctgacaacag agactcctgc    70380

ccagggccac ttcatttggt ttctggagcc cagtggtcct tcctgcctgg acttgggatc    70440

tttttggggaa gtttgggatc tggctgggcg tctgcataat ccatagaaat ccctgagagt    70500

cacttccctt ggctgacatc tccatgttcc ttacccatta ccttccaaag gagacccttá    70560

tctgaattac caaaggggc ttcccagagc agggaaacct ggttaaattt gtatttcaga     70620

ttaacagtat acttgagatg tacttgaagt agaaatgatt ggctgtgggt gtcggcattt     70680

gttttttcta attttaaata tgggaccatc atgaatttgg gtgtcacttt gtgcagggga    70740

cgtgggaatc gctgtcattt ttttttttttt ttaacatatg ctgccagaga aggcacttag    70800

gtggagaaat tactcttcgt gtgagcattc agtatataga acttcctttt ctgggggcag    70860

tgtcttatat atgatacaca ttttatcata tcatcttcta tagataatat aatgattaac    70920

acaaaacact cttctacaca cacagaatac tcttgtatca ctttgggttt tttttccttc    70980

gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gttatgagac aaggtctggc    71040

tctgtcaccc aggctgcagt gcagtgttgc agtcttggcc catgccccac cgcagcctct    71100

ggaatagctg tctgcaggcc aggcacggta gctcaggcat gtcgtctcag cactcttgga    71160

gaccaaagca ggctaatcac ctggagtcag gagtttgaga ccagcctggc caagatggtg    71220

aaacctcatt tctactaaaa gtacaaaaat tagccgggcg cggtggctca cgcctgtaat    71280

cccagctctt agggaggcag aggcaggagg atagcttgag cccaggagtt tgagacctgc    71340

ctgggcaata cagtgagacc ctgttctcca caaaaagaaa agaaaaaaaa gaaaaaaaaa    71400

ttttaaaaat gcaaaattag gtgggcatcg tggcacgtgc ctgtaatccc aggtacccca    71460

gaggctgaga caggagaatt gctggaaacc tggaggcaga gcttgcagtg agctgagatc    71520

acggccctgc actacagcct gggcaacaaa gtgagacttg tttcaaaaaa aaaaaaaaaa    71580

tttattgagg agctttatg gcctagcctg tgttctatcc tggagaatgt gtgtacaaca     71640

gtgtatattc ttaaacatca tcttagattc cattttggat gcttgcatgg ggactgtgtg    71700

tccctgtact gggacttatg tgaacacttg gcttcaaatc cattgctgtt ctctagaaat    71760

ccagcccaat tctcatggtt aaatataagg tatgtgtggt aggcattgct ttttctcttt    71820

ggggacagaa ctcaggagga ttgtctcttg atgaacaagg ctaacctgct gagcctttga    71880

agcaaggaac tggagatggt cctttttaggg gtttatattc tggattccag aaaacatgca    71940

gagagagtca ataaatgtat ctttatttt gtgtccattt taaccaggtg aggaaaattc     72000

cgtcaaaaaa cccagacttt tggagcgaga agatctcatg cagtcattct ccaaaagaaa    72060

gcactttctg ttgtctgaaa gcagagtgcc ttcttttgga gcgttactgt ttgagaaaaa    72120

ccacgttgaa gttgatgctg atcttggtaa cacatttgca gagcgtgctt atcatcagac    72180

ttgcatgatg ttggggttct gttttttgttt agttgttttg catcatgggg tctctgttgc    72240

ccaggctgga gtgcggtggc gcttccaacc tagatctctt gggctcaagt ggtcccgtgc    72300
```

-continued

```
ttgctttttt tttttttctt gaaacagagt ctctgtctct ggcccaggct tgagcgcagt    72360

ggcatgttat ctgctcactg caacctctcc tcccaagtag atgggattac aggtgcacgt    72420

gccacgacgc ctggctaata tttgcatttt tagcagagat gcagtttcat catgatggcc    72480

aggttagtct ccaactcctg acctcaggtg atccgcctgc ctcagcctcc caaaatgctg    72540

agattatagg tgtaagccac ccagcctagc ctccaatttt ttttaatgtg tgctgccaat    72600

gcaagcacat atgtgtagga attatttttc atgtgagcac atagtatatg gaacttaatt    72660

tttattgatg tacggtctca aaaatatata ttttatcata ttcttattat acatgtaaca    72720

tagtcatata cacacaaaac actcttctat acacagagaa tactctcgta tcactttggg    72780

taattttttg tttgtgtgtg tatgtttttg tttttttttt agataaggtc tgggtctgtc    72840

acccaggcta gagtgcagtg gtgccatctc agcttattgc aacctccacc tgccacttca    72900

gcctcttgag tagctgtcta caggcgcaca ccaccacgcc cggctaactt ttctgttttc    72960

tctacacatg aggtatcacc atgttgccca ggctggtctc aaactcttga actcaagtga    73020

tactcctgcc tcagcctcct aaagggctgg gtttagaggt gtgagccacc acacctcacc    73080

tgtacctgtg tgtttctgct cattttattg aggagctttt acagcctggc ctgtggtctc    73140

tcctggaggt gtgtttgtgtg tgtgacaatg catattcttc aacatcgtag attccatttt    73200

ggatgccccc gtcgggactg tgtgtcactg tactggaact cgagtgaaca cttagctcaa    73260

aatctattgc tgttctctag aatccagccc aattctcatg gttaaatata aggtatgtat    73320

agtcggcatt gcttttttgaa acaaggaact ggagatggcc ctgatagggg tttatgttct    73380

ggattccaga aatcatgcaa acagggccaa taaatgcatc tttatttttg tgtccatttt    73440

aacctggtca aggaaaattc caacaaaaaa tcaatggtgc tggagcaaga agatctcagc    73500

ctgtgaccct ctagagggaa gcgctttctg ttgtctgaaa gaaaagaaag tgcatctttt    73560

tagaggatta cagtttgaga aaagcaacgt taacgttcat gctgatctcg gcaatacatt    73620

tgcagagcgt gcttatcatc agacttggat gagggtgggc ttttgttcct ggtttgtttg    73680

ttttctaaga cggggtctct tttgcccagg ctggagagca gtggcacttc caacctagct    73740

ctcttgggct caggtggtcc tctttgcagg gtcacgatct ctgctcacta caatctcccc    73800

ttccgggtt gaagtggttc tcccatctca gtctcctgtg ttgctgggag tacaggccca    73860

tgccaccacg cccggctaat ttttgtattt ttagcagaga tggggtttca ccgtgttgac    73920

caggatggtc tccatctcct gacctcgtaa tccacctgcc tcggcctccc aaagtgctgg    73980

gtttacagtc atgaaccact gcacccggcc tttgatctta attttcaata tgagacccat    74040

catgaatttg ggcatcacct ctgcacaggg gccatggtga tctctgtcac tccattcatt    74100

tcttatgtgt ggagcaaaca tttatgtgta ggagtaattc tttatgtgag catacagtat    74160

atggaacttt cttttttttt gagatagggt ctggaaaata aatgatgtac agccaggcgc    74220

atgagtatat gagcagtttt tgtgtgtata cgacatgagc ggtggctcat gcctgcaata    74280

tcaacacttt ggcaggttga ggcgagtgga tcacttgagg tcaggagttt gagaccagcc    74340

tgaccaacat ggtgaaaccc tgtctctact aaaaatacaa aaaattagcc agctatggtg    74400

gcgcacgcct gtattcccat ctgctgggga agttgaggga ggagaatcac ttgaacggac    74460

agatggaggt tgcagtgagc caagatcacg ccaccacact ccagcctggg cgagagaata    74520

agactgtctc aaaaaaaaaa tatatatata catatatatt tatatagaga gagagactct    74580
```

-continued

```
gtctcaaaaa aaaaaatata tatatgggtg tgtttgtgtg tatatatata ttatatatga  74640

tgtatatttc atcatatagc catatatata attatataca caaaaaatac tcttctacac  74700

acagagatga ctgatatcac tttggggtgg tttttgcttg tgtgttcttt taaattttt   74760

tttgcaacaa gatctggctc agtcgcccag gttggagtgc agtgtttcag tcttggctca  74820

ctgcaacctt cgcctccac  cccagcctcc tgaattagtg tctacaggca tgtaccacca  74880

cacctggcct acatttgtat tttttttacag acagggtttc accgtgttgt acacgctggt  74940

cttgagctcc tgagctcaag tgaatctcct gccttggcct cctgatgtgc tgggattaga  75000

ggtatgagcc accacaccca actggtactt gtgtattcct gttcaaattt tattgaggag  75060

cttttaccac ctagcctgtg gtctatcctg gaggatgttt gtgtgtgcga caatgtatat  75120

agttcaacat cttagatcac attttggatg tttccaatgg gactgtgtgt ctccgcactg  75180

gaactcaaat gaacacttgg ctcagaatcc atttgctgtt ctctggaaat ccagtccaat  75240

tctcttggtt aagtataagg tatgtctagt aggcattgct ttttctgttt gagaacaaaa  75300

ctcgggagga ttgtcccttg atgaacaagg ctaacctgct gagcctttga agcaaggaac  75360

tggagatggt cctttttcagg cgtttttattc tggattccag aaaacatgca aacagggcca  75420

ctaaatgcat ctttattttt ctgtccattt aaacctggtc aaagaaaatt ccaacacgaa  75480

acccagagtg ctggagcaag aagatctcaa gctatgagtc tacaaaggaa agcgctttct  75540

gttgtcagaa agaagagaaa gcgcttccct tttgagggtt acggtttgag aaaagcagtg  75600

ttgaagttga tgctgatctt ggtaatacat ttgcagagca tgcttatcat cagacttgga  75660

tgatagcggg gttatgtttt ggttttgtgt ttttctaaga cagggtctcc gttgcccagg  75720

ctggagtgcg gtggcacttc caacctagct ctcttgggct caagtgatcc tcttttttatt  75780

tatttatgta ttcattttg agatggagcc tggctctgtc acccaggctg gagtagagtg  75840

ggatgatctc cactcattgc atcctctgcc tcccaggttc cagaaattct cccacctccg  75900

tgtcactagt agctgggatt acaaatgctc accactatga cctgccagtt tttgtacttt  75960

tggcacagac ggggtttcac catgtttgcg gggctggtct caactcctga cctcaagtga  76020

tctgcctcct tggcctccca cagtgctggg gattatagat ataagccacc gtgcccggcc  76080

cattcctgtc ttttttaattt aatctgctcg tccctgacat cgaaaatttt tcttgcttaa  76140

cagcttccac ttatttctcg gaatagacct ttttctgcag gaagggtgta gttgattcaa  76200

ccctcaccca ctcatgccaa ccgtagtgag tgctgtgact gcagctgcac tgtttatcct  76260

gtttttctgca ggtaattttt ccagtgtacc attccaacct gcaaaacctc acatttaaat  76320

gcaaatttct tggtaagctg tgaaatgttg gctgtggcta atatgagaaa caagctatta  76380

tagacaagat gaatctcagt tgcagtgata aatgtcacat gggacaaaac cacagatact  76440

ttcacaaaaa ccttgaggac cctagaaggg cctccctagt aacagtgggg atgcgcatcc  76500

gctcttgttg ccatagtgag tgatgcctgt tcgtccagcc ctcaacacct ttcactccgt  76560

ggaagttatg cctgcactgg tttacagaac ctcccttgac ttgacttgag gtagagttga  76620

agggaacctc agtgtccctt gcagatggga tgtgcattgc ttcgcaagag cacagaggtg  76680

gagtgcatgg gctttgagtt tttattgggt aaatgaagct gaaatacagg gtgtatgacc  76740

acgttatcaa cgcacacttg atttaggttt tgtattttag agacgggggt gtgagctgcc  76800

aaagcaagga cttatgtgta ggaattattc tttctgtgag catacagtat atggaacttt  76860
```

-continued

```
ctttcttttg agacagggtc tcaaaaatat atgatgtatg gccaggtgcg gtggatcacg   76920

cctgtaatcc cagcagtttg ggaggccgag gcgggtggat aacctgagat caggagggcg   76980

agaccagact ggccaacatg gtgaaaccat gtctctgcta aaaatacaaa aaattagcca   77040

gggctggtgg cgcacgcctg tagtctcagc tactccggag ggtgaggcag gagactatca   77100

ctttgagtgt gtgtctttgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt atgtgtttct   77160

agttttttaca agacacagcc tgactatatc accgaggctg gagtgcagtg gtgcaatgtt   77220

ggctcactgc aacctccacc tgccaccgca gcctcctgaa ttagtgtcta caggtatgca   77280

ccaccacacc tggctcactt ttgtattttt tgtacagatg aagcttcacc atgttgccca   77340

ggcttgtctg gaactcttga gctcaagtga tcctctcact tcggcgtcct gaagtgctgg   77400

ggttagagat gtgagccacc gcacccaaca ggtacttgtg tatttttta ttgaggagct   77460

tttacagcgt agcctgtggt ctctcctgga ggatgtttgt gtgtgcgaca atgtacattc   77520

ttcaacatct tagattccat tttggatgcc cccatgggta ctacatgtgc ctatactgga   77580

actcaagtga acacttggct caaaatccat tgctgttctc tagaaattca gttcgattct   77640

cttggttaaa gataaggtat gagtagtagg cattgctttt tctctttggg ggcaaaactc   77700

aggaggattg cccccttgatg aacaaggcta acctgctgag cctttgaaag aaggaactgg   77760

agatggtcct tttaggggggt ttatattctg gattccagaa aacatgcaaa cagggccagg   77820

aaaaatgcat ctttattttt gtgtccattt aaacctggtc aaggaaaatt ccaacaataa   77880

acccagagtg ctggagcaag aagatctcag gctgtgaccc tccagaggga agtactttct   77940

gttgtctgag agaaaagaaa gtgcttccct ttggactgtt tcggtttgag taaagcagcg   78000

ttgaagttga tgctgatctt ggtaatacat ttgcagagca cgctcatcat cagactcgga   78060

tgatgttggg gttctgattt tgttttctc caagacaggg tctctgttgc ccaggctgga   78120

gtgcagtggc agttccaacc tagctctcct gggcccaaga gaccctctat ttatttattt   78180

atttatttat ttatttattt atttatttat tcattcattc atttagagat ggaatctggc   78240

tctgtgaccc aggctggagt gcagtaggac aatctccact cactgcaacc tccatctccc   78300

aggttccagc agtctgcca cctcagcctc ccatgtagct gggattacag gcgcccacca   78360

ccatgtcatg ctaattttg tattttttagc agagatgggg ttacaccatg tttgctgggc   78420

tgttctcaac tcctgacttc aagtgatttg cctccctggc ttcccaaagt gctggtatta   78480

caggcgtgag ccactgtgtc cggcctcaag tggtcttcct gagtcagcct cccaagtagt   78540

tgggattaca tggggcgtga cacaacactt ggttcagctt ttaatttttg gtagagatgg   78600

ggtctctgtt gctcaggacg gtctcaactc ctgagctcaa gcgatcctac aggtgtgagc   78660

caccttgtcc tgatgaccca tttcaaagat agttgacttg gccaggcatc atggggcaca   78720

cagtcccagt tactgcaggg gccgggggcgg gagggtgctt tgattttaag gctataccgt   78780

gcacagatcc cacctttgaa tagccactgc actccagcct gggccaacat agcaagatcc   78840

catttcttta aaaacagatt acatagcacc tggtcccaca gatttcattt gggttggtca   78900

tgtcatacaa tggcctccca tcaatttagt ataatcaatc caaaccatgg ttccttcatt   78960

aagagagtgg gtaatcctcc aagtccatcc agtctattct gtaatcccca gtgggtgtcc   79020

gtattgatac aatttctttt tgttcctgtt cactcgtgtc ttttttagtgt aatctgcttg   79080

tccgtaacac tgaaatttgt ttttccccaa catcttgcca tcatttctcg gaatagacct   79140
```

64

-continued

```
gctttctctg caggaagggt gtagttgatt caaccctcac ccactaatgc caaccccagt   79200

gagttctttg actgtagctg ccatgtttat cctattttct ttgggtaacg attccaaggt   79260

accattccaa tgggcttaaa ccttgcatct aaatgccagt tacttgctaa gatgtcaaat   79320

gtgtcttata ttagctgtgg ctaatataag aaactgttgt agacaagatg aatctcagtc   79380

acagtgataa atgtagcatg caacaaaacc agttgttttc acaaaaatct tgaggaccct   79440

agaaggggct ccctcgtaac aggtggaatg cacagcagct cttcttgttg ccatagtgag   79500

cgatgcatgt tcttccagtc ctcaacacct tttatttatt tatttattta tttatttatt   79560

ttattattat tatttttttt tgagacagag tctcgctctg tcacccaggc tggagtgcaa   79620

tggtgtgatc tcagctcact gcaaccactg cctcccgggt tcaagcgatt ctcttgcctc   79680

agcctcacgt gtcgctagga ctacaaccgt gcaccaccac gcccggctaa ttttttgtatt   79740

tttaatagag acagggtttt gccatgttgg ccaggttggt ctggaactcc tgacctcagt   79800

tggtccacct gcctcagcct cacaaagtgc tgtgaataca ggtgtgagcc aacacgcccg   79860

gctatcaaca acttttccta cgtagaaatt attcgggcac tggtttatag aacctcacgt   79920

gggttcacgt agaattgaag gggacctcag cgtcccttgc agatgggatg tgcaatgtat   79980

ttgagatgta ctcgaacatt gctgttgagg tgtgggcatc ttttgctttt tcctaatttt   80040

aaatatggga ctagtctggg tatggtgact tccaccagta attctagcac tttgggaggc   80100

tgagacagga ggatcacctg aggtcagttg ttcgagacca gtctggccag catggtgaaa   80160

ccccgtctct actaaaaata caaaaattag ccgggtgtgg tggcactcac ctgtaatccc   80220

agctactcgg gaggctgagg caggagaatc acatgaatct gggaggcgga ggttacagcg   80280

agcagagatc acaccgttac actcctgcct gggcaacagt gtgagactct gtctctaaat   80340

aaataaataa ataaaaataa aaataattag gtgaatatgg gaccagcatg gacttggggtg   80400

tcgcctttgt gcagtggcca ggatattcta tgtcatttaa attttttttat gtgtacttcc   80460

aaagcaagca gttatgtata ggaattattc ttcctataag catgcaatat ttggaacttt   80520

ctttgagaca gggtctcaaa aatacatgat gtatatttca ttttatattc ttatatatta   80580

tgtacacaca aaatactctt ctaaacacag agaatactcc gatatcacct agggtgtgtg   80640

tgcgtgtgcg tgtgtgtgcg tgtgtgtgtg gttctttttct gagacaatat ctgcctctgt   80700

cacccaagat ggagtgtggt ggtgcaatct cggcttactg caacctccac ctcccaccta   80760

agcctgctga attagtctct acaggcatgc accaccacac ctggctaact tctgtaatttt   80820

ttgtacacat ggggtctcgc catgttgccg gggctggtct cgagctcctg aggcaggtga   80880

tcctcctgcc tgggcctcct aaagttcgag gagttagagg tctgagccac tgggccccac   80940

ttgtacttgt gtatttctgc tcaaatttta ttgagtagtt tttacatcct agcctgtgat   81000

ctactctgga gagtgtttgt gcatatgaca gtgtatattc ttcaacatcg tagactccat   81060

tttggatgct cccttcgtga ctgtgggtcc tgtactggaa ctcgagtgaa cacttggctt   81120

aaaatccatt gctgttctcc agaaatcctg cccaatttttc tcggttaaag gtacgtgtag   81180

taggcattgc ttttttctctt tggggacaaa actcaggagg attgcccctt gatgaacaag   81240

gctaacctgc tgattctttg aagcaaggaa ctggagatgg tccttataga gttttatatt   81300

ctggattcca taaacatgc atacagggtc aataaatgca tctttatttt tgtgtctatt   81360

ttaacttggt caaagaaaat tccaggaaaa aatccacggc atcagagcaa gaagatgtca   81420
```

-continued

```
ggctgtgacc ctcttgaggg aagcactttc tgttgtctga aagaagagaa agtgcttcct  81480

tttagaggct tactgtctga gaaaagcaac gttgtagttg atgctgatct ttgtaatatc  81540

tttgcagagc acgcttataa tcagacttgg atgatgttgg ggttttgttt ttcttttgtt  81600

tttttatcta agactgggtc tctgttgccc aggctgaagt gcagtggcac aatcttggct  81660

caccacaacc tccgcctccc gggttcaagt gattcttctg cctcagcctc ccaagtagct  81720

gggattatag gactgcgcca ccatgcctgg ctaattttgt attttttagta gagacagggt  81780

ttctttagga gcttttaagg cctcccttgt agtctatcct ggaggatgtt tgtgtgtgca  81840

acaatgtata ttcttcaaca tggtagattc cattttgact gctctaatca ggactgtgtg  81900

tccctgtgct ggaaatcaag tgaacacttg gctgaaaatc cactgctgtt ctctagaaat  81960

ccagcccaat tctcttggtt aaatataagg tatgcatagt aggcattgct ttttctttct  82020

ggacacaaaa ctcaggagga tttccccttg atgaacaagg ctaacctgct gagcctttgt  82080

aggaaggaac gggagatggt cttttttaggg gtctatgttc tggattccag aaaacatgca  82140

aacagagcca ataaataggt ctttattttt gtctctattt taacctggtc aaggaaaatt  82200

tctacaaaaa acccagggtg ctggagcaag aagatcccat gctgtgaccc tctagaggga  82260

agcgctttct gttgtctgaa agaaaagaaa gtgcatcctt ttagaggttt actgtttgag  82320

gaaagcaaca gtgaagttga tgctgatctt ggtaatacat ttgcagagca tgcttatcat  82380

cagacttgga tgatggtggg attctgtttt tattttgttt ttttttctaa gacagagtct  82440

ctcttgccca ggctggagta gggtagcact tccaacgtag atctttttagg ctcaaacggt  82500

cctctttttt tttttttttt ttttgaggcg gagtcttgct ctgtgaccca gacgagagtg  82560

caatggcgcg atcttgtgtg caagctcacc tcctgagttc aagcaattct tctgccccag  82620

cctcccaagt agctgggact acaggtgcct gccaccactt ccagctaatt tttgtatttt  82680

tagtagagac agggtttcac cacgttggcc aggctggtct caaactactg acctcaagat  82740

ccacccacct cagcctccca aagtgctggg attacaggcg tgggccattg tgcccagcgg  82800

tcctcttttt tgagatggag tcttgctctg tgacccaggc tggagtgcag tggcaggaac  82860

ttcgctccct gtaccctcca cctcccagat tcaagccatt ctctcctgag tcagcctccc  82920

tagtagctga gatcgcagac atgagccacc atacccagct aattttttgta ttttttattat  82980

ttatttattt actcatcgat ttttgaaaca gagtcttact ccgtccatca ggctggaggt  83040

cagtggcaca atcccacgtt caagcaattc tcctgcctca tcctcccgag tagctgggat  83100

cacaggcgca caccaccacg cccggctaat ttttgtgttt tttttgtttg ttcgtttttt  83160

tttttttttgt agagacaggg tttcaacatg ttggccagcc cagtctccaa ctcctgacct  83220

taagtgagcc catacacaat caagaagaga gcgagacctg ttcttttttt ctgtctttga  83280

ctatttgaga cagtcttgct ctgtcacccg agatggagta cattagtgtg atcttggctc  83340

actgcaacct ctgcctcctg gactcaagca attctctttt ttttttttttt ggagaaagag  83400

cctctctgtg tctcccaggc tggactgcag tggtgtgatc tcagctcact gcaacctcag  83460

ccttccaagt agctgggatt gcagacatgt acccccatac cagctatata tatatatgta  83520

ttttagacac agtttcacca tgttagccag gccattcttg aatcctgacc tcaggtgatt  83580

tgccgacgta ggcctcccga agtgctggga ttacaggtat gagccactgc actcagcctt  83640

ttttcctaat tttgaatatg ggacccatta tgaatttggg tgtcacctat gtgcgggggc  83700
```

-continued

```
tatggaaatc tctgtcaccc cattcatttg tgtgtgctgt caaagcacca atatgtggga   83760

attatgcttt atgtgagcat atagtatatg gaactttggt tttttttat acagggtctc    83820

aaaaaaaaat gagtatattt catcacaatg ttctgtgtat aattccatac acacaaaata   83880

gtcttctata cacagagaac actcttatat cactttggag ttgttttttgt ttgtgtattt   83940

tgttttaatt tttatgagac agggcctggc tatgtcgctg aggctggagg gcagtggtga   84000

gatcttggct cactgcaacc tccacctgcc acctcagcct cctggattag tgtctacagg   84060

caggcaccac caccctgggt taagttctgt attttttggta ctgatgaggt ttcagcacgt   84120

tccacaggct ggactcttaa ctcctgcgat caagtgatcc tcccgctgtt caaattttac   84180

tgaggagctt ttaaggcctc gcctgtggtc tgtcctgtag tgtccctgtc ctggaactca   84240

agtgaatact tggtttaaaa ttgattgctg ttctctagaa atccagccca attctcttgg   84300

ttaaatataa ggtatgtgta gtaggcactg ctttttcttt ctggaggcga aactcaggag   84360

gattgcccct tgatgaacaa ggctaacctg ctgagccttt gaagcaagga actggagatg   84420

gtcgttttag gggtttatgt tctggattcc agaaaacatg gaaacagggc caataaatgc   84480

atctttattt ttgtgtccat tttaacccag tgaaggaaga tttcaaccaa aaacccacgg   84540

tgctggagca agaagatctc aagctgtgac tctccagagg gatgcacttt ctcttatgtg   84600

aaaaaaaaga aggcgcttcc ctttagagcg ttacggtttg ggtaaagcaa cgttgaagtt   84660

gatgctgatc ttggtaatat atttgcagag catgcttata attaagactt ggatgatggt   84720

gggtttctgt tttgtttttt gttttaaatc agagtctcac tctgtcaccc aggctggagt   84780

gcaatggcgc aatctcggct cactgcaact tcccctcct gggttcaagt gattctcctg   84840

cctcagcctc ctgagtagtt aggattacag acatgcgcca cctcacccgg ctcagttttt   84900

gtatttggtg gagatggggt ttcaccatgt tagtcaggct ggtcttgaac tcctgatctc   84960

aggtgatcca cctgcctcag cctcccaaag cattgggatt acaggcgtga gccaccacgc   85020

caggcctgtt caacatctta gatttcattt tggatgttcc tgtgaggact gcgtgtccct   85080

gtgctggaac tcaagtgaac gcttggctca aaatccattg ctgttctcta gaaatccagc   85140

caaattctat tggtgaaata taaggtatgt ctagtagtca ttgcttttttc tctttggaga   85200

caaaactcag gaggattgcc ccttgatgaa caaggctaac ctgctgagcc tttgaaacaa   85260

ggaactggag atggtccttt caggggttta tattctggat ccagaaaac atgcaaacag   85320

ggccagtaaa tgcatctta tttttgtgtt cattttaacc tggtcaagga aaattgctac   85380

aaaaaaccca gggtgctgga gcaagaagat ctcatgctgt gaccctctag agggaagcgc   85440

tttctgttgt ctgaaagaaa agaacgcgct tccctataga gggttaccct ttgagaaaag   85500

cagcattgaa gttgatgctg atcttgctaa tacatttgca gagcatgctt atcatcagac   85560

ttggatgaag gtggggttct gtttttttttt tttttctaag acaggatctc tgttgcccag   85620

gctggaatgt ggtggcactt ccaacctagc tctcttgggc tcaaatggtc ctctcttttg   85680

ggatagagtc ttactctgtg acccaggctg gagtgcagtg gcgtgatctc agcttactgc   85740

cacctccacc tcccagtttc aagccgttct cctgcctcag attcctgagt atctgggatt   85800

ataggtacct gacaccacgc ctggctaata cttgcatttt tctttctttt ttcttttctt   85860

tttttttttt tttttttttga gatggagtct tactctgtca ccaggctgga gtgcagtggt   85920

gcgatcttcg cttatttcaa cctccgcctc ccagtttcaa gtgattctcc tgcctcagcc   85980
```

-continued

```
acccgactaa ctaggatttc aggcatgcac cacacgcctg gctaattttt tgtattttta   86040

gtagagacag ggtttcacca tgttggtcag gctggtctcg aactcccgac ctctggtgat   86100

cttcccgcct tggcctccga aagtgctggg attgcaggca ttagccaccc cgcccggcca   86160

ttatatattc ttatatatat aataccatat acgtgcaaaa tactcttcta catgaagaga   86220

atactcttat atcactttgg ggtttttttt gtttgtttgt gtgtgtgtga gtgtatgttt   86280

tatttgtttt tggataaggt ctggctctgt cacccagtct agagtgcagt tgtgccatct   86340

ctctcagctc actgcgactt ctacctccca cctaagcctg ctgaattagt gtctacaggc   86400

atgcaccacc acacctggct ccgttttgta ttttttatac acatgggctt acaccatgtt   86460

gccgagactg tctcgaaca cctgagctca ggtgatactt cagtttcagc ctcctaatgt    86520

gctgggatta gaggtgtgag ccaccgtgcc ccacttgtag ttgtgtgttt ctgttcaaat   86580

tttattgagg agttttttagg gcctagcctg tgatctaccc tggaggatgt ttgtgtgtac   86640

aacaatgtat attctttaac atcgtagatt ccattttgga tgctcccatc gggactgtgt   86700

gtccctgtgc tggaactctg gtgaacacct ggctcaatat ccattctctc tctctagaaa   86760

tccagcccag ttctcttggt taaatataag gtacatatgt ctatgaggca ttgcttttgc   86820

tctttgagaa caaaactcag gaggattgct ctttgatgaa caaagctaac ctgctgatcc   86880

tttgaagcaa ggaactggag atggtccttt taggggttta tattctggat tccagaaaac   86940

atgcaaacag ggccaataaa tgcatctttg tttttgtgtc cattttaacc gggtgaagga   87000

aaattccaac aaaaaaccca gagtgttgga gcaagaagat ctcatgctgt gaccctctag   87060

agggaagcac tttctcttgt ctaaaagaaa agaaagcgct tctctttaga ggattactct   87120

ttgagaaaag caacgttgaa gttgatgctt atcttggtaa taaatttgca gagaatgctt   87180

ataatcagac gtggatgatg ttggtgtttc atgtttgttt tgttttgttt ttaatacagg   87240

gtgtctgttg cccaggctgg agtgtggtgg tccctctcca acctagatct cttgggttca   87300

agtggccctc ttttttgggt cagagtcttg ctctgtggcc ctggctggag tgcagtgtca   87360

ggatctctgc tcactacaac ctctgcctcc tgggtaaaag cgattctcct gcctcagcct   87420

cccaagcaac tgggattaca ggcatgtgct accatgcccg gctaattttt gtaatttcct   87480

ttatttattt ttgagacaga gtcttactct ttcgcccagg ctggagtgca gtggtgcaat   87540

ctcggctcac tgcaacctcc aactcccacc tcagcctcct gaatagctgt ctacaggcat   87600

gcaccaccac acctggctaa cttttgtatt ttttgtacag acatggtttc tccatgttgc   87660

ctgggctggt cttgaactcc tgaactcaag tgatcctccc acctcggcct cctaaagtgc   87720

tgtgattaga ggtatgagcc accgtgcccc acctgtactt gtgtgtttct gctcaaattt   87780

tattggggag cttttatggt atagcctgtg gtctctctgg agaatgtttg tgtctatgac   87840

aatgtatatt cttcagtatg ttatgttcca ttttggatgc ttgcatgggg actgtgtgtc   87900

cctgtactga aactcaggtg aacacttggc tctccgtcca ttgctgttct ctagaaatcc   87960

agcccagttc ccttggttaa agataaggta tgtctagcag gtattgctct ttctcttgca   88020

gacaaaactc aggaggattg ccccttgata aacaaggcta acctgctgat tctttgaagg   88080

aaggaactgg agattgtcct tttaggggtt tatattctgg attccagaaa acacacaaat   88140

agaaaacagg gcaaataaat gcatctttct tttcgagtcc attttaacct ggttaaggaa   88200

gattccaaca aaaaatccac ggtgccacag caagaagatg tcaggctgtg tccctctaca   88260
```

-continued

```
gggaagcgct ttctgttgtc tgaaagaaaa gaaagtgctt cctttagag ggttaccgtt   88320

taagaaaagc aacgtttagg tggatgctga tcttggcaat aatacatttg cagagcatgc   88380

ttatcatcag agttggatga tggtgggggtt ctgttttttt gtttttttttt ttctgagaca   88440

gagtgtctat tgcccaggct ggagtgcagt ggcactttta acctagatct cttgggctca   88500

agtggtcctg tttttttggga taatctcaca ctgtgaccca gtccggagta cagtggcatg   88560

aacaccactc attgcatgct ttgcctccca ggttcaagtc attcttatga cccagcttcc   88620

agagcagctg ggattacagg catgagccac cacactggct aattttttgta ttttttaatag   88680

agatggggtt caccatgttg gccaggctgg tctccaacta ctgacctcat gatccaccca   88740

cgtcggcctt ccaaagtgct gggattacag acgtgagcca ctgtgcccgg ccaacacaga   88800

gaatactctt atatcacttt gggggttgttt ctgtttgtgt attttttaaa tattttttga   88860

gacacagtct ggcgctatta cctaggttgg agtgcagtt tgtgacctcg gctcacagca   88920

acctctacct cccagctgag cctcctgagt tagcatctgc aggcatgaac cacaacacct   88980

ggtaaccttt gtattttttgg acacatgagg tttcaccatg ttgcccaggc tagtcttgaa   89040

ctcctgagct caagtaatcc tcctgcctcc gactcctaaa gtgctgggat tacaggtgtg   89100

agccactgca ccccacctgt acttgtgtat ttctgttcaa attttattga ggagctttta   89160

cggcctagac agtagtctat cctggagaat gtttgtgtgt atgacaatgt atattctttt   89220

ttttttatttt tattttttgg agacggagtc tcactctgtc acccaggctg gagtgcaatg   89280

gcatgatctc ggttcactga aacctccgcc tcctgggttc cagcgatcct cctgtctcag   89340

cctgctgagt agctaggatt acaggtgggc gcctggctaa tttagattcc attttggatg   89400

ctcccatcgg gactgtgtgt ccctatgttg gaactcaggt gaacgcttgg ctcaaaaatc   89460

cattgctgtt ctctagaaat cctgcctaat tctcttggtt aaagataagg tatatgtagc   89520

aggcattgct ttttctcttt ggggacaaaa ctcaggagga ttgcgccttg atgaacaagg   89580

ctaacctgct gagcctttga agcaaggaac tggagatggt cctttttaggg gtttatgttc   89640

tggattccag aaaacatgca aacagggcaa ataaatgcat ctttattttg tgtccatttt   89700

aacctggtca aggaaaattc caacagcaac atcaaaaaac cagtgttgga gcaagaatat   89760

gtcatgctgt ggccctccag agggaagcgc tttctgttgt ctgaaagaaa acaaagcgct   89820

cccctttaga ggtttacggt ttgagtaaag cagcgttgaa gttgatgctg atcttggtaa   89880

tacatttgca gagcgtgctt atcatcagac gtggacgatg gtggggttct gttttggttt   89940

tgtttttttc taagacaggg tctccgttgc ccagactgga gtgcggtggc acttctacct   90000

agatctcttg ggctcagatg gtcttctttt tatttcattt ttttaattgt ttgagatgga   90060

gtctcactct gtcacccagg ctggagtaca gtggcaggat ctccacaact acagcctccc   90120

aggttccaga cattctccca cctcagcctc ccgagtagct ggaattataa gcacccaccg   90180

ccatgccctg cttttttgtat ttttagacaa gaaagggttt caccatattg gccaggctca   90240

tctcaactct tgcccttaag taatcctcct ccctggcctc ccaaagtgct gagattacag   90300

gcgtgagcca ccgcgcccag cctcaagtgg tcctcttgag tcagcctctc aagtagttgg   90360

gactacgtgg ggcgtgccac catacttggc taagttttta attttttggta caattggggt   90420

ctcttttttcc caggatagtc tcatctccac agcttatgtg gtcctacacg tgtgagccac   90480

ctcgtcttga tgacccattt caaagagagt tgacatggcc aggcattgtg gggcacacag   90540
```

-continued

```
tcccagccac tgcagaggcc agggtcggag ggacctttga tttccagact gtaccatgca    90600

ctgatcacac cttcgaatag ccactgcgct ccagcctggg ccaacatagc aagatcccat    90660

ctctttaaaa acagattaca tggcacctgg ttacagaggc tccatttggg ttggttattt    90720

gaaatgggtc tcccatcaat ttagtgtaat caatcgaaat catttccttc attaagagag    90780

taagtagccg gggcatggtg cctcatgcct gtaatcccag cactgtggga ggcaaaggca    90840

ggcggatcgc ctgaggtcag gagttcaaga ccagcctggc caatatggtg aaaccctatc    90900

actactaaaa atacaaaaat tagccgggtg tggtggcgtg aacctaggag gctgaggttg    90960

cagtgagctg agattgcacc attgcactcc aacctgggcg actgagctgg acttaaaaaa    91020

aaggtaagta agccttcaag tctatccaat cttaatttgt aatctcaaat ggatgtccat    91080

attaacaaaa ttttcttgtt tttcctgttt gtgtcttttt agtttaatct tcttgtcctt    91140

gacactgaaa tttttttctc tccaacaact tgccgtcgtt tctcggaata gagctgcttt    91200

ctctgcagga agggtgtagt tgattcaacc gccacccact cacgccagcc ccggtgagtt    91260

ctttgactgc agcttccctg attatgctat tttcttcggg taatgaaccc aaggtacctc    91320

gcatttaaag gctagttgct tggtaagctg tgaaatgttg gctgtggcta atatgagaaa    91380

caaactatgg tagacaagat gagtctcagt ggcagtgata attgtcacat gggacaaaac    91440

cacagatact tttcacaaaa accttgagga ccctagaagg gcctctctag taacaggtgg    91500

gatgcgccgc agctctcgtt gttgccgtag tgagcgatgc ctgttcgtcc agccctcaac    91560

acctttact ccgtggaagt tatgcctgca ctggtttaca gaacctccct tgacttgggt    91620

tgaggtagag ctgaagggaa cctcagtgtc ccttgcaggt gggatgttca ctacgtagca    91680

agagcacaaa ggtggagtgc gtgggctttg agtttctatt gggtaaatga agctgaaatg    91740

tagggcacat gagcacgtca tcaatgtaca attgatttaa tttttgtatt ttagaaacgg    91800

aggtctcgct atgccgccca gggtagaatg tgctctctcc ctctcctctt cctagtatct    91860

gggactacag gtgaatattt taatctatgc acaggcaaga agagggcaag gagggttctt    91920

ttgttctgtc tttgactttg tgaggcagtg tcactctgtc actcaagctg gagtgcaata    91980

atgtgatctc ggctcactgc aacctctgcc tcctgggttc aagcaatttt tttttttttt    92040

ttttttgag tcagtatctc actctgtccc tcagggtgga gtgcagcggc ccagtctctg    92100

ctcctgcaac ttctgactcc caagtaggta caattgcaga cacgtgtcac cacgcttggc    92160

aaaatttttt ttgtattttt agagctggga ttttaccttg ttggcgaggc tggtctggaa    92220

ctcctgacct caggtgactc gcccaccttg gcctcccaac aagttatgct gatcttggta    92280

ataacttcgc agagcgtgct tccatcagac atggaggatg gtggggtcct gttttgttgt    92340

tgttgttttt ctaagatagg gtctcttgcc caggctggag tgtgttggca cttccaacct    92400

aggtgtcttg ggctcaaatg gtcctctttt ttcggacagt cttgctctgt gacccatgct    92460

ggagtgtagt gacgtgatct cagctcactg caacctccac ctcccagttt taggcagttc    92520

tcctgcctca cattcctgag tagctgggat tataggtgcc tgacaccatg cctggctaat    92580

atttgcatgt tatttattca tgtatttatt tgttttgaga tggagtctca ctgtcactca    92640

ggccagaggg cagtggcagg acctcggctc actcaaacct ttgcctctca ggttcaagca    92700

agtcttctgc ctcaacctcc tgagtagctg gaatcacagg cacccgtcac cacgcccggt    92760

tactttgta tttttttttt caccatgttg gccaggctgg tctgaaaccc ctgacttcat    92820
```

-continued

```
gtgagccgcc cgcctcagcc acccaaagtg gtgggattac aggcataagc cactgcgccc    92880

ggccaacaat gtatattttt caacatggga gattcagttt tgaatgctcc catcgggact    92940

gtgtgtccct gtgctggaac tcaagtgaac gcttggctca aaatccattg ctgttctcta    93000

gaaatccagc ccaattctct tggttaaatg taaggtatgt gtagtaggca atgctttttc    93060

tggagacaga actcaggagg attgtccctc gatgatctag gctaacctgc tgagactttg    93120

aagcaaggaa ctggagatgg tccttttagg gtttatgtt ctggattcca gaaaacatgc     93180

aaacagggcc aataaatgca tcctcatttt tgtgtccatt ttaacctggt gaaggaaaat    93240

tccaacaaaa aacccacagt gctggagcaa gaagagctca ggctgtgacc ctctagaggg    93300

aagcactttc tgttgcttga aagaagagaa agcgcttcct tttagaggat tactctttga    93360

gaaaaacaac attgaagtta atgctgatct tggagatcat gcttataatc agacttggat    93420

gatgttgggg ttttgtgggg ttttttttggt ttttttttcct aagacagggt gtctgttgcc   93480

caggctggag tatggtggcc cctccaacct agatctcttg ggttcaagtg gccctctttt    93540

ttgggacaga gtcttgctct gtgaccctgg ctggagctca gtatcaggaa ctttgctcac    93600

tgcaacctct gcctcccagg ttcaaatgat tctcctgcct cagcctcccg agcagctggg    93660

attacaggca tatgccacca cgcccagcta atttttgtat tattgttatg tatttatttt    93720

ttaacttatt cattttagag acagagtctc actctgtcgc ccaggctgga gtgcagtggt    93780

gcgatctcgg ctcactgcaa cctccaactc ccagctcagc ctcctgaata gctgtctgca    93840

ggcatacacc accacacctg gctaactttt ggttttttttg tacagatgtg gtttccccat    93900

gttgcccagg ttggtctcga actccttagc tcaggtgatc ttccaccttg gcctcctaaa    93960

gtgctaggat tagtggtgtg agctgttgtg ccccacctat actcgtctgt ttctgctcag    94020

attttattga ggagcgttta cagggtagcc tgttgtctac cctgcaggat gtttgtgcct    94080

acaacagtgt atattcttca acatcttaga ttccatttcg gatgccccca tgaggactgt    94140

gcgctcctgt actggaactc aagcgaccac ttggctcaaa atccattgct attctctaga    94200

aatccagccc aattctcttg gttaaagata aggtatgtgt agtaggcatt gccttttctc    94260

tttgggaaca aaactcagga ggattgcccg ttgatgaaca aggctaacct gctgattctt    94320

tgaagcaaag aactgcagat ggtcctttta gggatttatg ctctggattc cagaaaacat    94380

gcaaacaggg caaataaatg catctttatt tttgcgtcca ttttaacctg gtcaaggaag    94440

attcccacaa aaaatccaca gtgccagagc aagaagatct caggctgtcg tcctctagag    94500

ggaagcactt tctgttgtct gaaagaaaag aaagtgcttc cttttagagg gttaccgttt    94560

gagaaaagca acattgaagt tgatgctgat cttggtaata cattttcaga gcatgcttat    94620

catcagagat ggatgatggt gggcttctgt ttttgttttg atttttttctt ttttttttttt   94680

ttgagatgga gtttcgttct tgctgcccaa gcactagtat gtaggaatta ttctttatgt    94740

gagcatatag tacatggaac tttgtttttt tgagacaggg tctccaaaat atatacatgt    94800

tatcatataa tcttctatgt ataattatat tcacacaaaa tagtcttctg cacacagaga    94860

atactcttat atcactttgg ggttgttttt gtttgtgtat tttttttttt tttaattttt    94920

tttgagacac catctggctc tattgcccag gctggagtgc agtgttgtga cctcaactca    94980

ctgcagcctc tacctcccac ctcagcctcc tgaattagtg tctacaggca tgaaccacta    95040

cacctggcta tcttttgtat ttttacagat gaggttttac tatgttgggc aggctagttt    95100
```

-continued

```
tgaactcgag ctcatgtaat tttcccgcct tcgactccta aagtgctggg attagaggtg   95160

taagccactg cactccaccc gtacttctgt acaaatgtta ttgaggagct tttacggcct   95220

aggcagtgct ctatcctgga gaatgtttgt gtgtaagaca atgcatattc ttttttttctt  95280

tcctgtcacc caggctggag tgcattggca cgatctcgtc tcactgcaac ctccgcctcc   95340

cgggttcaag caattctcct gcctcagcct cctgagtagc tgggattaca ggtgggcacc   95400

accacgcctg gcaaatttag attccatttt ggatgctccc atcatgactg tgtgtccctg   95460

tgctggaact caagtgacca tgtgactcaa tccattgctg ttctctagaa atccacctca   95520

attctcttgg ttaaaggtaa ggtatgtgta gtgggcattg ctttttctcc ttggagacaa   95580

aacttaggag gattcccctt gatgaacaag gctaatctgc tgagcctgga gattgtcctt   95640

ttagaggttt atgttctgga ttccagaaaa cggtcaaaca gcgaataaat gcatctttat   95700

atttgtgtcc atcttaacct ggtcaaggaa aatttcaaca aaaatcccag atggctggag   95760

cgagaagatc tcatgctgtg actctctgga gggaagcact ttctgttgtc tgaaagaaaa   95820

caaagcgctt ctctttagag tgttacggtt tgagaaaagc aacgttgaag ttgatgctga   95880

tcttggtaat acattcgcag agcatgctta tcaggcttgg atgacggcag ggttctgttt   95940

tggttttatt tttttccaag accagtctct gttgcccagg ctggagaggg aggggttgca   96000

ctccaaacta gatctcttgg ggtcatgtct tgctctatta ttattattaa ttcttatttt   96060

tgtgtgtgtg tgagacggag tctcgctctg tcaccaggtt ggagtccagt ggcggaatct   96120

cagctcactg caacctccga ctccgtggtt caagcgattc tcctgcctca gcctcctgag   96180

tagctgggat tacaggcacg caccgccatg ccgagctaat ttttgtattt ttagtagaga   96240

ccgggtttca ccacgttggc caggatggtc tcaaactcct gacctcatga tccacccgcc   96300

tcggcctccc aaagtgctgg gattacaggt gtgagcctcc gtgccagcc tgttatttta   96360

ttttgtttta ttttatttat tttattttat tttgagatgg agactggctc tgtcgcccag   96420

gctggaatgc agtggcagga tctccactca ctgtaactcc cacctctgtc gcccaggctg   96480

gagtgcagtg gcaggatctc cactcaccgt ggagttccag tgattctttc accttagcct   96540

cgcaaatagc tggtattaca agcacccacc aacacaccct gccaattttt gtattttttag   96600

acaagaaagg gtttcgccat gttggccagg ctggtctcga ctcctgacct taagtgatcc   96660

acctccctgg cctcccaaag tgctgggatt acaggcgtga gccaccacgt ccagcctcaa   96720

gtggtcttct tgtcagcctc gcaagtagtt gggctcaggt tttaatttt ggtagagatg   96780

gggtctcttt tgcctgggat ggtctcagct gagcttaagt gatcctaaat gtgtgagcca   96840

ccttgtccca tttcaaagat aggtgacacg gccaggcatc ctgggacaca cagggtccca   96900

gttactgcaa aggctagggt gggagggtcc tttgatttta aggctatacc atgcactgat   96960

cacacctttg aatagccact gcactccggc ctgggcacac tagcaagatc ccatctcttt   97020

aaaaacgcag attacatgcc atctggttcc tgaggctcca tttgggttgg tcacttcaaa   97080

tacaggcctt tcatcagttt agtttaatca atccaaacca tgtttccttc attaggagag   97140

taagggccag gtgtgtaatc caagcacttt gggagctgag agcaggcgga tcaggaggtc   97200

aggagttcga gaccagcctg accaatatgg tgaaaccccg tctctactaa aaatacaaag   97260

attaagtggg cgtggtggtg cgtgcttgta atcccagcta ctcaggaggc tgaggcagca   97320

gaatctcttc aacccaggag gcggaggttg cagtgagcca agatcgcgca ggtgcactcc   97380
```

-continued

```
agcctgggcg  acagagcgag  gctccatctc  aaaacaaaac  aaaacaaaaa  atataggcct    97440

ccacatctat  ccagtctatt  ctgtaatccc  aatggatgtc  aatattaata  caatgttctt    97500

attttttcta  tttatttgta  tctttttagt  tgaatctcct  tgtccctgac  actaaatttt    97560

ttttattttt  atttatttat  ttttttttgaa  acagtcttgc  tctgtcgccc  aggctgcagt    97620

acagtggcgc  aatctcggct  tactgtagcc  tctgtctccc  gggttccagt  gattctcctt    97680

ccccaactcc  cgggtaactg  ggattttcag  gcacacacca  ccaccccagc  taattttttt    97740

gtacgtttag  tagagacagg  gtttcaccat  attgggcagg  ctggccttga  actcctgaac    97800

taaggtgatc  cgcccacctc  ggcctcccaa  agtgctggga  ttagggataa  ggctaacctg    97860

cttattcttt  gtagcaagga  actggagatg  gtcattttag  gggtttatgt  tctggattcc    97920

agaaaacatg  caaacagggc  caataaatgc  atcctcattt  ttgtgtccat  tttaacctgg    97980

gcaaggaaaa  ttccaacaaa  aaacccagag  ttctggagca  agaagatctc  atgctgtgac    98040

cctacaaagg  gaagcacttt  ctcttgtcca  aaggaaaaga  aggcgcttcc  ctttggagtg    98100

ttacggtttg  agaaaagcag  cgttgaagtt  gatgcttatc  tcggtaatac  atttgtagag    98160

catgcttatc  atgaggcttg  gacgatggcg  gggttctgtt  ttggttttgc  ttttttattc    98220

taagacagga  tctctgttgc  ccaggctgga  gtgcggtggc  acatccaacc  taggtctttt    98280

ggattcaaat  ggttttttta  gcggacagag  tctctctatc  acccaggctg  aagtgcagtg    98340

gtgtgatctc  ggctcactgc  aacctccacc  tcccaggttc  aagcgagtct  cctgcctcag    98400

cttcccaagt  aggtgagatt  acaggtgccc  atcaccacac  ctggataata  ttttcatttt    98460

ttaaaattca  tttatttatg  ttttttgagat  ggagtctcac  tgttacccag  gctggagggc    98520

cgaggcgtga  tctctgctca  gtgcaacctc  tgcctcccgg  attcaagcaa  ttcttctacc    98580

tcagcctcct  gagtagctag  aattacggga  gcccaccacc  acacctggct  acttttttgtt    98640

ttttgttttt  tgtttttttt  ttagtagaga  tgggatttca  ccatgtttgc  caggctggtc    98700

tcaaacccct  gacctcaagt  tagccaccgg  cctctgcctc  ccaaagtgct  gggattacag    98760

gcatgagcca  ccacgcctgg  cctaatttt  atattttcag  cagaggcggg  gtttcaccat    98820

gttggccagg  ctggttgcga  actcctgacc  tcaggtgatc  tgcccacctc  agcctcccaa    98880

agtgctaaga  ttacaggcgt  gagccaccac  acatggccat  taacacccttt  tagtccatgg    98940

aaattattct  ggcactgatt  tataaagcct  catgtggggt  caggtagagt  caaaggggga    99000

cctcagtgtc  ccttgcagat  gggatgtgct  cagcaagagc  acggaggtgg  agtgcatggg    99060

gtttgagttt  tcactgggga  aatgaaacca  acatcttggg  tgcatgacca  ggtcatatat    99120

gcagtcatat  atgcaatatg  catggtggtg  ggtgcctcta  atcccagcta  ctcaggaggc    99180

tgacgcagaa  gaatcgcttg  aacccaggag  gcagaagttg  ccatgagccg  agatcccacc    99240

accgcatcca  gcctgggcgg  cagagtgaga  ctccgtgtca  aaaaaaagaa  gatctcaggc    99300

agtgaccctc  tagatggaag  cactgtctgt  tgtataaaag  aaaagatcgt  gcatcccttt    99360

agagtgttac  tgtttgagac  aagcaacgtt  gaagatgctg  ctgatcttgg  taatacattt    99420

gcagagcgtg  cttatcatca  gacttgcatg  atgtcggggt  tctgtttgtg  atttgaaatt    99480

tttccaagac  aggctttcta  ttgcccaggc  gtgggtggat  agcaccttcc  accaagattt    99540

cttgggctta  agtggtcctc  ttttttatttt  ttgattttttt  gagacacact  cttgtttcgt    99600

tgggagtgca  gtagcaggat  ctctgctcac  cggaaactcc  acctctcggg  ttccagtgat    99660
```

-continued

```
tctcccacct cagcctgccg aattgttggg aattcaggca tcaggcaccc accatcgtgt   99720

cctgcactct tgctgcccat cctggagagc actggcatga tctaggctca ctgcaacctc   99780

cgcctcctgg gttcgagtga tgcttctgcc tcagcctccc aggtagttgg gattacaggc   99840

acctactgcc ccacccagct aattttttatg tttttagtag agacgggttt caccatgttg   99900

gccaggctag tcttgaactc ccgctttcag gtgatccact agcctgtggt ctatcctgga   99960

ggatgtttgt gtgtgtgaca atgtatattc ttcaacatct tagactccat tttggatgct   100020

cccatcggaa ctatgtatcc ctgtgctgga actcaagtga acactcagct caaagtccat   100080

tgctgttctc tagaaatcca gcccagttct cttggttaaa tataaggtat gtgtagtagg   100140

cattgctttt tctctttaga ggcaaaactc aggaggggttg ccccttgatg aacaaggcta   100200

acctgcagag cctttgaaga aaggaactgg agatggtcct tttaggggtt tatgttctgg   100260

attctagaaa acaggcaaac agggccaata aatgcatctt tattgttgtg gccatttaa    100320

cctggtcaag gaagatttca acaaaaaacc cagagtgctg gagcaagaag atcccatgct   100380

gtgaccctcc aaagggaagc gctttctgtt tgttttctct taaacaaagt gcctcccttt   100440

agagtgttac cgtttgggaa aagccacgtt gaagatgatg ctgatcttgg taatacattt   100500

gcagaccatg cttgtaatca gacttggatg atgttgggag tctgttttttt tgtttgtttg   100560

tttggttggt tttttttgttt gttaggtttt tgttttttgt tttggtgtgt gtgttttgtt   100620

ttgtgttttt tttttttttct aagacaaggt ctctgttgcc caggagagac tagagaagca   100680

ctttttaaga taggcctgtt gggctcagat ggtccttta tgggatacag tcttgctctg    100740

tgacccagac tggagtgcag tggcgcgatc ttggctcaat gcaacctcca cctcccgggt   100800

tcgagtgatt ctcctgcctc agcttcctgg gtagctggga ttacagatgc ctgacatcac   100860

actcggctaa tatttgtatt tttctttttt attcattcat tcattttttga gatggagtgt   100920

tgctgtcacc cagcctggag ggcagtggca tgatcccggc tgactccaac ctctgcctct   100980

caggttcaag ccattctcct gcctcagtct cctgagtagg tggaattaca ggcacccacc   101040

actacaacca gctactttttt gattttgatt ttttttttttt ttttttttttt ttagtaaagg   101100

tggggtttca ccatgttggc caggctagtc tcaaacccct gacctcaagt gagccgctgg    101160

cctcggcctc ccaaagtgct gagaatacag gcgtgagcca ccgggcacag ccatcagcac   101220

cttttacttt atggaaattt ttctggcact ggtatagaac ctcacgtggg gtcaggtgga   101280

gttgagggga cctcagtgtc cctgcagatg ggatgagcaa gagcacggag gtggagtgca   101340

tggggcttca gtgtttattg gggaaatgaa gctgaaatct gggtgcatga ccaggagata   101400

aatgcatgag acggcggtct cactatgctg ccctggctga agtgggctta gatcctcctg   101460

cctctgcccc tccccagtcc ttggtagatg ggaccacatg tgaatattaa cccccccatgc   101520

acagacaaga agaaagtaag gactgttctt tggttcatac ctgaccccag ttaaacttgt   101580

attttagata aacaatgtat ttgagatgta cttgaacaac aaacgatttg ctgttcaggt   101640

gtgggcatct ttgttttgtt ttttttttttc ctaattttaa atatgggact agtgtgcata   101700

tggtggctct tgtctgtaat tcctgcactt tgtgaggctg agacaggagg atcacctgag   101760

atcagttgtt cgagaccagc ctggccaaca tgaagccagg aggctgagct ttcagtgagc   101820

tgaaatcttc tgctgcactc caccctgggc aacagagtga gactcagtct caagaaagta   101880

aaaaataggc cgggcgcggt ggcgcatgcc tgtaatccca gcactttggg aggccgagac   101940
```

-continued

```
gggaggatca cctgaggtca ggagttcaag accaacaggg ccaacatggc aaagcctcgt 102000

ctctactaaa aatacaaaaa ttagctgggt gcaatggtgc acatctgtaa ttccagctac 102060

tccggaggct gaggcaggag aatcccttga acccaggagg aggagatttc agtgagctga 102120

aatcaagcca tggcattcca gcctgggcca gagagcaaca ttccgtctca aaaataaatg 102180

aataaataaa ataaataaaa ataaatagat aaatatggga catcataaat ttgggtgtca 102240

cctttgtgta gcagccagcg taatctctgt cattccaatt ttttttttatg tgaactgcca 102300

aagcaagcac ttgtgtagga attttttcttc ctgtgagcat acaatatatg gaactttctt 102360

tgacacaggg tctcagaaat atatggtata tatttcgtta tatatatact tatatataat 102420

ataatcatat acacacaaaa tactgttcta aatacagaga atactctgat ataaccttgg 102480

gtattttttt ctttctttgt gtgtgtatgt tttttatttg tttggctggt ttttttttgt 102540

ttttgttttt tgtttttttgt ttttttgtttt tgttttttgtt ttgagacaga gtctcactct 102600

gtcgccgagg ctggagtgca gtgacaggat ctcgggtcac tgcaagctcc gcctaccggg 102660

ttcacgccat tctcctgcct cagcctcctg agtagctggg accacaggca cccaccacca 102720

cacctggcta attttttttt gtattttttag tagagacagg gtttcgccat gttagccagg 102780

atgatctcga tctcctgacc tcgtgatcca cccgcctcgg cctcccaaag tgctgggatt 102840

acaggcgtca gccaccgcgc ccggccagtt ggttattttt gagacaaggt ctggctctat 102900

cacccaggct ggagtgtagt ggtgcgatct tggctcactg caacctccac ctcccaccta 102960

aacctgctga attagtgtct acaggcatgc accaccacac ctggctcact tttgtgtttt 103020

tcatacacat gggtttacac catgttgctg gggctggtct caggaactcc tgagctcagg 103080

tgatcctccc gtcttggccc cctaatgtgc taggattaga ggtgtgagcc aacccacccc 103140

acccatactt acgtatttct gttcagattt tattgagttt ttatgaccaa gcctatggtc 103200

tatcctggag aatatttgtg tatgtgacaa tgtatattct tcaacatcgt agactcgatt 103260

ttgggtgctc ccatcgggac tgtgtgtacc tgtcctggaa ctcaagtgca cccttggctc 103320

ataatccatt gctcttctcc agaaatctta ccaattctcc tgcttaaata taagctacgt 103380

gtagtaggca ttgttttttc ttagcagata cgaaactcag gaagattgtc ctatgataaa 103440

caaggctaac ctgctgattg tttgaagcaa ggaactggag atggtccttt taggggttta 103500

tgttttggat tccagaaaac gtgtaaacag ggccaatacg tgcatcttta ttttgtgtcc 103560

agtttagcct ggtcaacaaa aatgtcaaca aaaaacccag agtgctggag taagaaggtc 103620

tcgggctgtg actctccaaa gggaagaatt ttctcttgtc taaaagaaaa gaacgcactt 103680

cccttttagag tgttaccgtg tgagaaaagc aatgctgaag ttgatgctga tcttgcaaat 103740

aactttgcag agcctgctta taatcagact ttgacaatgg tgggcgtctg ttttttttttt 103800

tctaagacag gatctctgtt gcccaggctg gagtatggtg gcacttccaa cctaggtctc 103860

ttgggctcaa atggtcctct tttttgggac agagtcttgc tctgtgaccc aagctagacc 103920

acagtggcac gatcttggct cacggcaatc tctgcctccc agtttcaagt gattcccctg 103980

cctcaacttc ctgagtagct gggattatag gtgtctgaca ccatgactgg ctataatttt 104040

cattttctt atttattttat ttttgagtct cgctgtctct caggctggag tgcagtggca 104100

gcctttgcct cttgggttca agcaattttc ctgcctcagc ctcccaagta gttggaatta 104160

tatgtgtcac catcatgccc tttttgtttt tttttagtag aaaatgggtt tcaccacgtt 104220
```

-continued

```
ggccaggcta gtctcaagcc cctgacctca agtgatcctc ccgcctcaga ctcccaaagt 104280

gctgaaaatg caggcgtgag ccactgcacc gagccatcaa caccttctac tccatggaaa 104340

tgatactggc gctggtttat agaacctcac ttggggtcgg gcagatttaa aagggacctc 104400

aggctgggtg tggtggctga cgcctgtaat cccagcactt tgggaggccg aggcgggtgg 104460

atcacgaggt caggagatcg agaccatcct ggctaacatg gtgaaaccct gtctctacta 104520

aaaatacaaa aaattagcca ggcgtggtgg cgggtgcctg tagtcccagc tactcgggag 104580

gctgaggcag gagaatggtg tgaacccggg aggcggagct tgcagtgagc cgagatggca 104640

ccactgcact ccagcctggg cgacagagca agactctgtc tcaaaaaaat aaataaataa 104700

ataagggggt gggggacctc attgtccctt gcagatggga tgtgccctgc ttagcaagag 104760

cacggaggtg gagtgcatgg ctttgagttt tcactggggc acggaggtgg agtgcatggc 104820

tttgagtttt cactgggtaa atgcagctga actcttggct gcacgaccag gtcatatgtg 104880

caacgagaca ggggtctcac tatgctgccc aggctaaaat gggcttaggt ccttttgcct 104940

ccacctctcc ccagtcctta gtagctggga ctacatgtga atattaacca tgcacaggca 105000

agaggaaaga aaggaccgtt ctttggttca cacctagccg ccagtcaaat tagtatttta 105060

gatgaagact gcatttgaga catacttgaa caacaaatga tttgctgttt aggtgtgggc 105120

atctttcttt tttcctagtt ttaataatgg caccaggcag agtacagtgg cccacgcctg 105180

taattccagc actttgggag gctgagacag gaggatcacc tgaggtcggg aatttgattc 105240

cagcctggcc aacatggtgc agccccatct ctactaaaaa tacaaaatta gcccagcatg 105300

gtggtggtat atgcttgtaa tcccagctac tctggaggct gaggcaggag agtcgcttga 105360

agctggaagg ctgatctttc aatgagctga gatcacgcca ctgcactcaa gcctcggcaa 105420

aaagagtgag actccatctc aaaaacataa aaaataggcc agacacggtg gtccactcct 105480

gtaatcccag cactttgaga ggccaggaca ggcggatctc ctcaggtcag gagtccaaga 105540

ctagctgggc aaacaaggca aaacctcgtc tatactaaaa ttaggaaaaa tggctgggaa 105600

cagtggtgga cacctgtaat ctcagctact tgggaggcca cggcaagaga atctcttgaa 105660

cctgggaaaa ggagattgca gtgagacgaa atcacaccat tgtactccat cctgggtgac 105720

agagtgagat tctgtttcaa aaattaaata aataggccga gcacagtgac tcatgcctgt 105780

aatcccagaa ctttgggagg ccgaggtggc ggatcacctg aggtcgggag ttcaagacca 105840

gcctaaccaa cacgtagaaa ccccatctct actaaaaata caaaattagc cgggcatggt 105900

ggcgcatgcc tgtaatccca gctgctcggg aggttgaggc aagagaatca cttgaacccc 105960

aggggcggga ggttgtggtg agccgagatt gtgccattgt attccagcct gggcaacgag 106020

tgaaactctg tctctaaata aataaataaa actattaaat aaacattaaa cgttaaaaaa 106080

taaaaataga taaatatgag atcatcatga atttgagtgt cacctttgcg cagggccat 106140

ggtaatcttt gtcattccaa ttttttcatg cgtgctgcca aagctagcac ttgtgtgtag 106200

gaagtattct tcctgtgagc atacaatata tggaagtttc ttttattatt attatttttt 106260

atgtttttgc gactgagttt tgctcttgtc gcataggctg aagtgcaatg gtgtgatctg 106320

ggctccctgc gatgtccacc tcttgggtta aagcgactct cctacctcag cctcctgagt 106380

agctgggatt acaggcatac acttccaggg ctagctaatt tgttgtattt tagtagacgg 106440

gatttctcca tgttggtcag ctggtctca aactcccgac ttcaggtgat ctgcccacct 106500
```

-continued

```
tggctttcca aagtactggg attgcagaca gccaccgcgg ctggccttca tatattctta 106560

tatatataat atcatgtaca cacaaaagac tcttttacac cctgagaata ctcttatatc 106620

actttgggca ttttttttgtt ggtgtgtgca tttttttgttt gttcgttcgt ttgttttttga 106680

gacaagatct ggccctgtca cctatgctgg agtgcagtgg tgtgatctcg gctcccggca 106740

acctcaacct cccacctcag cctcctgaat tagtgtctac aggcatgcac ctctatacct 106800

ggctaacttt tgtattttta cagatgaggt tttaccatgt ttcccaggct ggtgtctaac 106860

tcctgagaat ataaggtata tgtagtaggc gttgctttt ctctttgaag acaaaaccca 106920

ggacagttgt ccctcgatga acaaggctaa cctgctgaac gtttgaagca aggaactgga 106980

gatggtcttt gtatcggttt atgttctaga ttccagaaaa tatgcaaaca ggaccaataa 107040

atgcatcttt attttttgtgt ccattttgac caggtcaagg aaaatttcaa caagaaaccc 107100

agagtgccgg agcaagaaga tctcaagctg tgagtctaca aagggaagcc ctttctgttg 107160

tctaaaagaa aagaaagtgc ttctctttgg tgggttacgg tttgagaaaa gcaacgttga 107220

agttgatgct gatttcggta atacatttgc agagcatgct tatcacactt ggacgatggt 107280

ggggttctgt tttggttttg ctttttttatt ctaaggctct gtgttgctca tgctggagtg 107340

cagtgacatg tccaatatat ctcttggctt caaatggtca gcctgggcaa cacagggaaa 107400

ttctgtctca aaaataaac aaatgaataa aaatacaaaa taaagccggg catggtggct 107460

catgcctgta atcccagcac tttgggaggc cgatgcaggt agatcatctc aggtcaggag 107520

tttgagacca gtctgaccaa cgtggtgaaa atccgtctct actaaaaata caataacaac 107580

aaaaattagc ccagtgtggt ggtgggcacc tgtaatccca gctacttagg aggctgaggc 107640

aggagaattg cttgaacccg ggaggcagag gctgcagtga gccgagattg tgccacagca 107700

tccagccagg atgacagagt gagattccgt ctgaaaaaa aaaaaaaaa aaaaagctgg 107760

gcgctgtggc tcacgcctgt aatcccacca cttttgaaagg ccgaggcggg tggatcacga 107820

ggtcaggaga tcgagaccat cctggctaac acggtgaaac cccatctcta tttaaaaata 107880

caaaaaatta gcgaggcgtg gtggtgggtg cctgtagtcc cagctacccg ggaggctaag 107940

gcttgagaat ggcttgaacc caggaggcgg agcttgcagt gagccgagat cgtgccattg 108000

cactctagcc tcggcaacag agcaagactc cgtcaaaaag aaacaaaaac aaaaacaaaa 108060

aaaagaaccc tacagtactg gagcaagaag acctcatgct gtgaccctct agatggaagc 108120

actgtctgtt gtctaagaaa agatcgtgca tccctttaga gtgttactgt ttgagaaaag 108180

caacgttgaa gatgctgctg atcttggtaa tacatttgca gagcgtgctt atcatcagac 108240

ttgcatgatg ttggggttct ctttggtttg tttttttcca agacaggttc cctgttgccc 108300

aggcgggagt gggtggcacc tccaaccgag atctcttggg ctcaagtggt gatctttta 108360

tttttgattt tttgagatgc gctctcattc cgtttcccag gctggagtgc agcggcagga 108420

tccctgttga ccggaaactc cgcctcccag cttccggcga ttctcccacc tcagcctgcc 108480

gaatagttgg gaatagagat gcccgccatc gtgtcctgct agttattatt tttattgttg 108540

ttgttgttgt tgagatggag tttcactctt gatgtccagg ctggagtgca gtgttgcaat 108600

ttaggctcac tgcaacctcc acctcctggg ttcaagcgat tctcctgccg cagcctcctg 108660

ggtagctggg attacaggtg cctactgccc cacccagcta attttttgtgt tttgaataga 108720

gactgggttt caccatgttg ggcaggctgg tctcaaactc ccgacctcag gtgatccacc 108780
```

-continued

```
agccttggcc tcctaaagtg ctgggattac aggcgtgagc caccgcccct aatctcacgt 108840

ggtcctctag agtcagccta gactctggtc tatcctggag gatgtttgtg tgtgagacaa 108900

tgtatattct tcaacatcag cccaattctc ttagctaaat gtaaggtatg agtagtaggt 108960

attccttttt ctctttgggg acaaaactca ggacgatcgc cccttgatga acaaggctaa 109020

cctgctgagc ctttgaagca aggaattgga gatggtcctt tcaggggttt atgttctgga 109080

ttccataaaa catgtaaaca gggccaataa atgcattttt attttttgtat ccgttttaac 109140

ctggtcaagg aaaattccaa caagaaaccc agagtgctgg agcaagaaga tcccatgctg 109200

tgaccctcta gaggaagcac tttctgtttg ttgtctgaga aaaaacaaag tgcttccctt 109260

tagagtgtta ccgtttggga aaagcagtgt tgaagttgat gctgatgttg gtaatatatt 109320

tgcatgctta ttatcagact tggatgatgt tggggttctg ttttgttttt gttttctaag 109380

acagggtctc tgtggcccag gctggagtac agaggcactt ccaacctagg tctcttgggc 109440

tcatatggtc ctttttggga cagtcttcct ctgtgaccca ggctggagtg cagtggcacg 109500

atcttggctc actgcaatct ccacctcgcg ggttcaagct attctcctgc ctcagcttcc 109560

tgaatagctg ggattgcagg ggcccgacat cacacttggc taatatttgt attttttcttt 109620

tttattcatt tatttatttt tgagatggag tctcgtttcc ccagctggag agcggtggca 109680

tgatcccgac tgactccaac ctctgcctct caggttcaag caattctcct gcctcagcct 109740

ctgaagtagc tgaaactaca ggtggccgcc accacgcctg gctacgtttt gaattttttt 109800

tttttttttt ttcagtagag atggggctta ccatgttggc caggctggtc tcaaacccct 109860

gacctcaagt gagccactca ccttggcctc cgaaaatgct gagaatacag gcatgagcca 109920

ccaccgcgcg cctcccaaag gcgtgagcca tggtgcgtgg ccatcaacac ctcttacttt 109980

atggaaattt ttctggcact ggtatagaac ctcacatggg gtcaggtgga gttgagggga 110040

cctcagtgtc cctgcagatg ggatgagcaa gagcacggag gtggagtgca tggggcttca 110100

gtgtgtattg gggaaatgaa gctgaaatct tgggtgcatg accaggagat aaatgcatga 110160

gacgggggtc tcactatgct gccctggcta aagtggtctt agatcctcct gcctctgccc 110220

ctcccaggcc ttgttagatg ggactacatg taaatattaa cccatgcaca ggcaggaaga 110280

aagtaaggac cattttttgg ttcgtcccgg ccctcagtta aacttgtgtt ttagataaac 110340

aatgtatttg agatgtgctt aaacaataaa tgatacgcta tttaggtgtg ggcatctttg 110400

tttcccccta attttaatga tgggactagt ccaggtatgg tggctcctgc ctataattcc 110460

agcactttgg gaggccgaga caggaggatc acctgaggtc agttgttcga gaccggcctg 110520

gccaacatgg tgaaaccccg tccatactaa aaatacaaaa atcagccagg cctggttgca 110580

cacacctgta atcccagcta ctcgggaggc tgaggcagga gactcgcttg aagccaggag 110640

gctgagcttt cagtgagctg agattgcgcc actgcattcc agcctgggca actgagtgag 110700

tctcagtgtc aacaaagtaa ataatagtct aggcacagcg gcacacgcct gtaatcccag 110760

cactttagga ggctaagacg ggaggatcac ctgaggtcag gagttcaaga ccaacggggc 110820

caacgtggca aagccttgtc tctactaaaa ctacaaaaat tagctgggtg cggtggtgca 110880

catctgtgat ccagctact cgggaggcca agacaggaga accacttgaa cccaggagga 110940

ggcgatttca gtgagctgta atgaagccat ggcattccag cctgggccac agagcaagat 111000

tccgtctcaa aaataaataa aacaaataaa aatacgtaga taaatacggg accgtcgtga 111060
```

-continued

```
atttgagtgt caccttttgtg gagcagccac ggtaatctct gtcattccaa tttttttttat 111120

gtgcactacc aaagcaagaa cttgtgtagg aattattctt cctgtgagta tgcgatgtat 111180

ggaactttcc ttgagacagg gtctcaaaaa tatatcatgt atattttata tattcttatc 111240

atatataata taatcatgta cacacaaaat actcttctaa atacagagaa tactctgata 111300

tcaccttgcg tattttttgt ttgcatgtgt ctgtgtttgg ttgttttttt tttgtcatat 111360

ttttgtatcc ctacttatat atttattttt aattttatta ttatacttta agttctaggg 111420

tacatgtgca caacgtgcag gttagttaca tatgtataca tgtgccatgc tggtgtgctg 111480

cacccattaa ctcatcattt agcattaggt atatctccta atgctatccc tccccgctac 111540

ccccacccaa caacagtccc cggtgtgtga tgttcccctt cctgtgtcca tgtgttctca 111600

ttgttcagtt cccacctatg agtgagaaca tgcggtgttt ggttttttgt ccttgcgata 111660

gtttgctgag aatgatggtt tccagtttca tccatgtccc tacaaagggg ttggttattt 111720

ttgagacaag gtctgactct atcgcccagg ctggagtgta gtggtgccat ctcggctcac 111780

tgcaacctcc acctcccacc taatcctgct gaattagtgt ctgcaggcat gcacaaccac 111840

atctggctca cttttgtatt ttttatacac atgggtttac accatgttgc aggcgctggt 111900

ctcaaactcc ctcccaagct caggtgatcc tctgtctcag cctcctaaag tgctgggatt 111960

agaggtgtga gccaccacac cccactggta tttgtgtgtt cctgttcaaa ttttattgag 112020

gagttttttat aaccaagcct gtggtccatc ctggaggatg tttgtgtgca tgacaatgta 112080

tattcttcaa catcgtagac tcgatgttgg atgctcccat cgggactgtg tgtccctgta 112140

ctggaactcg agtgaacact tggctctaag ttcattgctg tttctagaa atccagccca 112200

attctcttgg ttaaatataa ggtgcacgta gtaggcattg ctttttcttt ctggagacaa 112260

aactcaggag gattgcccct tgatgaacaa agctaacctg ctgagacttt gaagcaagga 112320

actggagatg gtccttttaa gggtttatat tctggattcc agaaaatgtg caaacagggc 112380

caataaatgc atctttattt ttgtgtccat tttaacctag tcaaagaaaa ttacaacaaa 112440

aaatccacag tgctggagca agaagatctc atgatgtgac catctggagg taagaagcac 112500

tttgtgtttt gtgaaagaaa gtgcttcctt tcagagggtt actctttgag aaaagcagca 112560

ttgaagttga tgctgatctt ggtaatacat ttgaagagca tgcttatcat cagacttgga 112620

tgatcttggg gttttgtttt tttctaagac agggtgtctg tagcccaggc tcgagtgcgg 112680

tggcacttcc aacctagatc tcttgggctc aacaagtagc cctcttttc ggacagagtc 112740

tcgcgctgtg accctagctg gagtgcagtg gcaggaactt ggctcactgc cacctctgcc 112800

tcctgggttc aagcaattct cctgcctcag cctcccgagc agggttatag gcatgtgcca 112860

ccacacctgg ctaattttttg catttttatta tcgattgatt gattgattgt tgagacagag 112920

tctcactctg ttgcccaggc tgtagtgcag tggtgtgatc tcggctcact gcaacctcca 112980

cctcccacct cagccttctg aatacctgtc tacaggcatg caccaccaca cctcgccaac 113040

ttttgtgttt tttgtacaga tgaggtttca ccatgttgcc caggctggtc ttgaacccct 113100

gagctcaagt gatcctccca cctcggcctc ctaaagtgtg agtcactatg tcccgcccta 113160

cttgtgtgtt tctgcttaca ttttattgag gcgatttttt tttttttttt gagacggagt 113220

cttggtctgt tacctaggct ggagcgcagt ggcgcgatct ggctcactg caagctccgc 113280

ctcccaggtt catgccattc tcctgcctca gcctcctgag tagctgggac tacaggcgcc 113340
```

-continued

```
caccaccacg cccggctaat ttttttgtat ttttagtaga gatggagttt caccttgtta 113400

gccaggatgg tctagatctc ctgaccttgt gatcctcccg cctcggcctc ccaaagtgct 113460

gggattacag gcatgagcga ccgtattgag gcgcttttac aacatagcct gtggtctatc 113520

ctggggaatg tttgtgtgtg tgacaatgta tattcttaga catcttagat tccattttgg 113580

atgctcccat cggtactatg tgttcctata taggaactca agtgaacact ggcttaaaa 113640

tccattgctc ttgtctagaa atttagccca gttatcttgg ttaaagataa ggtgtgtctg 113700

gtaggcattg attttttcttt ccggagaaaa aacttaggag gatttcctct tgatgaacaa 113760

ggctagcctg ctgagccttt gaggcatggg acctggagat gatcctgtga ggggtttatg 113820

tttttggatt caggaaacac accagcagga caaataattg catctttatt tttgtgtcta 113880

tttttcaccag gctaaggaag attccaacaa catatccatg gtgctgaagt aagaagatct 113940

cgtgctgtga ccctctagag ggaagcactt tctgttgaaa gaaaagaaca tgcatccttt 114000

cagagggtta ctctttgaga agagcaacgt ttagtttgat gttgatcttg gtagtacatt 114060

tgcagagcat gctttttatca tcagacttgg ctgatggtgg tgttctgttt tttgttgttg 114120

ttttctacaa caggatgtct gttgcccagg ctagggtgtg gtggcactta caacctagat 114180

ctctagggct caaatggtcc tcttatttgg ggcagagtct tgctctgtga tccaggctgg 114240

agtgcagtgg caggaactct gctcactgca acctccgcct cccgggttca agtgattttc 114300

ctgccttggt tttctgagta ggtgggatta caggcgcaca ccaccacacc cagctagtat 114360

ttgtagtttt ctttattatt cttttttttta ttttaatttt tgagacgaag tctcgctgtt 114420

gcctacggtg gagtgcagtg gcgtgatctc ggctctctac aacgtctgcc tcccaggttc 114480

aagcaattct gctgcctcag cctcccgagt agctggaatc aacaggaaca caccaccatg 114540

cctggctact ttttggattt ttttttttagta gagacggagt ttcaccatgt tggccaggct 114600

ggtctcaaac tcctgacctc atgtgagcca cccacctcgg ccttccaaag tgctggaatt 114660

acagggcatga accacgacgt ctggcctaat ttttgtattt ttagaagaga cagggtttca 114720

ccatgttggc caggctggtc tcagctcctg acctcaagtg atcctccccc tcggcctccc 114780

aaagtgctgg gattacaggc gtgagccacc tcgcccagcc tcaagtggtc ctcttgactc 114840

agcctcccat gtagttggga ctacatgggg cgtgccacca cacttggcta agtttttaat 114900

ttttcataca gatatgatct ctgttgctca ggaaggtctc aacacctgag ctcaaggatt 114960

ccacaggcgt gagccacatt ctcctgctga cccttttcaa agatagttga catggccagg 115020

catcatgggg cacacagtcc cagccaccgc agatcccggg gtgggagggt cctttgattt 115080

ccagactatt ccatgcactg atcacacctt gtttttttgt ttgtttgttt gtttgtttgt 115140

ttgtttgaca gagtctcagt ttgttgcctg gcgggagtgc aatgatgtga tctcgggtga 115200

ctgcaacctc tgcctccaag gttcaagtga ttctcctgcc tcaccctcca aagtagctgc 115260

ggttacaggc atgcaccacc acacccagct cagttttttgc atttggtaga gacaggtttt 115320

caccatgttg gtcaggctgg tctcgaactc ctgatttcag gtgatccacc tgcctcagcc 115380

tcccaaagag ctgggattat aggcgttagc ctatcgcccc ggtctgtatt tcctaatttt 115440

aaatatggga cccatggtga atttgggtgt cactgtgtac aggggacatg ggaatctctg 115500

tcattccaat ttttttaatg catgctgttc tgtgtaggaa ttattcttcc tgtgagcaaa 115560

caacatagag agctttcttt ttttgacacc gggtctcaaa aatatatcat atacattta 115620
```

-continued

```
ttataatgtc tgatattgat aatataatca tacacacaca aaatactctt ctgtacacag 115680

agaatactga tatcactttg gggttttttt gtttgcgtgc gtttttttggg attttggggt 115740

gttttttttt tttttttttga gacaacatct ggctctgttg cccatgctgg agtgcagtgg 115800

tgcaattggc tccctgcaac ctccacctcc cacctcccac ttcagcctcc taaagagctg 115860

aatacaggca tgcaccacca cacctgacta actttttgtat tttttgtaca cacagggttt 115920

accatgtttc ccaggctgga ctggaactcc agagctcaag tgatcctccc gacttggcct 115980

ccttaagtac tgcagttaga ggtatgagcc gccgagaccc accgtacttg tgttttttcta 116040

ttcaaatatt attgaggagc ttttatggcc taacctgtgg tctatcctgg aggttgtttg 116100

tgcgtacaat acatagtctt caatatcttt tttttttttt tcattttttg agagggagtt 116160

tcgctcctgt cacctaggct ggagtgcaat gacatgatct cagttcactg caacctccgc 116220

ctcctgggtt caagtgattc tcctgcctca gcctcctgag tagctgggat tacaggcacc 116280

cgccaccatg cctagctaag tttgtatttt cagtagagac gggcttctcc atgttggtca 116340

ggctgggctc agactcctga cctcaggtga tccgcccgcc tcggcctccc aaagtgccgg 116400

gattacaggc gtgagccacc gcgcccagtc atcatatatt cttatcatat atatagtagg 116460

atgtttgtgt ataaacaat gtacatttttc aacattgtag attccatttt ggatgctccc 116520

attgggactg tgtgtccctg tgctggaact caagtgaaca cttggctcaa aatccattgc 116580

tgttctctag aaatccagcc caattctctt ggttaaatat aaggtatgtg tagtaggcat 116640

tgctctttct ctttagagac aaagctcagg attgcccctt gatgaacaag gctaacctgc 116700

tgattctttg aagcaaggaa ctggagatgg tccttttagt ggtttatgtt ctggattcca 116760

gaaaacatgc aaacagggcc aatacatgca tctttacttt tgtgtccatt ttaacccggt 116820

gaaggaaaat tccaacaaaa aacccacaat gctggagcaa gatctcaggc tgtgaccctc 116880

tagagggaag cgctttctgt tggctaaaag aaaagaaagc gcttcccttc agagtgttaa 116940

cgctttgaga aaagcaacgt tgatcttggt aatacacttg cagagaatgc ttataatcaa 117000

ccatggaagg tggtgggggtt ttgtgtttgt ttgttttgtt ttgttttcta agacagggtg 117060

tctgttgccc aggctggagt gtggcggccc ctccaaccta gatctcttgg gttcaagtgg 117120

ccctcttttt tgggacagag tcttgctctg tgaccctgcc ctggctggag tgtcctgtca 117180

ggatctccac tcactgcaac ctctgcctcc tggggtcaag ggattctcct gcctcagcct 117240

cccgagcagc tggattaca ggtatgtgcc accacctg gcttatttat ttatttattt 117300

atgagacaga gtcttgctgt gtcatccatg ctggagagca gtggtgcaat ctcggctctc 117360

tgcaacctcc acctcccacc tcagtctcct gaattagtat ctacaggcat gtaccaccat 117420

acctggctaa cttttgtatt tttacagatg aggtttacc atgtttcccg ggctggtgtc 117480

taactcctga gctcaagtga tcctcctgcc ttggcctacg taagtgctgc ggttagaggt 117540

gtgagccacc gcgcccacc tgcccttgtg tatctctgtt caaatgttac tgagaagcat 117600

ttacgggata atgcccggag gatgtttgtg tgtgtgacag tgtacattct tcaacatctt 117660

agattccatt ttggatgctc ccctcgggac tgtgtgtctc tgtcctggaa ttcaagtgaa 117720

cacctggctc tccatccatt gctgttctct agaaatccag cccaattctc ttggttaaat 117780

ataaggtagg tgtagtaggc attgcttttt ctctttgggg acaaaactca ggaggattgc 117840

cccttgatga acaaggctaa cctgctgatt ctttgaagca aagaactgga gatggtcctt 117900
```

-continued

```
ttaggggttt ttattcagga ttccagaaaa catgcaaaca gggccaaaaa ttgcatcttt 117960

atttttgtgt ccattttgac ctggtcaagg aaaatttcaa caagaaaccc agagtgccgg 118020

agcaagaaga tctcaagctg tgactgcaaa gggaagccct ttctgttgtc tgaaagaaga 118080

gaaagcgctt ccctttgctg gattacggtt tgagaaaaac aacactgaag ctgatgccga 118140

tcgtggtaat acatttgcag agcatgctta tcatcaggct tggacaatgc cggggttctg 118200

ttttcggttt tgctttttta ttctaagaca ggatctctgt tgcccaggct ggagtgcagt 118260

gacatgtcca acccaggtct cttgaattca aatggtcctt tttaggggc agagtctttc 118320

tctgtcaccc aggctgatat gcagtgaggc gatctcggct cactgcaacc tctgcctccc 118380

aggttcaagc aattcctg cctcggcttc ccaagcagct gagattacag gcgttcatca 118440

ccatacctgg atgatatttg tattttttaa aatttattta tttatttatt tttgagacgg 118500

agtctcgctg tcacccagtc tggagggcag tggcacaatc tcggctcact gcaacctctg 118560

cctccccggt tcaagcaatt cttctgcctc agcctcctga gtagctggaa ttacagaagc 118620

acaccaccgc acctagttac ttttttgtata ttttttttaa gtagagactg gatttcaccg 118680

tgttggctag gctggtctca aattcctgac ctcaagtgat ccacccacct ctgactccca 118740

aatttctggg atcacaggta tgcgccccca tgcctggcct aattttttgta tttttagcag 118800

agacgtggtt tcaccatgtt ggccaggctg aactcagctc ctgaccttag gtgatctgcc 118860

cgcctgggcc tccaaagtg ctgagaatac aggcgtgagc caccgtgcct ggccattaac 118920

accttttggt ccacggaaat tattctggca ctggtttata gaacctcgct tggggtcagg 118980

tagagttgaa ggggaccca atgtccttgc aggtgggatg tgcactgctt agcaagaaca 119040

cggaggtgga atgcatgggg tttgagtttt tattggagaa ataaagccaa aatcttgggt 119100

gcatgaccag gtcgtatatg caacaatacg ggcgtctcac tatgccgccc aggctaatgt 119160

gggcttagat cctcctgcct ctgcccctcc ccagtcctta gtagctggga ctacatgtga 119220

atattaactc acgtacagga agaggaaagt aaggactgtt ctttgattca cgtcccaccc 119280

ccagttaaat ttgtattta gataaacaat gtatttgaga tgtacttgaa caacaaatga 119340

tttgctgttt agatgtgagc atctttttttt gctcctgatt ttaaacatag gacaaggtca 119400

ggtatggtgg ctcacgcctg taattccatc attttggtag gcagagacag gaggatcacc 119460

tgaggtcagc tgcttgagac cagcctggcc aacatggtga aacccatct gtactaaaaa 119520

tacaaaaatt agccatgcgt ggttgtgctg cacgcctgta atcccagcta ctcaggagga 119580

tgaggcagga gaatcgcttg aagccgggag gcagaggttg cagtgagctg agatcgcgcc 119640

agtgaactac agcctgggca aaagaataag attcaatctc aaaaaaataa aaaataggcc 119700

aggcacggtg gcacacacct gtaatgctag cacttttgga ggtcgagacg ggggcatcac 119760

ctcaggtcag gagttgaaga ccagctgcgg catcacggca aagcctcatc tctacgaaaa 119820

atacaaaaat tagccaggtg cagtggcagg tgcctgtaat accagctact cgggagacca 119880

aggcaggaga atcgttccaa ctgggcggca gaggttgcag tgagccaaga tcgtgccact 119940

gcactgcagc ctgtcgacag agtaagactt ggtctaaaaa aaaaaaataa ataaataaat 120000

aaaagataaa tatggaacca tcatgaattt gggtgtcacc tctgtgtggg ggccagggta 120060

atctctgtca atccaattttt ttttttatgtg caccagcaaa gcaagcactt atgtttaggt 120120

attattcttc ctgtgagcat acaatatgta gatctttatt ttctttgaga catggtctca 120180
```

-continued

```
aaaatgtatg atgtggctgg gcacagtggc tcaagcctgt aatcccagca ctttgggagg 120240

ctgaggcgtg tggatcaccc gaggtcagga gttcaagacc agcctggcca acatggtgaa 120300

aatccgtctc tacgataaat acatatatat atatatgtat atatgccggg catggtggca 120360

ggtacgggta atcccagcta cttgggagcc tgaggcagga gaatcgcttg aacctgggag 120420

gtagaggtta ctcatatcac tatgagattg tttttttgttc ttgtgtgtgt ggttttttgtt 120480

tgttttttgag acaaggtctg gctctgtcac ccaggcaaaa gtgtagtagt gcgatctcgg 120540

cttactgtaa cctccatctc ccacctatgc gtcctgaatt agtgtgtcta caggcatgca 120600

ccaccacagt gggctacctt ttttttttga gagggaattt tgctcttgtt gcacaggctg 120660

gagtacaatg gcaagatttc agatcactgc aacctccgcc ttccgggttc atgtgattct 120720

cctgcctcag cctcccaagt agctgcgatt acaggcatgc accatcacac ttggctaatt 120780

ttgtattttg agtagataca ggtttcccca tgcttgtcag gctggtctcc aactcctgac 120840

ctctagtgat ccacctgcct cggactccca aattgctggg attacaggca tgagctacca 120900

cacccagcca cctggctaac ttttgtagtt tttctacaga ctacaaaatg gtttcaccat 120960

tttacctgag actacaaaat ggtttcacca ttttacctga gactacaaaa tggtttcacc 121020

attttacctg agctggtctc caacacctga gctaaagtga tcctcctgcc tcggcctcat 121080

aaaatgttgg gattagaggt gtgagccacc gtgcctcacc cgtacttgtg tatttctttta 121140

tttttattga tttatttatt ttgagacaga gtttcactct tgttgcccaa gctggagtgc 121200

aatggcacaa tctcggctca atgcaacctc cttctcttag gttcaagcga ttctcctgcc 121260

tcagcttccc gggtagctgg gattaaaggc gtccaccacc acaccagct aatttttgtg 121320

ttttttagtag agacagggtt tcagcatgtt ggccagactg gtctcaaact cctaacctca 121380

ggtaatccac ctgcctcagc cttccaaact gctgggatta caggcatgag ccactgcgcc 121440

tagcctcaag tggtcctctt aagtcagcct aaactgtggt ctatcctgga ggatgcttgt 121500

gtgtgtgaca atttatattc ttcaacgtct tagattctat tttggaggct cccaagggga 121560

ttgtgtgtcc ctgtgctgga actcaagtga acacttggct gtacatccat tgctgttctc 121620

tagaaattca gcccaattct cttggttaaa gataaggtat gtgtagtagg cattgctttt 121680

tctttccaga gacaaaactc aggaggattg ccccttgatg agcaaggcta acctgctgat 121740

tctttgaagc aaagaaccag agatggtcct tttaggggtt tatgttctgg attccagaaa 121800

acaggcaaac aggaccaata aatatatttt tattttctta tccactttaa cctggtcaag 121860

gaaaattcca acaagaaacc cagagtgctg gagtgagaag atcccatgct gtgaccctct 121920

agagggaagc actttctgtt gtctgaaaga aaccaaagcg cttcctttg gagcgttacg 121980

gtttgagaaa ctcaatgttg aagttgatgc tgacttcagt aatacatttg tagaggatgc 122040

ttatcatcag acttggatga tatcggggtt ctgtgctttt tttttttttt ttctcctaag 122100

acaaaatctg tattttccag gctggagtcc ataagcactt ccaacctagg tctcttgcgc 122160

tcagatagtc ctctttttttg ggacagagtc ttgctctgtg acccaggctg gagtgcagtg 122220

gcgtgatctc ggctcactgc aacctctgtc tcctgggctc aagcaattct ccttcctgag 122280

cttcctgagg agctgggatt acaggcgcct gacatcatcc ttggctaaca tttgtatttt 122340

tcttttttat tcatgtattt attttacttt cagatggagt ctcgctgtcg accaggctag 122400

agggcagtgg cacgatcccg gctgactaca acctgtacct ctcaggttca agcaattctc 122460
```

-continued

```
ctgcctcagc ctctggagta gctggaatta caggaacaca ccaccaggcc cggctacttt 122520

ttgtattatt attattatta ttattttttt tttttttcac taaagagggg gtttcaccat 122580

gttgtccaga gaatacaagc atgagccact gcgcagccat caacaccttt tactgcatgt 122640

aaattattct ggcactggta tagaacctca catggggtca ggtggagttg aggggacctc 122700

agtgtccctg cagatgggat gagcaagagc acggaggtgg agtgcatggg gcttcagtgt 122760

ttattgggga aatgaagctg aaatcttggg tgcatgacca ggaaataaat gcatgagaca 122820

ggggtctcac tgtgccgccc tggctaaagt ggtcttagat cctcctgcct ctgcccctcc 122880

ccagtcctag gtagatggga ctacatgtga atattaaccc atgcacagac aagaagaaag 122940

taaggactgt tattttgttc gtacccagcc cccagttaaa tttatcatat atataatata 123000

tcatatatat aacataatca tatacacaca aaatgctgat ttgaatacag agaatactct 123060

gatatcactt tgggtatttt ttggtttgtt tctgtgtgtg tgtgttttat ttgtttggtt 123120

ggttattttt gagacaaggt ctggctctat cacccaggct ggagtgtagt ggtgcgttct 123180

cagctcactg caacctccgc cttccaccta agcctgctgc attagtgtct acaggcatgc 123240

accaccacac ccggctcact tttgtatttt ttgtacacat ggggttacac catgttgccg 123300

gggctggtct cgaactcctg acctcaggtg attctcccgt cttggcctcc taaagtgcta 123360

gaattagagg tgtgagccac cgtgccccac ctgtacttgt gtatttatgt taaaattgtg 123420

ttaaggagtt tttatgacca agcctgtgat ctattctgga gaatatttgt gcgtatgaca 123480

atgtatattc ttcaacatcg tagattccat tttggatgct cccactggga ctgtgtgcct 123540

atactggaac tcaagtgaac acttggctca aaatccattg ctgttctcta gaaatccagc 123600

ccaattctct tggttaaata taaggtatgt gtagtaggca ttgctttttc tttctagaga 123660

caaaactcag gaggattgcc ccttgatgaa caaggtaacc tgctgattct ttgaaacaag 123720

aaactggaga tggttccttt aggggtttat gttctggatt ccaggaaaca tgcaaacagg 123780

gcccacaaat gcatctttat gtttgtgtcc attttaacct ggtcgaagaa cattccaaca 123840

aaaaatccac catgcaccga gcaagaatat ctcaggctgt gaccatctgg aggtaagaag 123900

cactttctgt tttgtgaaag aaaagaaagt gcttcctttc agagggttac tctttgagaa 123960

aagcaacgtt gaagttgatg ctgatcttgg taatacattt ggagagcatg cttatcatca 124020

gacgtggatg acggttgggt tttgtttttg ttttattttt tatcttaggc agggtctctg 124080

ttgcccaggc tggagtgtgt tggcacttcc aacctagatc tcttggtctt aaatggtcct 124140

cttttttgggg ggcggagtct cactctgacc caggctggag tgcaatggca ggaactcccc 124200

tcactgcaac ctccacctcc cgggttcaag cgattctcct gcctcagttt ccgagtcgc 124260

taggattaca ggctcactcc tccacacctg gctaatattt gtagttttct ttattattca 124320

tttatttatg tgtttttgag aaggagtctc gctgtcgccc aggctggagt gcagctgcac 124380

aatctcagct cactgcaact tctgccactg gagtaactgg gatttcaggt gcgtgccacc 124440

acacttggcc aatttttat gtgtgtattt ttagacccgg ggttttccca tgttggccag 124500

gctggtctgg aactcctgac ctcaggtgac ccatgcacct cggcctccca gagtgctggg 124560

attacaggca tcagccaccg caccggccc tgtctctgac ttttgcgaac tgaggaagta 124620

acctttgaa atttactctg aagtgtgaat gattttagca tattttcaac caccaacatt 124680

ctagttcagg agattttcat caccccaaag aggcttattc ccatttgcag tcagttccca 124740
```

-continued

```
cccactcctt ccacccagac cgtgacaaac actttgcatc tctctagctc tggatctgcc 124800

tcttgtgggc atgtcacata gatcagtttt gaataggtgg cctgttgtga ccactgtaat 124860

tgaggataat gggttggtcc tggttgtctg cagtgtgaat cttaccactg aagggtggtc 124920

cctggatgga agcaggaggc tgggagaact gggcggaaca tcctttggga atggagtcgg 124980

gcgggcagac cctgatgcct gggaagctca caagggtgga agaccacatc ttcctccctg 125040

agaactgcaa ggtgaccctc ctggggtact ggaaggagtg aaggcctctg gactgggaac 125100

accagggcat tgcaccggtg caggcaggat gagccaaggg gaacggagag ccaggcatcg 125160

ctaactggcg acaatttggg tttgatctgg acggagtctg tgtcttctgg tagagagaac 125220

ccctgggatt ttcgctctgc tcctggctgt ctttcagtca tggaatctga tgacaaagac 125280

tcccgcccag agccaagaca tttggtttct ggaccccagt ggtcctttct gcctggactt 125340

gggatctttt ggggaagttt gggatctggc agggcatctg cataatccat agaaatccct 125400

gagagtccct tccctttgct gacatctcca tgttcctacc tattagcttc caaaggagac 125460

tcctatctga attgccgaag gcagcttccc aggccaggga tacccagtta aatttgtatt 125520

tcagatcaat agtatatttc agatgtactt gaacaagaaa tgatttgctg tttaggtgtg 125580

ggcatttgta tttccccctt tttttttttt tttttttttt tttgacagag ttttgctctt 125640

cttacccagg ctggaatgca atggcacaat cttgactcac tgcaacctcc acctcccagg 125700

ttcaagcgat tctcctgcct cagcagcccg agtagctggg attacaggca tgcgccacca 125760

cacccggctc agttttttgca tttagtggag atggggttc accatgttag ccaggctggt 125820

ctcaaactcc tgacctcaag tgatttccct gcatcggcct cccaaagtgc tgggattata 125880

ggcatgagcc tccacgccta gcctcaagtg gtcctcttga gtcaacctag actacagtct 125940

atgctagaga atgtttgtgt gtgtgacaat gtatgttctt gaacatcata gattccactt 126000

tggatgctcc tgtcgggact gtgtgtccct gtgctggaac tcaagtgaga gttggctgaa 126060

aatccattgc tgttctctag aaatccagcc caagtctctt ggttagagat aaggtatgtc 126120

tagtgggcat tgctttttct ttttggggac aaaactcaga aggattgccc cttgatgaac 126180

aaggctaacc tgctgattct ttgaaggaag gaactggaga tggtcttttta ggggtttata 126240

ttctggattc cagaaaactt gcaaacaggg ccaatacatg catctttata tttgtgtccg 126300

ttttgaactg gttaaggaaa atttcaacaa gaaacccaga gtgccggagc aagaagatct 126360

caagctgtgg gtctgcaaag ggaagccctt tctgttgtct aaaagaagag aaagcgcttc 126420

cctttgctgg attacggttt gagaaagcga cgttgaagtt gatgcatttg cagagcatgc 126480

ttatcatcag gcttggacaa tggcggggtt ctgtttggt tttgcttttt cattctaaga 126540

caggatctct gttgcccagg ctggagtgcg gtggcagtgg catgtccaac ctagccctct 126600

tggattcaaa tggtcctttt ttgcaagcaa agtctctctc tctcacccag ctggagtgc 126660

agtgatgtga tctcggctcg ccgcaacccc cgcctcctgg gttcaagcga ttctcctgct 126720

tcagcttccc aagtagctga gattacaggc acccatcacc acacctggat aatatttgta 126780

ttttaaaaa ttcattttatt tatttatgag acggagtctc gctgtcaccc atgctggagg 126840

gcagtgacac gatctcggct cactgcaatc tctgcctcct gggttcaagc aattcttcct 126900

cagcctcctg actagctgga attacaggag cacaccaccg cacctggcta cttttttgtat 126960

ttttttttta gtagaaatgg gatttcacca tgttggttag actggtctca aactcctgac 127020
```

-continued

```
ctcaagtcat ccgcccacct ctgactcttt ctgggattgc aggtatgcgc ccccacgcct 127080

ggcctaattt ttgaatgttt agcagagatg gggtttcacc atgttggcca ggctgaactc 127140

agctcctgac cttaggtgat ctgcctgcct cggcctccca aagtgctgag aatacaggcg 127200

tgagccaccg cgcctggcca tcaacacctt ttaccccaca gaaattattc tggcactggt 127260

ttatggaact tcacttgggg tcaggtagag gtgaagggga ccccaatgtc ccttgcagat 127320

gggatgtgta ctgctcagca agagcatgga ggtggagtgc atggggtttg agttttcatt 127380

ggggaaatga agctgaaatc ttgggtgcat gaccaggtcg tatatgcaac gagacgggcg 127440

tctcactatg ccgcccaagc taaagtgggc ttagatcctc ctgcctctgg ccctccccag 127500

tccttagtag ctgggactac atgtgaatat taactcatgt acaggaagag gaaagtaagg 127560

actgttcttt gattcatgcc ccacccccac ttaaatttct atttcagata aacaatgtat 127620

ttgagatgta cttgaacaac aaatgatttg ctgtttaggt gtgggcatct ttttttgttc 127680

ctaattttaa gtataggaca aggctgggta ccacggctca cacctgtgat tccatcattt 127740

tgggaggcca agacaggagg atcacctgag gtcagttgtt tgagaccagc ctggccaaca 127800

tggtgaatcc ccatctctac taaaaataca aaacttagcc cagtgtggtg gtggtacacg 127860

cctgtaatcc cagctactca ggaggctgag gcaggagaat cacaggaagc cgggaagctg 127920

agctctcagt gagctgagat cgcaccactg aactccagcc taggcaacag tgagactcaa 127980

tctcaaaaaa ataaaaaata ggccgggtgc ggtggcacac gcttgtaatc ccagcacttt 128040

gggaggtcga cgggtggga tcacctcagg tcagagttca agagcagccc cgccatcaag 128100

acaaaacctc ctctctacta aaaatgcaaa atatagctag gcgtggtggt acacacctgt 128160

agtctcagct acgtgggagg cggcagcagg agaatctctt gaacccgtga gaaggagatt 128220

gcagtgagct aaaatcacac cattgcactg cagcctgggc gactccatct caaaaaataa 128280

atacataaat aaataaatac ataaatacat aaaaaataac ccagagtact ggagcaagaa 128340

gatctcaggc agtgaccctc tagatggaag cactgtctgt tgtctaagaa aagatcgtgc 128400

atccttttag agtgttactg tttgagaaaa tcaacgttga agatgctgct gatcttggta 128460

acacatttgc agagcgtgct tatcatcaga cgtgcatgat gttggggttc tgtttgtttt 128520

gtttttttt tccaagacag tgtctctgtt gcccagacta gagtgggtgg cacctccaac 128580

cgagatctct tgggctcaag tggtcctctt tttattttt gatttttga gacccactct 128640

ggtttcactg ggagtgcagt agcagaatct ctgttgaccg gaaactccac ctctcaggtt 128700

ccagtgtttc taccacctca gcctgccgaa tcattgggaa ttcagttgcc tgccatcagg 128760

tcttgctaat tattattgtt tttttgtttt tttttttga ggcggagttt cgctcttgtt 128820

gcccaggctg gagggcaata gcgcgatctc ggctcaccgc aacctcggcc tcccgggttc 128880

aagtgattct cctgcctcag cctcccagat agctggaatt acaggtgcct accaccccac 128940

ccagctaatt tttgtgtttt cagtagagat ggggtttcac catgttgggc aggctggtct 129000

caaactcctg acctcaggtg atccaccagc cttggcctcc caaagtactg ggattacagc 129060

tgtgagccat cacccctaat ctcaaatggt cctgtagagt cagcctagac tgtggtctat 129120

cttggaggat gtttgtgtgt gagacaatgt atattcttca acattgtaga ttccattttg 129180

gatgcttcca tcgggactgt gtgcccctgt cctggaactc agctgaacac ttggctcaaa 129240

atccattgct gttctctgga aattctgccc taatctcttg gttaaatata aggtatgtgt 129300
```

-continued

```
agtaggcttt gctttttctc tttgggaca aaaactcagga gggttgcccc ttggtgaaca 129360

aggctaacct gctgagcctt tgaagcaagg aactggagat ggtccttta ggggtttatg 129420

ttctggattc cagaaaatat gcaaacaggg ccaataaatg catctttatt ttgtgtgtat 129480

tttaacctgg tcaaggaaaa ttccaacaag aaacccagag tgctggagca agaagatccc 129540

atgctgtgac cctctagagg aagcactttc tgtttgttgt ctgagaaaaa acaaagtgct 129600

tccctttaga gttactgttt gggaaaagca gtgttgaagt tgatgctgat gttggtaata 129660

tatttgcatg cttatcatca gacttggatg atgttggggg tctgggtttt ttttgttttc 129720

taagacaggg tctctgtggc ccaggctgga gtacagaggc acttccaacc taggtctctt 129780

gggctcaaat ggtcctttt gggacagagt cttgctctgt gactcaggct ggagtgcagt 129840

ggtgcaatct cagctcactg caccctccac ctcctgggtt caagtgattc tcctgcctca 129900

gcttcctggg attacaggca cctgacatca tgcccagcta atatttgtat ttttctttt 129960

tattcattca tttatttatt ttttaggtgg agtcttgctg ttgccaagtc tggagggcca 130020

tggcacgatc ccggctgact ccaacctctg tctctcaggt tcaagcaatt ctcctgcctc 130080

agcctcctga gtagctggaa ttacaggcgc ttaccaccac gcctgactgc ttttcgaatg 130140

tgtgcgtatg tgtgtgtatg tgtgttagag agaaagagag agagagat ggagtttcac 130200

tcttgttgcc caggctggag ggcaatgaca tgatctcggc ccatacaacc tcagcctcct 130260

gggttcaagt gattctcctg cctcagcctc ctgagtagct aggattacag gcatgtgcca 130320

ccacacctgg ctaattttgt atttttagta gatatgggggc ttccccatgt tggtcaggct 130380

ggtctcgaac tcctgacctc aaatgattca cctgcctcag tctcccaaag tgctgggatt 130440

acaggtgtga gccaacatgc ccggcctgaa ttttttttt tttttttttt ttttcaagta 130500

aagacggggt ttcaccatgt tgaccaggct ggtctcaaac ctctgaactc acgtgagctg 130560

ctcgcctcgg cctcccaaag gcatgagcca tggtgcgtgg ccatcaacac ctcttacttt 130620

atcgaaattt ttctggcact ggtatagaac ctcacgtggg gtcaggtgga gttgaaggga 130680

cctcagtgtc cctgcagatg ggatgagcaa gagcacggag gtggagtgca tggggcttca 130740

gtgtttattg gggaaatgaa gctgaaatct tgggtgcgtg accaggaaat aaatgcatga 130800

gacgggggtc tcactatgcc accctggcta aagtgggctt agatcctcct gcctctgccc 130860

cccgcagtcc ttgctagatg ggactacatg tgaatattaa cccatgcaca gacaagaaga 130920

atgtaagaac cattatttgg ttcacaccgg gccctcagtt aaacttgtat tttagacaaa 130980

caatgtatct gagatgtcct tgaacaacaa atgatttgct gttcaggtgt gggcatcttt 131040

gttttttccc taattttaat gatgggacta gtctgggtac ggtggctccc gcctgtaatt 131100

ccagcacttt gggaggctga gataggagga tcacctgagg tcagttgttt gagaccagcc 131160

tcgccaacat gatgaaacct cgtctgaact aaaaatatag atattagcca gacgggggtgg 131220

tggtgcaccc ctgcaatccc agctactcag gaggctgagg caggagaatc acttgaagcc 131280

aggaggctga gctttcagtg agctgagatt gagccactgc actccagcct gggcaacaga 131340

gtgagactca gtctcaaaaa agtaaaaaat aggctgggtg tgggccgggc gcggtggctc 131400

acgcctgtaa tcccagcact ttgggaggcc gaggtgggtg gatcacaagg tcaggagact 131460

gagaccatcc tggctaacac ggtgaaaccc tgtctctagt aaaaatacaa aaaaaaaaa 131520

aaaattagcc agacgtgatg gtgtgcgcct gtactcctag ctactcagaa ggctgaggca 131580
```

-continued

```
ggagaatggc ctgagcccgg gaggcggagc ttgcagttag ctgagatcgc accactgcac 131640

tccagcctgg gtgacagagc aagactccgt ctcaaaaaaa aaaaaaaaaa aaaaaaggcg 131700

gggtgtggta gtgcacatct gtaatcccag catttcggga ggccaagaca ggaattacct 131760

gaggtcagga gttcaagacc aacagggcca acatggcaaa acctcgtctc tactaaaaat 131820

acaaaaatta tctgggtgca gtggtacaca tctgtaattc cggctaccca gaggctgagg 131880

caggagaata gcttgaaccc aggaggagga gatttcagtg agctgaaatc acaccattgc 131940

acttcagcct gggccacaga gcaagattgt gtctcaaaaa taaataaata ataaaaatga 132000

cataaaatca ataaataaaa ataaatacat aaatacagga acatcattaa tttggatgtc 132060

acctttgtgc aggggccagg gtaatctctg tcattccaat tttttttatg tgcactgcca 132120

aagcaagcac tcatgtagga attatccttc ctgtgagcat ataatatatg gaacattctt 132180

tgagacaggg tctcaaaaat atgatgtgta tttcatcata tatataatat aatcgtatac 132240

acacaaaata ctgtttaaat acagagaata ccctgatatc accttgggta tttttctttg 132300

tttctgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtttgtt tggttatttc 132360

tgagacaagg tctggctcta tcgcccaggc tggagtgtag tggtgtgatc tcaactcact 132420

gcaacctccg ccccccacct aaacctgctg aattagtgtc tacaggcatg caccagcaca 132480

cctggctaac ttttgtattt tttgtacata tggggttaca ccatgttgcc ggggctggcc 132540

tctaactcct gagctcaggt gatcctcccg cctcagcccc taaagtgctg ggattagagg 132600

tgtgagccac cgcaccccag ccatacttgt gtatttctat tcaaatttta ttgaggagtt 132660

tttaccgccc agcctgtggt ctatcctgga gaatgtttgt gtgtgcgaca atgtatattc 132720

ttcaccatcg tagattccgt tttggatgct cccatcggga ctgtgtgtcc ctgtgctgga 132780

actcgagtga acacttggct caaaatccac tgctgttctc tagagatctg tagggtccag 132840

ccctactggg cctgtgggtt tttctcttcg tgagcagata ggagagattg tagaaataaa 132900

gacacaagac aaagagagag aagaaaaggc agctgggcct gggggaccac taccaccaag 132960

acgtggagac cggtagtggc cccgaatgcg tggccgcgcc gttatttatt gtatacgagg 133020

caaaagggca gggtaagaag tgtgagtctt ctctaatgat aggtaagatg acgcgagtca 133080

cgtgtccacc ggacaggggg cccttccct atttggtagc ttaggcggag agagattggg 133140

gacagcttac gtcattattt cttctatgta tttctcggag agatcaaaga ctttaatact 133200

ttcacttatt ctgctaccgt tatctagaag gcggagccag gtgtgcagag cggaacgtga 133260

aagtggacca ggagcgtgac cgctgaagca cagcatcaca gggagacgtt taggccacca 133320

gacggctgcg ggcgggcttg actgatgtca ggctttccac aagaggtggt ggagcagagt 133380

cttctctaac tcccctggag aaagggagac tccctctccg ggtttgggaa ggtaaggggg 133440

tccttcccag gcactggcgc taccgctgtg ctaagtgacg ggtgccttcc ccctggtgtt 133500

accgctggac cagggagccc tctagtggcc gtgtccgggc atgacagagg gctcacgctc 133560

ttgtcttctg gtcgcttctc accgtgtccc ttcagctcct atctctgtat ggcctggttt 133620

tccctaggtt atgattgtag aacaaagatt attataatat tggaataaag agtaatgcta 133680

caaactaatg attaataata ttcatatata atcatatcta taatctattt ctagtataac 133740

tagtcttatt ctatatattt tctttgttat actggaacgg cttgtggtga gtttctttat 133800

tataccggaa cagcttgtgc cttcggtctc ttgcctcggc acctgggtgg cttgccaccc 133860
```

-continued

```
acagaaatcc tgcccgtttc tcttggttaa atataatgta tttctagtag gcattgcttc 133920

ttctttccag agacaaaact caggaggatt gtgctatgat aaacaaggct aacctgctga 133980

ttctctgaag caaggaactg gagatggtcc ttctaagggt ttatattctg gattccagga 134040

aacatgcaaa caggacccat aaatgcatct ttattttggt gcccattttg acctggtcag 134100

gagaattcca acaaaaaatc cacggtgttg gagcaagatc tcaggctctc aggctgtggc 134160

catctagagg taagaagcac tttctgttgt cttaaagaaa agaaagtcct ttttttttt 134220

tttttttttt tttgagacaa tgtctcgctc tgtcgcccag gctggaatgc agtggcgtga 134280

tcttggctca ctgcaagctc cgcctcccgg gttcatgcca ttctcctgcc tcagcctcct 134340

gtgtagctgg gactacaggc gcccgccacc aagcccggct aatttttttgt attttttagta 134400

gagacggggt ttcatcttgt taggcaggat ggtctcgatc tcctgacctc atgatccacc 134460

cgcctcggcc tcccaaagtg ctgggattac aggcgtgagc caccacgccc gcccagaaag 134520

tgctttcttt cagagggtta cggtttgaga aaagcagcat tgaagttgac gctgatcttg 134580

gtaatacatt tgcagagcat gcttatggtc agacgtggat gatggtgggg ttttgttttt 134640

gttttgtttt ttatctgaga cagggtgtct ctgttgccca ggctggagtg cagtggcaca 134700

tccaacctag atctcttggg ctcaagtggt cctcttTtTg aaacagagtc tcactctgtt 134760

accctggctg gagttcagtg gcaggaactt ggctcactgc aatctctgtc tcctgggttc 134820

aagcaattct ctggcctcag cctcccgagc agggttacag gcatgtgcca ccacgcccgg 134880

ctaattttTg cattttttta attgatttat ttgtttgttg ttgagacagt ctcactctgt 134940

tgcccaggct gtagtgcagt ggtgtgatct cagctcaccg caacctccac ctcccatgtc 135000

agcctcctga atacctgtct ccaggcatgc accccacac ctggctaact tttgcatttt 135060

ttgtacagat gaggtttcac catgttgccc aggctggtct tgaacccctg agctcaagtg 135120

gtcctcccac ctcggcctcc taaactgctg tgattaatgg tgtgagccac cgtgccacac 135180

ccgtacttgt ttgtttctgc tcaaattgta ttgaggagct tttacatcct agtctgtggt 135240

ctatcctgga ggatgtttgt gtatataaca atgtacattt tcaacatttt agattccatt 135300

ttggatgctc ccatcgggac tgtgtgtccc tgtgctggaa ctcgagtgaa cacttggctc 135360

aaaatccatt gctgttctct agaaatcctg ccctattctc ttggtgaaat ataaggtatg 135420

tctagtcggc attgattttt ctttctggag acaaaactca ggagggttgc ccctgcatga 135480

acaaggctaa cctgctgagc ctttgaagca aggaactgga gatggttttt ttaggggttt 135540

atattctgga ttccagaaaa catgcaaaca gggacaatga atgcatcttt atttttctgt 135600

ccattttaac ctggtaaacg aaaatttcac caaaaaaccc agagtcctgg agcaagaaga 135660

tctcaggctg tgaccctcca aagggaagaa ctttctgttg tctaaaagaa aagaacgcac 135720

ttcccttttag agtgttaccg tgtgagaaaa gcaacgttga agctgatgct gatcttggta 135780

ataagtttgc agagcctgct tatcatcaga cttggacgac ggtgtagttc tgttttggtt 135840

ttgagttttt tgtttgtttg ttttgttttg cttttgagat ggaggcttgc tctgtcgccc 135900

aggctggagt gcagtggcgt gttctcagct cactgcaacc tccgcctccc aggttcacgc 135960

cattcttctg cctcttgagt agctgggact acaggcgccc gccaccacgc ctggctaatt 136020

ttttgtatTt ttagtagaca cagagtttca ctgtgttagc caggatggtc ttgatctcct 136080

gaccttgtga tccacccgcc ttggcctcca aaagtgctgg gattacaggc gtgaaccact 136140
```

89

-continued

```
gcgcccggcc ttaattttttg tattttttagt agagacagga ggctgagctt tcagtgagct 136200

gagttcgttc cactgcactc cagcctgggc aacagagtga gactccatct caaaaaaata 136260

aaaaataggc cgagcgtggt ggcacatgcc tgtaatccca gccctttggg aggccgagac 136320

aggtggatca cctgaggtca ggagttaaag gctggctggg ccaacaaggc aaaacctcga 136380

ctctactaaa aatacaaaat tacacctgta atcttagctg cttggggggc tgtggcagaa 136440

gaacctcttg aacccaggaa gaggagattg cagtgagacg aaatcatacc attgcactct 136500

agcctgggcg acagagcgag attctgtctc aaaaaataaa taagtagggc agacagggtg 136560

gctcacgtct gtaatcccag cactttggga ggcaaggcgg gtaaatcaca aggtcaggag 136620

ttcgagacca gcctggccaa catggcgaaa ccccatctct actaaaaata caaaaaagta 136680

gctgggcatg gtggctggca cctgtagtcc cagctacttg ggaggctgag gcaggagaat 136740

cgtgtgaacc caggaagcgg aggttgcagt gagccgagat cgggccattg cactccagcc 136800

tgggcgacag tgcgagactc tgtatcaaaa ataagtaaat aaataaacaa aataaaagta 136860

aaaagaatta aatagataaa tatggtacca ttatgaattt gagtgtcacc tttgtgcagg 136920

ggtcatggta atctttgtta tttcaatttt tttatgcgta ttgccaaagc aagcacatat 136980

gcgtaggaat tatacttcct gtgagaatac aatatatgga gctttctttt ttgtttttttc 137040

tgtttgtttg ttttttgaga cacagtttca ctcttgttgc ccaggctgga gtgcaatgtc 137100

acgatctcag ctcacggcaa cctctgcctc ctgggttcaa gcgattctcc tgcctcagcc 137160

tcccaagtag ctgggattgc ttgcatgtgc caccaagcct agctaatttt ttgtatttag 137220

agtagagatg gggtttctcc atgttggtca ggctggtctc gaactcctga cctcagatga 137280

tccatccacc tcagcctccc aaagtgctgg gattacagat gtgagccacc atgcccggcc 137340

atgatatatt tttatatatg taatatcaca tacacacaaa atactcttct atgcacagag 137400

aatagtctta tatcactttg ggtatttgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg 137460

tgtgtgtgtg tgtttgtttt ggttggttat ttttgagaca aggtctggct ctgtcatcca 137520

ggctggagtg tagtggtgtg atctcagctc actgcaacct ccaccccga cctaagccta 137580

ctgaattagt gtctacaggc acgcactacc acacctggct cacttttgta ttttttgtac 137640

acatgggggtt tcacaatgtt gccggggctg gtctcaaact cctgtgctca ggtgatcctc 137700

ccatcacggc ctcctaaagt gctggaatta gaggtgtgag ccgccacgcc ccacctgtac 137760

ttgtgtatct ctgttcaaat gttactgagg agctttttaca gcgtaacctg tggtctatcc 137820

tggaaaatgt ttgtgtgtga dacaatgtac attcttcaac atcttagatt gcagtttgga 137880

tgctcccgtc aggactgtgt gtccctgtgc tgggactcaa gtgaacactg ggctctccat 137940

ccattgctgt tgtctagaaa tccagcccaa ttctcttggg taaatatgag gtatgtgtag 138000

taggcattgc tttttctttc tggagacaaa gctcaggagg attgcccctt gataaacaaa 138060

gctaacctgc tgattctttg aagcaaggaa ctggagatgg tccttttagg ggtttatatt 138120

ctggattcca gaaaacatgc aaacaggacc aataaatgcg tgcttatttt tgtgtctgtt 138180

ttaacctggt caaggaaaat tccaacaaaa aatccacgat gctggagcaa gaagatctca 138240

ggctgtgtcc ctctagaggg aagcgctttc tgttgtctga aagaaaagaa aatggttccc 138300

tttagagtgt tacgctttga gaaaagcatc gctgatcttg gtaacacatt tgcagagaat 138360

gcttataatc agacgtggat gatgttgaag ttttgcgttt gttttgtttt gttttttttttc 138420
```

-continued

```
ctagacaggg tgtctgctgc ccaaactgga gtgcggtggc acttccaacc tagacctctt 138480

gggtttaagt ggccctctat tttgggatag agtcttgctc tgtggccctg gctggagtgc 138540

agtgtcagga actctgctca ctgcgacctc tgcctcctag gttcaagcga ttctcttgcc 138600

tcagcctcct gagcagctgg gattacgggc atgtgccacc atgcctggct aattttttgta 138660

tttttttatta tttatttatt tatttatttt tgagacagag tctcgctctg tcacccaggc 138720

tgaagtgcag tggtgcgatc ttggctcacc gcaacctcta cctcccacct cagcctcctg 138780

aacagctgtc tccaggcgtg caccaccaca cctggctaac ttctgtattt gttttacagt 138840

catggtttca ccatgttgcc cgggctcatc ttgaactcct gagctcaagt gatcctcccg 138900

cctcagcctc ctaaagtgct gtgagccacc gtgtcccaac agtacttgtg tgtttccgtt 138960

caaattgtat tgaggagctt ttacagcata gcctgtggtc tctccgggag aatgttttttg 139020

tttacgacaa tgtatattct tcaacatcgt agattccatt tttggatgccc tcattgggac 139080

tgtgtgtccc tgtactggaa ctcaagtgaa cacttggctc aaaatccatt gctgttctct 139140

agaaatccag cctaattctc ttggttaaag gtaaggtatg agtagtaagc attgcttttt 139200

ctctttggga acaaaactca ggaggattgc cccttgatga acaaagctaa cctgttgatt 139260

ctttgaggga aggaactgga gatggtcctt ttagggggttt atgttctgga ttctagaaaa 139320

cacacaaacc ggacaaataa atgcatcttt attttttgtgt ctattttaac ctcgtcaagg 139380

aagattccaa caaaaaatcc acagtgccgg agcaagaaga cctcaggctg tgacactcta 139440

gagggaagcg ctttctgttg tctgaaagaa aggaaagtgc atcctttttag agtgttactg 139500

tttgagaaaa gcaacattga agctgatgct gatcttggta ataaatttgc agcgaatgct 139560

tataatcaga cttggatgat gttgggcttc tgagttttttt tttgtttttgt tttgtttagt 139620

tttggggttt ttctgttttt tgttttttttgt tttttttttt tttgaggccg agtcttgctc 139680

tttcgcccag gctggagtgc agtggcgcta tctcggctca ctgcaagttc tgcctcccgg 139740

gttcacgcca ttctcctgcc tcagcctcct gtgtagctgg gactacaggc gcccgccagc 139800

acacccggct aattctttgt attttttagta gagacggggt ttcaccgtgt tagccaggat 139860

ggtctcgatc tcctgacctc gtgatccacc cgcctcagcc tcccaaagtg ctgggattac 139920

aggcgtgagc caccgcgtcc agccttgtta ttgttttttga gactgagtct tgctctgtgg 139980

cccaggctgg agcgcagtgg cgtgatctcg gctcactgca acctccatct cccaggctca 140040

agcaattctc ctgcctcagc ctcctgagta gctgggatta caggcctgtg ccaccatgcc 140100

cggctaatta tttgtatttt tagtagagac agggtttgca ccatgttggc caggctggtc 140160

tcgaactcct gacctcaggt aatccaccca cgtcgatctc ccaaagtgct gggattacaa 140220

ctgtgagcca ctgcgcccgg cctgtttttc tctaccacag ggtgtctgtt gcccaggctg 140280

gagtgcggtg gcattttttaa catagatctc ttgggtcga gtggtccttt tttttggttc 140340

agtcttgctt tgtgacccag gctggagggc agtggcagaa actctcctca ctgcaacctc 140400

cgcctcctag gttcaagcca ttctcctgac tcagcctcct gagcagctgg gattaccggt 140460

gtgagccacc acacccagct aattttttgta ttttttattta tttgtttatt tatttattta 140520

ttgttgagac ggagtcttgc tgtgtctccc aggctggagt gcagtggcgc gatcgtggct 140580

tactgcaacc tcctcctcct tggttcaacc aattctcctg cctcagcctc ctgagaagct 140640

aggattacag gcatgcacca ccatgcctgg ctaatttaga ttccatttttg gatgctccca 140700
```

-continued

```
tcaggactgt gtccctgtac tggaactcag gtgaacactt ggttcaaaat ccgtcgcttt 140760

tctctagaca tccagctcag ttctcggtaa agataaggta tgtgtagtag gcattgcttt 140820

ttcccttttag agacaaaact caggaggatt gccccttggt gaacaaggct aacttgcaga 140880

ttctttgaag caaggaactg gagatggtcc ttttaggggt ttatgttctg gattccagaa 140940

aacatgcaaa cagggccaat acatgcatct ttattttttgt gtccgttttg acctggtcaa 141000

ggaaaatttc aacaagaaac ccagagtgcc ggagcaagaa gatctcaagc tgtgactgca 141060

aagggaagcc ctttctgttg tctaaaagaa aagaaagtgc ttcccttggg tgaattacgg 141120

tttgagaaaa gcaacgttga agttgatgct gatctcggta atacatttgc agagcatgct 141180

tatcacactt ggacggtggt ggggttctgt tttggttttg cttttttatt ctaagacagg 141240

gtctgtgttg cccatgctgg agtgcggtgg cacatcccac ctaggtctct tggattcaaa 141300

tggtcctttt tggggggcaga gtctctctat caccgaggct ggagtgcagt gatcccatct 141360

tggctcacta caacctccgc ctcccaggtt caagcaattc tcctgcttcg gcctcccaag 141420

tagctgagat ttacaggtgc ccatccccac acctggataa tatttggttt tattcatgta 141480

tttatttatt tttaagatgg agtctcactg tcacccagac tggagggcag tggcacgatc 141540

tcggctcgct gccacctgcg cttccctggt tcaagtaatg cttctgcctt agcctcctga 141600

gtagctggaa ttacagaagt acaccaccac acctggctac ttttttatatt tcatttttaa 141660

tacagactgg atttcaccat gttggctagt atgatatata ttttgtcata tattcttata 141720

tatataatca tatacacaca aaatactctt ctgcacacga agagtattct tatatcgctt 141780

tgggtttttt tgtttgtgtg tttgttttgt gtttgtttct ttgttttttga gacaacgtct 141840

ggctctgttg ctcaggctaa agtgtagtat tgcaagctca gctcactgca acctccacct 141900

cccacctaaa gtccctgaa ttagtgtcta caggcatgca ccaccacacc tggctcactt 141960

ttttttctga gaaggaattt tgcttttgtc gctcaggctg gagtgcaatg gggtgatttc 142020

agctcactgc aacctctgac tcccggcttc aagcaattct cctgcctcag cctcccaagt 142080

agctgggatt acaggcatgc accaccacac ctggctaatt ttgtattttt agtagagatg 142140

ggtttcacct tctttctcag gctggtcttg aactcctgac ctcaagtgat ccacctgcct 142200

cgacctccca aagtgctagg attacaggt agagacattg cacctggcca cctaacttttt 142260

gtagtttttt tacagacagg gcttcaccat attgcccaag ctggtctcca gctactgagc 142320

tcaagtgatg ctcctgtctc ggccactgtc cctcacccaa acttgtgtat ttcttttctt 142380

ttctttttttt tttttttttt ttgagatgga gtctggctct gtcacccagg ctggagtgca 142440

gtggcacgat cttggctcac tgcaagctcc gcctccccag ttcatgatat ttttctgcct 142500

cagcctccca agtagctggc actacaggca cccgccacca cgcctggcta atttttttgta 142560

tttttagtga agacggggtt tcactggatt agccaggatg gtcttgatct cctgagctcg 142620

tgatctgcct gccttggcct cccaaagtgc tgggattaca ggcttgagcc accgcaccca 142680

gctttttttgt tttttttgttt tgttttttttg agatggggtc tcgctctgtc acccagcctg 142740

gagtgcaatg gcacgatctc ggttcactgc atcctacccc tcccgggttc aagcgattct 142800

cctgcctcat cctcccaagt aactgggatt acaggtgccc accaccgcgc tggctaatt 142860

ttttgtattt ttagtagaga cggggtttca ccgtattagc caggatggtc ttgatctcct 142920

gacctcgtga tctccctgcc tcagcctccc aaagtgctgg gattacaggt gtgagccact 142980
```

-continued

```
gcacccggcc tttttttttt tttttttttt tttgagatgg gatctcgctc tgtcacccag 143040

gctggagtgc aacggcatga tctcagctca cggcaacctc cccctcccgg gttcaggtga 143100

ttctactgcc tcagcctccc aagtagctgg gattacaggt gcccacgacc acgcctggct 143160

aatttttttgt attttttagta gagatggggt ttcatcaagg tggccaggct ggtctcaaac 143220

tcctgacctc atgatctact ggcctcggcc taccgaagtg ctgggattac aggcatgagc 143280

caccgcgccc agcttctgta tttcttttca aattttattg aggattttttt atgtcctagc 143340

ctgtggtcta tcctggagga tgtttgtgtg tgagacaatg tatattcatc aacatcttag 143400

attccatttt gattgcttcc gtagaaactg tgtgtccttg tgctggaact ccggtgaaca 143460

cctggctcaa tatccattgc tcttctctag aaatccagcc cagttctctt ggttaaatat 143520

aagatatgtg tagcaggcat tgctttttct ttccagagac aaaactcagg aggattgccc 143580

cttgatgaac aaagctaacc tgctgattct ttgaagcaag taactggaga tcctcctttt 143640

aggggtttat attctggatt ccagaaaaca tgcaaacagg gccaataaat gcatctttat 143700

gtttctgtcc attttaactt gatctaggaa aattccaaca aaaaacccac ggtgctggag 143760

caagatctca ggctgtgacc ttctcgagga aagaagcact ttctgttgtc tgaaagaaaa 143820

gaaagtgctt cctttcagag ggttacggtt tgagaaaagc aacgttgaag ttgacgctga 143880

tcttggtaat acatttgcag agcgtgctga tcatcagacg tggataatgg tggggttttg 143940

tttttttatct aagacagggt gtctgttccc caggctggag tgcggtggca cttccaactt 144000

agatctcttg ggttcaagtg gccctctttt tgggacagag tctcactctg tggccctggc 144060

tggagtgcag tggcaggaac ttggctcact gcaatctctg cctcctgggt tcaagcaatt 144120

ctcctgcctc agcctccgga gcagctgggg ttacaggctg tgccaccatg cccagctaac 144180

ttttgcattt ttattattga tttattgatt tattttttgag acagggtctg ctctgtcac 144240

ccaggctata gggcagtggt gcgatctcgg ctcactgcaa cctccacctc ccacctcagc 144300

ctcctgaata cctgtctcca ggcatgcact accacacctg cctaactttt gtattttttg 144360

tatagatgag gtttcaccat gttgcccagg ctggtctcgg acccttgagc tcaattgctc 144420

ctcccgcctg ggcctccaaa actgctgtga ttaatggtgt gagcaagcgt gccctactct 144480

tgtgtgtttc tgctcaaatt ttatggagga gcttttacat cccagcctgt ggtctatcct 144540

ggagaatgtt tgtgtgtgtg acaatgtata ttcttcaaca ttttagattc catttggatg 144600

ctcccatccg gactgtgtgc ccctgtactg gaactcaagt gaacacttgg ctcaacatcc 144660

attgctgttc tcatgaattc caggccaatt gtcttggtta aagacaaggt atgtgggctg 144720

ggcgtggtgg ctcatgcctg taatcccagc actttgggag accgaggtgg gaggatcacg 144780

aggtcaggag ttcgagacaa gcctgaccaa cacggtgaaa cccatctcta ctaaaaatac 144840

aaaaattagc tgggcgtggt ggctccacca gtaatctcag ctacttggga ggctgaggca 144900

ggagaattgc ttgaacccag gaagcggagg ttgcagtgag ctgagatcgc gccactgcac 144960

tccagcctgg gtgacagagc gagacttcat ctcaaaaaat aaaaaataaa aaggtatgtg 145020

tagtaggcat tgctttttct cttttgtagat aatactcagg aggactgcct cttgaacaag 145080

gctaacctgc tgagcctttg aagcaaggaa ctggagatgg tccttttagg gggttatgtt 145140

ctggattcca gaaacatgc aaataggggac aatgaatgca tctttatttt tctgtccatt 145200

ttaacctggt caaggaaaat ttcaacaaga aacccagagt gctggagcaa gaagatctca 145260
```

-continued

```
agctgtgagt ctacaaagga aagcgctttc tgttgtctga aagaaaagaa atcgcttccc 145320

tttggagtgt tacggtttga gaaaagcagc gttgaagttg atgctgatct cggtaataca 145380

tttgcagagc atgcttatca cacttggacg gtggcggggt tctgtttttgg ttttgctttg 145440

ttattctaaa acagggtctg tgttgcccat gctggagtgc ggtggcacat cccacctagg 145500

tctcttggat ttaaatggtc ctttttgggg gccagagtct ctctctgtca ccgaggctga 145560

agtgcagtca tcccatcttg gctcactaca acctccgcct cccaggttca agcaattctc 145620

ctgcttcagc ttcccaagta gctgagattt acaggcgccc atccccacac ctggataata 145680

tttgggtttt tttttttattt attttttaaga tggggtctca ccgtcaccca ggctgtagtt 145740

cagtggcttg atctcggctt actgcaatgt atgccaccca ggatcaagtg attctcctgc 145800

cccagactcc tgagtagctg gaattacacg cacctgccac tacacccggc tacttttttga 145860

attttttttt tttttttttaa agtaaagatg ggctttcacc atgttggcca ggctggtctc 145920

aaacccctga cctcaagtca gctgcttgcc tcagcctccc aaagtgctga gaatacaaac 145980

atgagccact gcgtggccat caacacctct tactttatgg aaattttttct ggcactggta 146040

tagaacctca cgtgggtca ggtggagttg aggggacctc agtttcccttt gcagatggga 146100

tgtgcactgc tcagcaagag cacagaggtg gagtgcatgg ggcttcagtg tttattgggg 146160

aaatgaagct aaaatcttcg gtgtgtgacc aggagataaa tgcatgagat ggggatctca 146220

ctatgctgcc caggctgaag tgggcttaga tcctcctgcc tctgcccctc cccagtcctt 146280

ggtacatggg actacatgtg aatattaacc ccccatgcac agacaagaag aaagtaagga 146340

ctgttctttg gttcatacct gaccccagtt aaacatgtat tttagataaa caatgtattt 146400

gaaatgtact tgaacaacaa atgatttgct gtttaggtgt gggcatcttt tttttttcttc 146460

ctaactttaa atatgggact agtccaggta cggtggctca tgcctgtaat tccagcactt 146520

tgggaggcgg agacaggagg atcacctgag gtcagttgtt cgagaccaga ctggccaaca 146580

tggtgaaacc tcgtctgtac taaaaataaa aaaattagtg agacgtggtc ttggtgcatg 146640

cctgtaatcc cagctactcg ggtggatgag gcaggagaat tgcttgaggc tgggaggctg 146700

agctttcagt gagctgagat caagcctctg cactccagcc tgggcaacag agtgagactg 146760

agtctcaaaa aagtaaaaaa tcagctgggt gcgctggcaa acacttgtaa tcccagcact 146820

ttgggaggcc gagacgggag gatcacctga ggtcatgttc aagactaaca gggctgaaat 146880

agcaaaacct catctctatt aaaaatacaa aaattagctg ggtgcagtgg tgtatatctg 146940

tatttccagc tacttggagg ctaaggcagg agaatcgctt gaacccagga ggaagagatt 147000

tcagtgagct gaagccatgc cattgcactc cagcctgggc cacagagcaa gattccatct 147060

caaaaataaa ataaataata aaatgaaat taaatagata aaataaaata gataaatatg 147120

agaccatcat gaatttggat gtcacttttg tgcaggggcc agggtaatct ctgtcattcc 147180

aatttttttt atgtgcactg ccaaagcaag cactcatgtg taggaattat tcttcctgtg 147240

agcatataat atatggaact ttgagacaga gtctccaaaca tatataatgt atattttatc 147300

atatattctt tatatataaa atatcatata gacacaaaat actgttctaa atacagaaa 147360

tactctgata tcaacttggg tattttttgt ttctgtgtgt gtgtattttg tttggttggt 147420

tatttttgag acaaggtcta gctctatcac acaggctgga gtgtagtggt gcgttctcgg 147480

ctcactgcaa cctccgcctc ccacctaagc ctgctgcatt agtgtctaca ggcatgcacc 147540
```

-continued

```
accacacccg gctcactttt gtattttttg tacacatggg gttacaccat gttgccgggg 147600

ctggtctcga actcctgagc tcaggtgatt ctcctgtctt ggcctcctaa agtgctggga 147660

ttagaggtgt gagccaccat gccccatcgg tacttgtgat ttaggttcaa attttgatga 147720

gtttttatga ccaagcctgt ggtctatcct agagaatgtt tgtgtgtttg acaattcaac 147780

atcgtagagt tgattttggg tgctcccatt gggactgtgt gtccctgtac tggaacttga 147840

gtgaacactt ggctcataat ccattgctct tctctagaaa tccagcccaa ttctcttggt 147900

taaatataag gtatgtgtag caggcattgc tttttccttc cagagacaaa actcaggagg 147960

attgcccctt gatgaacaag gctaacctgc tgattctttg aagcaaagaa ctggagatgg 148020

tccttttaga ggtttatatt ctggattcca gaaaacatgc aaacagggcc aataaatgca 148080

tctttatgtt ttcgtccatt ttaacttgat ctaggaaaat tccaaaaaaa aaaacccacg 148140

gtgctggagc aagaagatct caggttgtga ccttctcgag gaaagaagca ctttctgttg 148200

tctgaaagaa aagaaagtgc ttcctttcag agggttacgg tttgagaaaa gcaacgtcga 148260

agttgacgct gatcttggta atacatttgc agagcgtgct gatcatcaga catggataat 148320

ggtggggttt tgttttttgtt ttatttttttt atctaagaca aggtatctgt tgcccaggct 148380

ggagtgcggg ggcacttcta acctagatct cttgggttca agtggccctc ttttcgggat 148440

agagtcttct ttgctctgtg gccctggctg gagtgcagtg gcaggaactc ggctcaccgc 148500

aacctctgcc tcctgggttc aagcaattct cctgcctcag cctgtcgagc agctgggggtt 148560

acagacatgt gccaccacgc ctggctaatt tttgcatttt tattgtcgat cgattgattg 148620

attttttgaga cagagtctgg ctctgtcacc caggctgtcg ggcagtggtg cgatcttggc 148680

tcactgcaac ctccacctcc cacctcagcc tcctgaatac ctgtctacag gcatgcacaa 148740

ccacaccttg ctaactttttg tattttttgt acagatgagg tttcaccatg ttgcccaggc 148800

tggtctcgga cccctgagct caagtactcc tcaaacctgg gcctcctaaa ctgctgtgat 148860

taatggtgtg agccaccgtg ccctactctt acttgtgtgt ttctgctcaa attttattaa 148920

ggagctttta tggcctcgcc tgtggtctgt cctggaggat gtttgtgtgt gtgacaatgt 148980

atattcttca acatcttcga ttccatttttg ggtgcctcca tggggactgt gtgtccctgt 149040

actggaacgc aagtgaagac ttggctcaga gtccatttgc tgttctctag aaatccagcc 149100

taatcctctt gtgcaaatat aatatatatc tagtaggcat tgcttttttct ttctggagac 149160

aaaacacagg aggattgccc cttgatgaac aggactaacc tgctgattct ttgaagcaag 149220

gaactggaaa tggtcctttt agggatttat gctctggatt ccagaaaaca cgcaaacagg 149280

gccaataaat gcatctttat ttttgtgtcc attttgacct ggtcaaggaa gattccaaca 149340

aaaaatccac agtgccggag caagaagatc tcaggctgtg tccctctaca gggaagcgct 149400

ttctgttgtc tgaaagaaag gaaagtgcat ccttttagag tgttactgtt tgagaaaagc 149460

aacgttgaag ttgatgctga ttttggtaat acatttgcag agcatgctta tcatcagact 149520

tggatgatgt tgggtctgt ttttgctttg tttttttttc caagacagtg tgttgttgc 149580

ccaggctgga gtgcggtggt acttcccacc tagatctctt gggctcaaga ggtctttttt 149640

tattttttctt tctcaagaga gagtctggtg gtgacaccca ggctggagtg cagtggtgca 149700

ttatcagctc actgcagcct tcccctcccc ggttcaagtg attctttcac ctcagcctcc 149760

cgagtagctg ggattacagg tgtgggctac cacacccggc taatttttgt attttttagca 149820
```

-continued

```
gagacagggt tttaccatgt tggggaggct ggtctcaact cctgtcctca agcgatccac 149880

ctcccttgcc tcccaagtac tgagattaca ggcgtgagca actgcgcccg gcctcaagtg 149940

gtcctcttaa gtcagcctac caagtttttgg gactacatgg ggcatgccac cacacttggc 150000

taagttttta attttttttt tttttttttt tttttttttt gagacggagt ctcactctgt 150060

cgcccaggct ggagtgcagt ggcaagatct cggctcactg caagctcggc ctccgggggtt 150120

cacgccattc tcctgcctca gcctcccgag tagctgggac tacaggtgcc cgccaccacg 150180

cctggctagt tttttgtatt tttagtagag acggggtttc accctgttag ctaggatggt 150240

ctcaatctcc tgacctcgtg atccacccgc ctcggcctcc caaagtgctg ggattacagg 150300

cgtgagccac cgcgcccggc cgatagtttt taatttttga tagaaaggga atctctcttg 150360

cctaagatgg tctcaactcc tgagctcaag ggatcctaaa ggtgtgagcc gccttgtcct 150420

gatgacccat ttcaaacgta gctgacatgg ccaggcatca tggggcacac agtcccagct 150480

actgcagaag ccggggtggg agggtccttt gatttccagg ctataccatg tgctgatcac 150540

acttttgatc ccgagtagct gggattacag gcagccaccg ccaggccggc taattttttat 150600

ttatttactt atttttttcag acggtgtttc cctcttgttg cccaggctgg agtgcaatgg 150660

catgatctcg gatcactgca acctccacct ccctggttca agcgattctc ctgcctcagc 150720

ctcccgagca gctgggatta caggcatgca tcaccacgcc cggctaattc tttgtatttt 150780

tagtagagat gggatttctc catgttggtc aggctgatct tgaactccca accttaggtg 150840

atccacccac ctcggcctcc caaagtgctg ggattacagg catgagccat tgtgcccggc 150900

ccatttcatt tatttttatg tgtgctgctg aagcaagcac ttatgtgtag gaattgttct 150960

tcctgtgagc atatgttggc cagcctggac cacataccaa gatcccatct ctttaaaaac 151020

acagattacg tggcacctgg cacctggtcc cagagacttc atttgggttg gtcatttgaa 151080

acactagcct cccatcaatt tagtgtaatc aatccaaatc atgtgtcctt cattaagaga 151140

ctaagaacgc ctccacgtct atccagtcta ttttgtaatc cccaacggtt gtcaatatta 151200

ataaaatttc ttttcttttt cctattcatt tgtgtcttta gttttttcttc cccaaaaact 151260

tgccatcatt tctcggaata gacctgcttt ctctgcagga agggtgtggt tgattcaacc 151320

cttacccact aatgccaacc ccagtgagtt cttttatcct attttctatg ggtaacgatt 151380

ccaaggtacc attccaccgg gcaaaagctc acatctaagt gtcagttgct cggtaagatg 151440

tgaaatgttt gctgtggcta atataagaaa caaactattg tagacaagat gaatctcagt 151500

ggcagtgata aatgtcgcac aagacaaaac cacagatcct tttttttttt tttttttttt 151560

ttagacaaag tttcactctt gttgcccagg ctggagtgca atggtgcgat ctcggctcac 151620

tgcaacctcc gcctcctgga ggcgattcaa gcgattctcc tgcctcagcc tcccaagtag 151680

ctgggattac aggcatgcac caccacgccc aggtaatttt gtattttttag tagagacggg 151740

gtttcgccat gctggtcagg ctggaactcc tgacctcaga tgatcctccc acctcagcct 151800

cccaaagtgc tgggattaca ggcgtgagcc actgtgcccg gccaaccaca gatactttca 151860

cgaaagcctt tagggcccta gaaggggctc cctagtaaca ggtgggatgc gaggcagctc 151920

tcgttgttgc cgtagtgagc gatgcctgtt cgtccagccc tcaacacctt ttactccgtg 151980

gaagttatgc ctgcactggt ttacagaacc tcccttgact tgggttgagg tagagctgaa 152040

gggaacctca gtgtcccttg caggtgggat gtgcactgct tagcaagagc acggaggtgg 152100
```

-continued

```
agtgcatggg ctttgagttt ttattgggaa aatgaagctg aaatgtaggg cgcatgacca 152160

catcataaat gcacatttga tttaattttt ctattttatt tttatttatt tattttgaga 152220

tggagcctcg ctctgttgcc caggctggag tgcactggcc tgatctcggc tcactgcaac 152280

ctccacctcc cgggttcaag caattattgt gcctcagcct cccaggtagc tgggattaca 152340

cgcatgcttc cacgcccggc cgattttttgt attttttagta gagacggggt ttcaccatgt 152400

tggccaggct ggtttcaaaa tcctgacctc aagtgatccg cccgcctcgg cctctcaaag 152460

tcctgagatt acaggcgtga gccaccatga ccagcctaat ttttctattt tagagacagt 152520

ggtctagcta tgccacccgg gctaaactag gctttagaga tcttcctgcc tctgcccctc 152580

cacggtctct ggtagtttgg actacaaatg aacattagca tatttgcaac caccaccact 152640

ctagtttgga agattttttat cacccccaaag aagcttatac ccatttgcct tcagtaccca 152700

ccccctctt ccactcagac cctggcaact actctacatc tctctagctc tggatttgcc 152760

tcttgtgggc atttcacaaa aaccagtctt gaatgggtgg cctgttgtga ccacttttaa 152820

tataatgggt tggttctggt tgtctgaagt gtgaatcttg ccaatgaagg atggccctg 152880

gatggaagca ggaggctggg agaactgggc ggaacatcct ttcggaatgg agtggggtgg 152940

gcacaccctg atgtctggga agctcacaag ggtggaagaa cccatcttcc tctctgataa 153000

ctgcaaggtg accctcctgg ggcactggat ggagtgaagg catctggact gggaacacca 153060

gggcattgca ctggtgcagg caggatgagc cgaggggaaa ggagtgccag gcatcattct 153120

ctggtgacag tttgggtttg atctggatgg agcaggtgtc ttctggtaga gagagtccct 153180

gggattttttg ctctgctcct ggctgtcttt cagtcatgga atctgatgac aaaggctccc 153240

actctgggcc acttcatttg gtttctggag cccagtggtc ctttctgccc ggactcagga 153300

tcttttgggg aaatttggga cctcgcagga catctgcaca atccatagaa atccctgaga 153360

gcccctttccc tttgctgaca tctccgtatt cctacctatt gccttccaaa aaaagacccct 153420

tatctgaatt gccaaagggg gcttcccaga gcagggaaac ccggttaaat ttgtatttca 153480

gattaacagc atatctagaa tctactcgaa caagaagtga tttgttgttt aagtgtgaga 153540

aattttttttc ccctaatttt aaatacggaa cccatcatga atttggctgt cacctttgcg 153600

caggggccgt gggaacctat catttcattg tttaatgtgt gctgccaaag caagcactta 153660

agtgtgggaa ttattcttca cgtgaggata caatagatgg aacgttatta ctttttttctt 153720

tcataattga gattttattg gttgaagatc ggtacagaca tttcaatttg tacacaattc 153780

ttaacatacg taccgaaaat ctaaaaagcc atgtattgta aatcgttttg ttttgttttg 153840

tttttttgag acagagtttc gctcttgtca cccaggctgg agcgcaatga cgcaatctcg 153900

gctcaccgca acctccgcct cccgggttca agcaattctc ctgcctcagc ctcccaagta 153960

gctgggatta caggcaaatg ccaccatgcc cggctaattt ttgtattttt ttttttttaa 154020

gtagagacag ggcttctgcc tgtcggtcag gctggtctcg aattcccgac ctcaggtgat 154080

ctgcccgcct cggcctctta aagtgctgag attacaggcg tgagccaccg cacccggcca 154140

tgtattgtaa ttcttctaca aagttattcc ggcgactttc cagcttaaaa tttggaagca 154200

cattttcctt aagaggctat caagtaccag tatcttcaca tgttgatcag ctgttacgga 154260

cgtccctcca attcacaact aaaaatagca tgtaccctac atattcaaat ttttcatctt 154320

tcacaacgca gaaacaaact tattaggaga acagaactac cacaatcaaa gatgttacag 154380
```

-continued

```
agtccacaca attctaacag ggagagccat ggtcagggag tggttttctt taggaaacaa 154440

ttccaaaata cgacaggaga atagaagtaa tttaaaatgt tcaagacact aaatgcagag 154500

ctgattccat gctgccattt aatatgcttt gtattatagg atataaacac gaaccctggc 154560

cgggtgcagt ggctcacgcc tgtaatccca gcactctggg aggccgaagt gggcagatca 154620

cctgaggtca ggagttcaag accagcctgg cccacatggt gaaaccccat ccctactaaa 154680

aatatgaaaa ttagccaggc atggtggtgc gcgcctgtaa tcccagctac tccggatgct 154740

gaggcatgag aatcgcttga acccgggagg tggagattgc agtgaactga aatcacgcca 154800

ctgccctcca gcctgggcga caagaacaag actctgtttc aaaaaaaaaa aaaaaaaaaa 154860

agtttctgga actactaaaa aacttgcatt tacaaaatag ttgataaaaa gattcctctg 154920

ggttttacaa gaagcgagac agggagcact gatgagacgt ggtatacggt gaatcagact 154980

gggcatcaga ggctgggcct cctcagtttt cctttcccca ttttctgcag ataaatcttt 155040

agtttcttgg ttagccactt ctgcccgttt tccctttgct cccctttgcc cttctgttca 155100

cacttttttg tctgaagatg tatccttcgt tgctgccttt ttcggcttca tttccactgg 155160

ttttttttgtt ttgtttgtt ttgtttgtt tgagacgtag tttcaccctg ttgctcaggc 155220

tggagtgcaa tggcgtgatc tcggctcaca gcaacttctg ccttccggtt caagcgattc 155280

tcttgcctca gcctcccgag tagctgggct tataggcgcg caccgccatg cccggcttat 155340

ttttgtattt ttagtagaga cgggggtttc accatgttgg ccaggctggt ctcgaactcc 155400

tgacctcagg tgatccgccc gcctcagcct cccaaagtgt tgtgattaca agcgtgagcc 155460

accgcacccg gccttgcttc cacttttgca ggagcaggtt tagctgacaa ccgtgcgatc 155520

tcctcgtggg ctcttccttg gcggcccta tggcggagct aacctgcctc ttgggcatcc 155580

tggtggcgga gagggcgcgt gccggctgtc tgcgggccgc ggctgccgag agccttggcg 155640

aagctgggct gcctggcggc tgcggctcct cccgccgccc gagctgctga gacccacagc 155700

ggggtcggtg ggagaaccga atggaacccg aaactttctt attttgagac aggatctggc 155760

tctgtcaccc aggctggagt gcttggctca ctgcaacgtc tgcctcaagt gatccttcca 155820

cctcaacctc ccaagtagct gagattacag gcgcgcgtgc cactatgcct ggctaatttt 155880

tgtactcttt gtagagatgg gggtctcgct atgttgccca cgctggtctt gaactcctgg 155940

gctcaaatga tcctcctggc ctggcttccc aaagtgctgg ttgtaacgcc agcagtttgg 156000

gaggccacag tcggcgggat ggattagcta gcaacaaaca ttccaggcag agaatggtgc 156060

tctctcaact ctcagtcagc aagggggctag tatatattga aggggctcag ggcatgtcac 156120

cccaaagtca tcgcgtcagc atatggatta tttcgacctg gaagcctgtg ggaaaaagca 156180

gatgcatctg acctccccct tcctacgtaa aagtagattg taaaatttat caagaggaaa 156240

acgcccttcc tgcgccagga agagaagaat gttcctatca gcaggggcca ggagtccata 156300

tgctaaacaa ctcagctact aacccttatc ttccttaagt tccccactgt ttcctggtca 156360

cttcccctag cccaagcctc tttgtcttgt cacatcccca caacttatca ttcctttttt 156420

ttttttgagg tggagtttag ctcttgttgc ccaggctaga gtgcgatggc gcaatcttgg 156480

ctcactgcaa cctctgcctc ccgggttcaa gtgattctcc tgcctcagcc tcccaagtag 156540

ctgggattac aggcgcccac caccacgctc ggctgatttt ttgtattttt agtagagatg 156600

gggttttgcc atgctggcca ggctggtctt gaactcctga tctccggtga tccgcccgcc 156660
```

-continued

```
tcagcctccc aaagtgctgg gattgattac aggcgtgagc caccgcgccc ggccatcatt 156720

ctctttttttg ttttgttgtg gttgttgttg tttgagacag cgtctggctt tgtcacccaa 156780

gctggagtgc agtggcgcca tctcagctca ctgcgacctc tgcctccggg gttcaagcaa 156840

ttctcatacc tcagcctccc gagtagctgg aaccacaggc atgagccacc atgcccggct 156900

agttacaggg ttttcctatg ctctccaggc tggagtgcag tggcgcaatc atagttcact 156960

gcagtcttca actcctgggc tcaagcaatc ctcccacctc agcctcttaa actgctggga 157020

ttacaggtgg tagccatcat gccctgcccc agagaagtct ttaggcttca gccaggcacg 157080

gtggctcagg ccggtaaacc cagcactttg ggaggctgag gtgggaggat cgcttgtgcc 157140

caggagttga aggctgcaat cagctatgac tgcaccacag cactccagtc tgggcaacaa 157200

agtgagaccc tgtctcaaaa aacaacaccg taggcccagc acggtggctc ctgcctgtaa 157260

tcccagcact ttgggaggcc aaggcaggtg gatcacttga ggtccagagt tcaggaccag 157320

catgaccaac atggtgaaac cccgtctcta ctaaaaatat acaaattagc caggtgtggt 157380

ggcagacacc tgtaatccca gctacttggg agactgaggg aggataattg cttgaacccg 157440

ggaggcggag gttgcggtga gccaagatcg cgccattgca ctccagcctg gttgacagag 157500

caagaccctg tctcaaaaag aaaggaaaag aaaaagaata caccagaagg tacccagaga 157560

ggccagtgtg gatgtacagc cagcacataa gatgctggtt agggacaggc gcagtggctc 157620

acgcctgtaa tcccagcact ctgggaggcc caggcagggg gatcacctga ggtcaggagt 157680

tcaagaccag cctggccaac atggcgaaac cccgtctgta ctagcaaata caaaaattac 157740

ttgggcgcgg tggcacgtgc tataatccca gctactccgg aggctgaggg tggaaaattg 157800

cttgaacccg ggaggctgag gttgcagtga ccgagatcg caccactgta ctccagcctg 157860

ggcaacaaga gcgaaactcc gtctcaaaaa attaaataaa taggccgggc gcggtggctc 157920

acgcctgtaa tcccagcact ctgggaggcc gaggagggcg gatcacgggg tcaggagatc 157980

aagaccatcc tggccaacat ggtgaaaccc cgcctctact aaaaatacaa aaacttcgcc 158040

ctgtatggcg gcacacggct gtattcccag ctactcggga ggctgaggca ggagaacggc 158100

ttgaacccgg gaggcagagg ctacagtgag ccgggatcac accgctgcac tccggcctgg 158160

gcagcaagag caaaactctg tctcaaaaaa caaaaaacag aaaaacaaaa agaatcaagt 158220

aagtcgaagc cacactgata acagccaatt tttgtgaacc aagggagtgt caattcaaga 158280

atttacatag atgtctactt ttgctatctc ctatgtgcca agcaagatac aggctctggg 158340

caatcagaaa caaaagagac tcactcgttc ctctcacagt actcagtcct tactgagata 158400

aggacaaaag aaaatgtcct gtctggaatg cagggaaacc agaacttcag gtcaggggac 158460

atttccattg aattgtgtgg agttgaagct gaaaatactt tttttttttt tttttttttt 158520

acatcacggc atggtttatt acgtgatttt tttactatac aaacaaaaaa tacagaaatg 158580

caatatgtga atacagctaa atgcagaatg gtgacttttt tctcttcaag aggccatgat 158640

tcccatttct agtaaaataa agagaccgca tacaggttgg ttgtgagatt cacaatttttg 158700

cctagaaatg atctataaat gcatttttcc ccctgctac ctaccgtaaa tcgtaaaaag 158760

ggagttaaag caaagtttcc ttgttggttc ctaccatatg gaagatgcta tattctattt 158820

tagcagggtc aatatttgga aaatatctaa attaaatatt attacaaaaa tgaagctgta 158880

atgagattct ggctaaagag ggcactaaat gagaataata tatatttaaa gaatccaaaa 158940
```

-continued

```
caaacaaaca aaaagaggtt attataaaaa gctctaggtg cactgtaagc atatagggtt   159000

tttttttcat gtgttttttt ttaaacaatg gaagtgtcaa aaatagggtc aactgtgtta   159060

gactaaatta cattattgta tatgctgcat tgaatggaac ctttgtatta taattatcat   159120

agagaagcac agtttgcatc atattatggc aattcatcgt caatgaaaac cttccagagt   159180

ccttttattt tggaatctcc tgtaaactat caaaccacca gaacatgact gtacaacagt   159240

aaaatgttct cttgcattaa actgaagaga cctgtttaat aaaaaaagaa aaagaaaatg   159300

taggaaaggt acttagagct gttactttct aagtacacaa caccctagac aattcgaggc   159360

atcttaatct ccatcaagaa caacaacaac aaaaataatt tttgtcatgt tgttaaatcc   159420

atcattatgg atcaaactgg tgcaacttgg tcaaatgaat ccaacaaaca ctgatgtcca   159480

agctggcata ttggcaacta atacacaact ggtggtcaat agagagttta aaagatcttc   159540

cctttcttgt tgttcttttc caaggttctc aaagagttct gttgctctaa aatacgttgt   159600

tgagcttccc agtttgcttt ctcatcctca aactgacgac gtttctcctc taattctttg   159660

tgccgtgctc ccaaattctt tttcagttgc acatggcact gctggagcta aatcacagca   159720

caatatatac cccaaggata ctgccttcct ctgacccttt ttccattaac ttcagtgata   159780

atatcactac ccaccacagc aagaggtaaa cggtccttta tctttttaac acgtttcttt   159840

tcttcttcat catctgtttc tggaaattca tatattttaa ttttatgttc ttggatttct   159900

ttcattatct gttttgtaaa ctgttgacat tcctctggtg tgagtgtgtc tgctttggca   159960

gtaagtggga tgatattcac tttttcatgc aaatgtttca taaactcaac atccagtggt   160020

ttaagtctca acaaaaggca atgtcaagta gttacaaaca tgcactaccc aatcctgcct   160080

gaaggtggga gtcttcagtt atgtaatggt cctgttatca ggcatctgac gtctgctcac   160140

tcgcgattct gcatttaggt agtcctcaaa tttactatca atgtaatcga taacaggctg   160200

ccagcaatta ctactatcca ctgcatctcc aaatcctgag gtatcaacta tcctgagcag   160260

caactaaaca ccaccttctt tgattaaaac tttggattgt tccatccagg cttctatttt   160320

cccatagagg tccaaaaaac gcccttgttt gttaagttga tatatgtaaa ccttttctcc   160380

aggctgttcc ttgaggttta cataattggg aactccttca agcatctgta aataaacctt   160440

ttcagctgta gatctctcta ttttcagtta atttgcagac caccaactat aggagccaag   160500

ttgaaagaga aaaagttttc tcttcccagc actttcttta ggatgctttt cattgcttcc   160560

caactggagg cctcgcccct ccacccacct gccctagtcc tcagctgcct ccagttctgt   160620

ccacttaaat acagactccc ggtagtagag aacttttta aaattttatt attattatta   160680

ttattattat tgacacagtc ttactctgtc gtccaggctg gagagcagtg gcacaatctc   160740

agctcactgc agcctctgcc tcctgggttc cagcgattct cctgcctcag cctcctgagt   160800

agctgggatt acagacaccc gccaccatgc ccggctaatt tttgtatttt tggtagagac   160860

gggggtttca ccatgttggc caggctggtc ttgaactcct aacctcaggt gatcctccta   160920

cctcggcctc ccaaagtgct gggattacag gcgacagcca atgtgtgcac              160970
```

<210> SEQ ID NO 61
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

-continued

```
<400> SEQUENCE: 61

actgggacga catggagaaa a                                          21


<210> SEQ ID NO 62
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 62

gccacacgca gctc                                                  14


<210> SEQ ID NO 63
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 63

tgcaaggaaa gcattgaaca a                                          21


<210> SEQ ID NO 64
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 64

gaggagtcac ctggacaatc act                                        23


<210> SEQ ID NO 65
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 65

cacatgaagc agcacgactt ct                                         22


<210> SEQ ID NO 66
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 66

aactccagca ggaccatgtg at                                         22


<210> SEQ ID NO 67
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 67

gcggtggttg cccaacagga                                            20
```

-continued

```
<210> SEQ ID NO 68
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 68

acgacccgtg gtcatcttta                                                   20


<210> SEQ ID NO 69
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 69

tagaggatca cgtaattgca gga                                               23


<210> SEQ ID NO 70
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 70

gttgtcaaag ctgagccttc tat                                               23


<210> SEQ ID NO 71
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 71

atgccagacc gtcttgatac a                                                 21


<210> SEQ ID NO 72
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 72

tgacccaagt atttcagccc a                                                 21


<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 73

gaacaacggt ttcgctcttt g                                                 21


<210> SEQ ID NO 74
<211> LENGTH: 23
<212> TYPE: DNA
```

-continued

```
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 74

gcttctacat taggccagac ttt                                                    23


<210> SEQ ID NO 75
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 75

acccgcttaa cagcgtcaac a                                                      21


<210> SEQ ID NO 76
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 76

ccaaagaggt gcgggagttt                                                        20


<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 77

gccaatgagg gttcgagttc                                                        20


<210> SEQ ID NO 78
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 78

aacaacatcc cgtcgttcat c                                                      21


<210> SEQ ID NO 79
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 79

acgaatccca gtgtgttttg g                                                      21


<210> SEQ ID NO 80
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide
```

-continued

```
<400> SEQUENCE: 80

tgctcaaaaa cggtatggac at                                              22


<210> SEQ ID NO 81
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 81

caaccaagca aatgtgagga                                                20


<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 82

ggagacttgc ctggtgaaaa                                                20
```

1. A method of inhibiting or treating a microbial infection in a subject, comprising:
 selecting a subject with a microbial infection or at risk for contracting a microbial infection; and
 administering to the subject a therapeutically effective amount of one or more inhibitory microRNAs (miRs) encoded by the chromosome 19 miRNA cluster (C19MC), thereby inhibiting or treating the microbial infection.

2. The method of claim 1, wherein administering the one or more inhibitory miRs encoded by the C19MC comprises administering a nucleic acid molecule encoding the C19MC or a biologically active portion thereof.

3. The method of claim 1, wherein the microbial infection is a viral infection.

4. The method of claim 3, wherein the viral infection is an infection by an RNA virus.

5. The method of claim 4, wherein the RNA virus is a coxsackievirus, poliovirus, vesicular stomatitis virus, human immunodeficiency virus or hepatitis C virus.

6. The method of claim 3, wherein the viral infection is an infection by a DNA virus.

7. The method of claim 6, wherein the DNA virus is a vaccinia virus or herpes simplex virus.

8. The method of claim 1, wherein the microbial infection is a bacterial infection.

9. The method of claim 1, wherein the microbial infection is a parasitic infection.

10. The method of claim 1, wherein inhibiting the microbial infection comprises preventing the microbial infection.

11. The method of claim 1, wherein the method comprises inhibiting or preventing intrauterine transmission of the microbial infection.

12. The method of claim 1, wherein the subject is administered a nucleic acid molecule encoding the entire C19MC.

13. The method of claim 1, wherein the biologically active portion of the C19MC, or the one or more inhibitory miRs, comprises:

 (i) miR-517-3p, miR-1323, miR-516b-5p, miR-525-5p, miR-512-3p and miR-515-3p;
 (ii) miR-517-3p, miR-516b-5p, and miR-512-3p;
 (iii) miR-517-3p;
 (iv) miR-516b-5p; or
 (v) miR-512-3p.

14. A method of inducing autophagy in a cell, comprising contacting the cell with an effective amount of one or more inhibitory miRs encoded by the C19MC, thereby inducing autophagy in the cell.

15. The method of claim 14, wherein administering the one or more inhibitory miRs encoded by the C19MC comprises administering a nucleic acid molecule encoding the C19MC or a biologically active portion thereof.

16. The method of claim 14, wherein the biologically active portion of the C19MC, or the one or more inhibitory miRs, comprises:

 (i) miR-517-3p, miR-1323, miR-516b-5p, miR-525-5p, miR-512-3p and miR-515-3p;
 (ii) miR-517-3p, miR-516b-5p, and miR-512-3p;
 (iii) miR-517-3p;
 (iv) miR-516b-5p; or
 (v) miR-512-3p.

17. The method of claim 14, wherein the method is an in vitro method.

18. The method of claim 14, wherein the method is an in vivo method and contacting the cell comprises administering to a subject an effective amount of one or more inhibitory miRs encoded by the C19MC, or a nucleic acid molecule encoding the C19MC or a biologically active portion thereof.

19. The method of claim 18, wherein the subject suffers from a disease associated with a deficiency in autophagy.

20. The method of claim 2, wherein the nucleic acid molecule comprises a vector.

* * * * *