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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, 15/11, 15/10, C07K 14/47, C12Q 1/68, G01N 33/50, 33/574

A2

(11) International Publication Number: **WO 99/19481**

(43) International Publication Date: 22 April 1999 (22.04.99)

(21) International Application Number: PCT/US98/21276

(22) International Filing Date: 8 October 1998 (08.10.98)

(30) Priority Data:
60/062,021 10 October 1997 (10.10.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: MAMMALIAN GENES INVOLVED IN VIRAL INFECTION AND TUMOR SUPPRESSION

(57) Abstract

The present invention provides methods of identifying cellular genes necessary for viral growth and cellular genes that function as tumor suppressors. Thus, the present invention provides nucleic acids related to and methods of reducing or preventing viral infection or cancer. The invention also provides methods of producing substantially virus–free cell cultures and methods for screening for additional such genes.

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MAMMALIAN GENES INVOLVED IN VIRAL INFECTION AND TUMOR SUPPRESSION

BACKGROUND

Field of the Invention

The present invention provides methods of identifying cellular genes used for viral growth or for tumor progression. Thus, the present invention relates to nucleic acids related to and methods of reducing or preventing viral infection and for suppressing tumor progression. The invention also relates to methods for screening for additional such genes.

Background art

Various projects have been directed toward isolating and sequencing the genome of various animals, notably the human. However, most methodologies provide nucleotide sequences for which no function is linked or even suggested, thus limiting the immediate usefulness of such data.

The present invention, in contrast, provides methods of screening only for nucleic acids that are involved in a specific process, *i.e.*, viral infection or tumor progression. For viral infection, the nucleic acids isolated are useful in treatments for these processes because by this method only nucleic acids which are also nonessential to the cell are isolated. Such methods are highly useful, since they ascribe a function to each isolated gene, and thus the isolated nucleic acids can immediately be utilized in various specific methods and procedures.

For, example, the present invention provides methods of isolating nucleic acids encoding gene products used for viral infection, but nonessential to the cell. Viral infections are significant causes of human morbidity and mortality. Understanding the molecular mechanisms of such infections will lead to new approaches in their treatment and control.

Viruses can establish a variety of types of infection. These infections can be generally classified as lytic or persistent, though some lytic infections are considered persistent. Generally, persistent infections fall into two categories: (1) chronic (productive) infection, *i.e.*, infection wherein infectious virus is present and can be recovered by traditional biological methods and (2) latent infection, *i.e.*, infection

wherein viral genome is present in the cell but infectious virus is generally not produced except during intermittent episodes of reactivation. Persistence generally involves stages of both productive and latent infection.

Lytic infections can also persist under conditions where only a small fraction of the total cells are infected (smoldering (cycling) infection). The few infected cells release virus and are killed, but the progeny virus again only infect a small number of the total cells. Examples of such smoldering infections include the persistence of lactic dehydrogenase virus in mice (Mahy, B.W.J., *Br. Med. Bull.* 41: 50-55 (1985)) and adenovirus infection in humans (Porter, D.D. pp. 784-790 in Baron, S., ed. *Medical Microbiology* 2d ed. (Addison-Wesley, Menlo Park, CA 1985)).

Furthermore, a virus may be lytic for some cell types but not for others. For example, evidence suggests that human immunodeficiency virus (HIV) is more lytic for T cells than for monocytes/macrophages, and therefore can result in a productive infection of T cells that can result in cell death, whereas HIV-infected mononuclear phagocytes may produce virus for considerable periods of time without cell lysis. (Klatzmann, et al. *Science* 225:59-62 (1984); Koyanagi, et al. *Science* 241:1673-1675 (1988); Sattentau, et al. *Cell* 52:631-633 (1988)).

Traditional treatments for viral infection include pharmaceuticals aimed at specific virus derived proteins, such as HIV protease or reverse transcriptase, or recombinant (cloned) immune modulators (host derived), such as the interferons. However, the current methods have several limitations and drawbacks which include high rates of viral mutations which render anti-viral pharmaceuticals ineffective. For immune modulators, limited effectiveness, limiting side effects, a lack of specificity all limit the general applicability of these agents. Also the rate of success with current antivirals and immune-modulators has been disappointing.

One aspect of the current invention focuses on isolating genes that are not essential for cellular survival when disrupted in one or both alleles, but which are required for virus replication. This may occur with a dose effect, in which one allele knock-out may confer the phenotype of virus resistance for the cell. As targets for therapeutic intervention, inhibition of these cellular gene products, including: proteins, parts of proteins (modification enzymes that include, but are not restricted to glycosylation, lipid modifiers [myriolate, etc.]), lipids, transcription elements and RNA

regulatory molecules, may be less likely to have profound toxic side effects and virus mutation is less likely to overcome the 'block' to replicate successfully.

The present invention provides a significant improvement over previous methods of attempted therapeutic intervention against viral infection by addressing the cellular genes required by the virus for growth. Therefore, the present invention also provides an innovative therapeutic approach to intervention in viral infection by providing methods to treat viruses by inhibiting the cellular genes necessary for viral infection. Because these genes, by virtue of the means by which they are originally detected, are nonessential to the cell's survival at a level of expression necessary to inhibit virus replication, these treatment methods can be used in a subject without serious detrimental effects to the subject, as has been found with previous methods. The present invention also provides the surprising discovery that virally infected cells are dependent upon a factor in serum to survive. Therefore, the present invention also provides a method for treating viral infection by inhibiting this serum survival factor. Finally, these discoveries also provide a novel method for removing virally infected cells from a cell culture by removing, inhibiting or disrupting this serum survival factor in the culture so that non-infected cells selectively survive.

The selection of tumor suppressor gene(s) has become an important area in the discovery of new target for therapeutic intervention of cancer. Since the discovery that cells are restricted from promiscuous entry into the cell cycle by specific genes that are capable of suppressing a 'transformed' phenotype, considerable time has been invested in the discovery of such genes. Some of these genes include the gene associated by rhabdomyosarcoma (Rb) and the p53 (apoptosis related) encoding gene. The present invention provides a method, using gene-trapping, to select cell lines that have a transformed phenotype from cells that are not transformed and to isolate from these cells a gene that can suppress a malignant, or transformed, phenotype. Thus, by the nature of the isolation process, a function is associated with the isolated genes. The capacity to select quickly tumor suppressor genes can provide unique targets in the process of treating or preventing, and even for diagnostic testing of, cancer.

DETAILED DESCRIPTION OF THE INVENTION

The present invention utilizes a "gene trap" method along with a selection process to identify and isolate nucleic acids from genes associated with a particular function. Specifically, it provides a means of isolating cellular genes necessary for viral infection but not essential for the cell's survival, and it provides a means of isolating cellular genes that suppress tumor progression.

The present invention also provides a core discovery that virally infected cells become dependent upon at least one factor present in serum for survival, whereas non-infected cells do not exhibit this dependence. This core discovery has been utilized in the present invention in several ways. First, inhibition of the "serum survival factor" can be utilized to eradicate persistently virally infected cells from populations of non-infected cells. Inhibition of this factor can also be used to treat virus infection in a subject, as further described herein. Additionally, inhibition of or withdrawal of the serum survival factor in tissue culture allows for the detection of cellular genes required for viral replication yet nonessential for an uninfected cell to survive. The present invention further provides several such cellular genes, as well as methods of treating viral infections by inhibiting the functioning of such genes.

The invention also provides cellular genes whose overexpression is associated with inhibition of viral growth and/or reproduction.

The present method provides several cellular genes that are necessary for viral growth in the cell but are not essential for the cell to survive. These genes are important for lytic and persistent infection by viruses. These genes were isolated by generating gene trap libraries by infecting cells with a retrovirus gene trap vector, selecting for cells in which a gene trap event occurred (*i.e.*, in which the vector had inserted such that the promoterless marker gene was inserted such that a cellular promoter promotes transcription of the marker gene, *i.e.*, inserted into a functioning gene), starving the cells of serum, infecting the selected cells with the virus of choice while continuing serum starvation, and adding back serum to allow visible colonies to develop, which colonies were cloned by limiting dilution. Genes into which the retrovirus gene trap vector inserted were then isolated from the colonies using probes specific for the retrovirus gene trap vector. Thus nucleic acids isolated by this method are isolated portions of genes. Additionally, utilizing this method, several cellular genes were isolated whose

overexpression prevents viral infection or tumor growth, and they provide methods of treating viral infection or tumor growth/suppression by overexpression of these genes.

Thus the present invention provides a method of identifying a cellular gene necessary for viral growth in a cell and nonessential for cellular survival, comprising (a) transferring into a cell culture, *e.g.* growing in serum-containing medium, a vector encoding a selective marker gene lacking a functional promoter, (b) selecting cells expressing the marker gene, (c) removing serum from the culture medium, (d) infecting the cell culture with the virus, and (e) isolating from the surviving cells a cellular gene within which the marker gene is inserted, thereby identifying a gene necessary for viral growth in a cell and nonessential for cellular survival. The present invention also provides a method of identifying a cellular gene used for viral growth in a cell and nonessential for cellular survival, comprising (a) transferring into a cell culture growing in serum-containing medium a vector encoding a selective marker gene lacking a functional promoter, (b) selecting cells expressing the marker gene, (c) removing serum from the culture medium, (d) infecting the cell culture with the virus, and (e) isolating from the surviving cells a cellular gene within which the marker gene is inserted, thereby identifying a gene necessary for viral growth in a cell and nonessential for cellular survival or a gene whose overexpression prevents viral reproduction but is not fatal to the survival to the cell. In any selected cell type, such as Chinese hamster ovary cells, one can readily determine if serum starvation is required for selection. If it is not, serum starvation may be eliminated from the steps.

Alternatively, instead of removing serum from the culture medium, a serum factor required by the virus for growth can be inhibited, such as by the administration of an antibody that specifically binds that factor. Furthermore, if it is believed that there are no persistently infected cells in the culture, the serum starvation step can be eliminated and the cells grown in usual medium for the cell type. If serum starvation is used, it can be continued for a time after the culture is infected with the virus. Serum can then be added back to the culture. If some other method is used to inactivate the factor, it can be discontinued, inactivated or removed (such as removing the anti-factor antibody, *e.g.*, with a bound antibody directed against that antibody) prior to adding fresh serum back to the culture. Cells that survive are mutants having an inactivating insertion in a gene necessary for growth of the virus. The genes having the insertions can then be isolated by isolating sequences having the marker gene sequences. This mutational process

disturbs a wild type function. A mutant gene may produce at a lower level a normal product, it may produce a normal product not normally found in these cells, it may cause the overproduction of a normal product, it may produce an altered product that has some functions but not others, or it may completely disrupt a gene function. Additionally, the mutation may disrupt an RNA that has a function but is never translated into a protein. For example, the alpha-tropomyosin gene has a 3' RNA that is very important in cell regulation but never is translated into protein. (*Cell* 75 pg 1107-1117 , 12/17/93).

As used herein, a cellular gene "nonessential for cellular survival" means a gene for which disruption of one or both alleles results in a cell viable for at least a period of time which allows viral replication to be inhibited for preventative or therapeutic uses or use in research. A gene "necessary for viral growth" means the gene product, either protein or RNA, secreted or not, is necessary or beneficial, either directly or indirectly in some way for the virus to grow, and therefore, in the absence of that gene product (*i.e.*, a functionally available gene product), the virus does not spread. For example, such genes can encode cell cycle regulatory proteins, proteins affecting the vacuolar hydrogen pump, or proteins involved in protein folding and protein modification, including but not limited to: phosphorylation, methylation, glycosylation, myristylation or other lipid moiety, or protein processing via enzymatic processing. Some examples of such genes include vacuolar H+ATPase, alpha tropomyosin, gas5 gene, ras complex, N-acetyl-glucosaminy-l-transferase I mRNA, annexin II, c-golgi CM130 and calcyclin.

Any virus capable of infecting the cell can be used for this method. Virus can be selected based upon the particular infection desired to study. However, it is contemplated by the present invention that many viruses will be dependent upon the same cellular genes for survival; thus a cellular gene isolated using one virus can be used as a target for therapy for other viruses as well. Any cellular gene can be tested for relevancy to any desired virus using the methods set forth herein, *i.e.*, in general, by inhibiting the gene or its gene product in a cell and determining if the desired virus can grow in that cell. Some examples of viruses include HIV (including HIV-1 and HIV-2); parvovirus; papillomaviruses; hantaviruses; influenza viruses (*e.g.*, influenza A, B and C viruses); hepatitis viruses A to G; caliciviruses; astroviruses; rotaviruses; coronaviruses, such as human respiratory coronavirus; picornaviruses, such as human rhinovirus and enterovirus; ebola virus; human herpesvirus (*e.g.*, HSV-1-9); human adenovirus; for animal, the animal counterpart to any above listed human virus, animal retroviruses, such

as simian immunodeficiency virus, avian immunodeficiency virus, bovine immunodeficiency virus, feline immunodeficiency virus, equine infectious anemia virus, caprine arthritis encephalitis virus, arenaviruses, arvoviruses, tickborne viruses or visna virus.

The nucleic acids comprising cellular genes of this invention were isolated by the above method and as set forth in the examples. The invention includes a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, and SEQ ID NO:127 (this list is sometimes referred to herein as "SEQ LIST 1" for brevity). Thus these nucleic acids can contain, in addition to the nucleotides set forth in each SEQ ID NO in the sequence listing, additional nucleotides at either end of the molecule. Such additional nucleotides can be added by any standard method, as known in the art, such as recombinant methods and synthesis methods. Examples of such nucleic acids comprising the nucleotide sequence set forth in any entry of the sequence listing contemplated by this invention include, but are not limited to, for example, the nucleic acid placed into a vector; a nucleic acid having one or

more regulatory region (*e.g.*, promoter, enhancer, polyadenylation site) linked to it, particularly in functional manner, *i.e.* such that an mRNA or a protein can be produced; a nucleic acid including additional nucleic acids of the gene, such as a larger or even full length genomic fragment of the gene, a partial or full length cDNA, a partial or full length RNA. Making and/or isolating such larger nucleic acids is further described below and is well known and standard in the art.

Also provided in this invention are the double-stranded nucleic acids corresponding to the nucleic acid sequences set forth in SEQ ID 1 through SEQ ID 136, inclusive. It is recognized that "nucleic acid" as used herein, can refer to either or both strands of such double-stranded nucleic acids, such strands often referred to as the "positive" and "negative" strands. Either strand of such double-stranded nucleic acids may encode the polypeptides of this invention, and the coding sequences for such polypeptides may be translated in either direction along the strand. Examples of polypeptides encoded by either strand are disclosed herein.

The invention also provides a nucleic acid encoding the protein encoded by the gene comprising the nucleotide sequence set forth in any of the sequences listed in SEQ LIST 1, as well as allelic variants and homologs of each such gene. The gene is readily obtained using standard methods, as described below and as is known and standard in the art. The present invention also contemplates any unique fragment of these genes or of the nucleic acids set forth in any of the sequences listed in SEQ LIST 1. Examples of inventive fragments of the inventive genes can include the nucleic acids whose sequence is set forth in any of the sequences listed in SEQ LIST 1. To be unique, the fragment must be of sufficient size to distinguish it from other known sequences, most readily determined by comparing any nucleic acid fragment to the nucleotide sequences of nucleic acids in computer databases, such as GenBank. Such comparative searches are standard in the art. Typically, a unique fragment useful as a primer or probe will be at least about 20 to about 25 nucleotides in length, depending upon the specific nucleotide content of the sequence. Additionally, fragments can be, for example, at least about 30, 40, 50, 75, 100, 200 or 500 nucleotides in length. The nucleic acids can be single or double stranded, depending upon the purpose for which it is intended.

The present invention further provides a nucleic acid comprising the regulatory region of a gene comprising any one of the nucleotide sequences set forth in SEQ LIST 1, as well as homologs of each such gene. Additionally provided is a construct

comprising such a regulatory region functionally linked to a reporter gene. Such reporter gene constructs can be used to screen for compounds and compositions that affect expression of the gene comprising the nucleic acids whose sequence is set forth in SEQ LIST 1, or any homologs thereof.

The nucleic acids set forth in the sequence listing are gene fragments; the entire coding sequence and the entire gene that comprises each fragment are both contemplated herein and are readily obtained by standard methods, given the nucleotide sequences presented in the sequence listing (*see. e.g.,* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989*; DNA cloning: A Practical Approach*, Volumes I and II, Glover, D.M. ed., IRL Press Limited, Oxford, 1985). To obtain the entire genomic gene, briefly, a nucleic acid whose sequence is set forth in any of SEQ ID NO:1 through SEQ ID NO:127, or preferably in any of the sequences listed in SEQ LIST 1, or a smaller fragment thereof, is utilized as a probe to screen a genomic library under high stringency conditions, and isolated clones are sequenced. Once the sequence of the new clone is determined, a probe can be devised from a portion of the new clone not present in the previous fragment and hybridized to the library to isolate more clones containing fragments of the gene. In this manner, by repeating this process in organized fashion, one can "walk" along the chromosome and eventually obtain nucleotide sequence for the entire gene. Similarly, one can use portions of the present fragments, or additional fragments obtained from the genomic library, that contain open reading frames to screen a cDNA library to obtain a cDNA having the entire coding sequence of the gene. Repeated screens can be utilized as described above to obtain the complete sequence from several clones if necessary. The isolates can then be sequenced to determine the nucleotide sequence by standard means such as dideoxynucleotide sequencing methods (*see, e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989).

The present genes were isolated from rat; however, homologs in any desired species, preferably mammalian, such as human, can readily be obtained by screening a human library, genomic or cDNA, with a probe comprising sequences of the nucleic acids set forth in the sequence listing herein, or fragments thereof, and isolating genes specifically hybridizing with the probe under preferably relatively high stringency hybridization conditions. For example, high salt conditions (*e.g.,* in 6X SSC or 6X

SSPE) and/or high temperatures of hybridization can be used. For example, the stringency of hybridization is typically about 5°C to 20°C below the T_m (the melting temperature at which half of the molecules dissociate from its partner) for the given chain length. As is known in the art, the nucleotide composition of the hybridizing region factors in determining the melting temperature of the hybrid. For 20mer probes, for example, the recommended hybridization temperature is typically about 55-58°C. Additionally, the rat sequence can be utilized to devise a probe for a homolog in any specific animal by determining the amino acid sequence for a portion of the rat protein, and selecting a probe with optimized codon usage to encode the amino acid sequence of the homolog in that particular animal. Any isolated gene can be confirmed as the targeted gene by sequencing the gene to determine it contains the nucleotide sequence listed herein as comprising the gene. Any homolog can be confirmed as a homolog by its functionality.

Additionally contemplated by the present invention are nucleic acids, from any desired species, preferably mammalian and more preferably human, having 98%, 95%, 90%, 85%, 80%, 70%, 60%, or 50% homology, or greater, in the region of homology, to a region in an exon of a nucleic acid encoding the protein encoded by the gene comprising the nucleotide sequence set forth in any of the sequences listed in SEQ LIST 1 or to homologs thereof. Also contemplated by the present invention are nucleic acids, from any desired species, preferably mammalian and more preferably human, having 98%, 95%, 90%, 85%, 80%, 70%, 60%, or 50% homology, or greater, in the region of homology, to a region in an exon of a nucleic acid comprising the nucleotide sequence set forth in any of the sequences listed in SEQ LIST 1 or to homologs thereof. These genes can be synthesized or obtained by the same methods used to isolate homologs, with stringency of hybridization and washing, if desired, reduced accordingly as homology desired is decreased, and further, depending upon the G-C or A-T richness of any area wherein variability is searched for. Allelic variants of any of the present genes or of their homologs can readily be isolated and sequenced by screening additional libraries following the protocol above. Methods of making synthetic genes are described in U.S. Patent No. 5,503,995 and the references cited therein.

The nucleic acid encoding any selected protein of the present invention can be any nucleic acid that functionally encodes that protein. For example, to functionally encode, *i.e.*, allow the nucleic acid to be expressed, the nucleic acid can include, for

example, exogenous or endogenous expression control sequences, such as an origin of replication, a promoter, an enhancer, and necessary information processing sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Preferred expression control sequences can be promoters derived from metallothionine genes, actin genes, immunoglobulin genes, CMV, SV40, adenovirus, bovine papilloma virus, etc. Expression control sequences can be selected for functionality in the cells in which the nucleic acid will be placed. A nucleic acid encoding a selected protein can readily be determined based upon the amino acid sequence of the selected protein, and, clearly, many nucleic acids will encode any selected protein.

The present invention additionally provides a nucleic acid that selectively hybridizes under stringent conditions with a nucleic acid set forth in SEQ LIST 1 or with a nucleic acid encoding the protein encoded by the gene comprising the nucleotide sequence set forth in any sequence listed in SEQ LIST 1. This hybridization can be specific. The degree of complementarity between the hybridizing nucleic acid and the sequence to which it hybridizes should be at least enough to exclude hybridization with a nucleic acid encoding an unrelated protein. Thus, a nucleic acid that selectively hybridizes with a nucleic acid of the present protein coding sequence will not selectively hybridize under stringent conditions with a nucleic acid for a different, unrelated protein, and vice versa. Typically, the stringency of hybridization to achieve selective hybridization involves hybridization in high ionic strength solution (6X SSC or 6X SSPE) at a temperature that is about 12-25°C below the T_m (the melting temperature at which half of the molecules dissociate from its partner) followed by washing at a combination of temperature and salt concentration chosen so that the washing temperature is about 5°C to 20°C below the T_m of the hybrid molecule. The temperature and salt conditions are readily determined empirically in preliminary experiments in which samples of reference DNA immobilized on filters are hybridized to a labeled nucleic acid of interest and then washed under conditions of different stringencies. Hybridization temperatures are typically higher for DNA-RNA and RNA-RNA hybridizations. The washing temperatures can be used as described above to achieve selective stringency, as is known in the art. (Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; Kunkel et al. *Methods Enzymol.* 1987:154:367, 1987). Nucleic acid fragments that selectively hybridize to any

given nucleic acid can be used, *e.g.*, as primers and or probes for further hybridization or for amplification methods (*e.g.*, polymerase chain reaction (PCR), ligase chain reaction (LCR)). A preferable stringent hybridization condition for a DNA:DNA hybridization can be at about 68°C (in aqueous solution) in 6X SSC or 6X SSPE followed by washing at 68°C.

The present invention additionally provides a polypeptide comprising the amino acid sequence encoded by the gene comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, and SEQ ID NO:127 (*i.e.*., SEQ LIST 1). Additionally, polypeptides comprising the amino acid sequence encoded by a nucleic acid that selectively hybridizes under stringent conditions with a nucleic acid in SEQ LIST 1 are provided. Further, polypeptides comprising the amino acid sequence encoded by a nucleic acid having a region within an exon wherein the region has at least 50, 60, 70, 80, 90, or 95% homology with a nucleic acid in SEQ LIST 1. These polypeptides can be readily obtained by any of several means. For example, the nucleotide sequence of coding regions of the gene can be translated and then the

corresponding polypeptide can be synthesized mechanically by standard methods. Additionally, the coding regions of the genes can be expressed or synthesized, an antibody specific for the resulting polypeptide can be raised by standard methods (see, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1988), and the protein can be isolated from other cellular proteins by selective hybridization with the antibody. This protein can be purified to the extent desired by standard methods of protein purification (see, *e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989). The amino acid sequence of any protein, polypeptide or peptide of this invention can be deduced from the nucleic acid sequence, or it can be determined by sequencing an isolated or recombinantly produced protein.

The terms "peptide," "polypeptide"and "protein" can be used interchangeably herein and refer to a polymer of amino acids and includes full-length proteins and fragments thereof. As used in the specification and in the claims, "a" can mean one or more, depending upon the context in which it is used. An amino acid residue is an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are preferably in the L isomeric form. However, residues in the D isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the polypeptide. Standard polypeptide nomenclature (described in *J. Biol. Chem.*, 243:3552-59 (1969) and adopted at 37 CFR § 1.822(b)) is used herein.

As will be appreciated by those skilled in the art, the invention also includes those polypeptides having slight variations in amino acid sequences or other properties. Amino acid substitutions can be selected by known parameters to be neutral (*see, e.g.,* Robinson WE Jr, and Mitchell WM., AIDS 4:S151-S162(1990)). Such variations may arise naturally as allelic variations (*e.g.,* due to genetic polymorphism) or may be produced by human intervention (*e.g.,* by mutagenesis of cloned DNA sequences), such as induced point, deletion, insertion and substitution mutants. Minor changes in amino acid sequence are generally preferred, such as conservative amino acid replacements, small internal deletions or insertions, and additions or deletions at the ends of the molecules. Substitutions may be designed based on, for example, the model of Dayhoff, *et al.* (in *Atlas of Protein Sequence and Structure 1978*, Nat'l Biomed. Res. Found., Washington,

D.C.). These modifications can result in changes in the amino acid sequence, provide silent mutations, modify a restriction site, or provide other specific mutations. Likewise, such amino acid changes result in a different nucleic acid encoding the polypeptides and proteins. Thus, alternative nucleic acids are also contemplated by such modifications.

The present invention also provides cells containing a nucleic acid of the invention. A cell containing a nucleic acid encoding a protein typically can replicate the DNA and, further, typically can express the encoded protein. The cell can be a prokaryotic cell, particularly for the purpose of producing quantities of the nucleic acid, or a eukaryotic cell, particularly a mammalian cell. The cell is preferably a mammalian cell for the purpose of expressing the encoded protein so that the resultant produced protein has mammalian protein processing modifications.

Nucleic acids of the present invention can be delivered into cells by any selected means, in particular depending upon the purpose of the delivery of the compound and the target cells. Many delivery means are well-known in the art. For example, electroporation, calcium phosphate precipitation, microinjection, cationic or anionic liposomes, and liposomes in combination with a nuclear localization signal peptide for delivery to the nucleus can be utilized, as is known in the art.

The present invention also contemplates that the mutated cellular genes necessary for viral growth, produced by the present method, as well as cells containing these mutants can also be useful. These mutated genes and cells containing them can be isolated and/or produced according to the methods herein described and using standard methods.

It should be recognized that the sequences set forth herein may contain minor sequencing errors. Such errors can be corrected, for example, by using the hybridization procedure described above with various probes derived from the described sequences such that the coding sequence can be reisolated and resequenced.

As described in the examples, the present invention provides the discovery of a "serum survival factor" present in serum that is necessary for the survival of persistently virally infected cells. Isolation and characterization of this factor have shown it to be a protein, to have a molecular weight of between about 50 kD and 100 kD, to resist inactivation in low pH (*e.g.*, pH2) and chloroform extraction, to be inactivated by boiling for about 5 minutes and in low ionic strength solution (*e.g.*, about 10 mM to about 50 mM). The present invention thus provides a purified mammalian serum protein having a

molecular weight of between about 50 kD and 100 kD which resists inactivation in low pH and resists inactivation by chloroform extraction, which inactivates when boiled and inactivates in low ionic strength solution, and which when removed from a cell culture comprising cells persistently infected with reovirus selectively substantially prevents survival of cells persistently infected with reovirus. The factor, fitting the physical characteristics described above, can readily be verified by adding it to non-serum-containing medium (which previously could not support survival of persistently virally infected cells) and determining whether this medium with the added putative factor can now support persistently virally infected cells, particularly cells persistently infected with reovirus. As used herein, a "purified" protein means the protein is at least of sufficient purity such that an approximate molecular weight can be determined.

The amino acid sequence of the protein can be elucidated by standard methods. For example, an antibody to the protein can be raised and used to screen an expression library to obtain nucleic acid sequence coding the protein. This nucleic acid sequence is then simply translated into the corresponding amino acid sequence. Alternatively, a portion of the protein can be directly sequenced by standard amino acid sequencing methods (amino-terminus sequencing). This amino acid sequence can then be used to generate an array of nucleic acid probes that encompasses all possible coding sequences for a portion of the amino acid sequence. The array of probes is used to screen a cDNA library to obtain the remainder of the coding sequence and thus ultimately the corresponding amino acid sequence.

The present invention also provides methods of detecting and isolating additional serum survival factors. For example, to determine if any known serum components are necessary for viral growth, the known components can be inhibited in, or eliminated from, the culture medium, and it can be observed whether viral growth is inhibited by determining if persistently infected cells do not survive. One can add the factor back (or remove the inhibition) and determine whether the factor allows for viral growth.

Additionally, other, unknown serum components can also be found to be essential for growth. Serum can be fractionated by various standard means, and fractions added to serum free medium to determine if a factor is present in a reaction that allows growth previously inhibited by the lack of serum. Fractions having this activity can then be further fractionated until the factor is relatively free of other components. The factor can then be characterized by standard methods, such as size fractionation, denaturation and/or

inactivation by various means, etc. Preferably, once the factor has been purified to a desired level of purity, it is added to cells in serum free medium to confirm that it bestows the function of allowing virus to grow when serum-free medium alone did not. This method can be repeated to confirm the requirement for the specific factor for any desired virus, since each serum factor found to be required by any one virus can also be required by many other viruses. In general, the closer the viruses are related and the more similar the infection modes of the viruses, the more likely that a factor required by one virus will be required by the other.

The present invention also provides methods of treating virus infections utilizing applicants' discoveries. The subject of any of the herein described methods can be any animal, preferably a mammal, such as a human, a veterinary animal, such as a cat, dog, horse, pig, goat, sheep, or cow, or a laboratory animal, such as a mouse, rat, rabbit, or guinea pig, depending upon the virus.

The present invention provides a method of reducing or inhibiting, and thereby treating, a viral infection in a subject, comprising administering to the subject an inhibiting amount of a composition that inhibits functioning of the serum protein described herein, *i.e.* the serum protein having a molecular weight of between about 50 kD and 100 kD which resists inactivation in low pH and resists inactivation by chloroform extraction, which inactivates when boiled and inactivates in low ionic strength solution, and which when removed from a cell culture comprising cells persistently infected with the virus prevents survival of at least some cells persistently infected with the virus, thereby treating the viral infection. The composition can comprise, for example, an antibody that specifically binds the serum protein, or an antisense RNA that binds an RNA encoded by a gene functionally encoding the serum protein.

Any virus capable of infecting the selected subject to be treated can be treated by the present methods. As described above, any serum protein or survival factor found by the present methods to be necessary for growth of cells infected with any one virus can be found to be necessary for growth of the cells infected with many other viruses. For any given cell-virus combination, the serum protein or factor can be confirmed to be required for growth by the methods described herein. The cellular genes identified by the examples using reovirus, a mammalian pathogen, and a rat cell system have general applicability to other virus infections that include all of the known as well as yet to be discovered human pathogens, including, but not limited to: human immunodeficiency

viruses (*e.g.*, HIV-1, HIV-2); parvovirus; papillomaviruses; hantaviruses; influenza viruses (*e.g.*, influenza A, B and C viruses); hepatitis viruses A to G; caliciviruses; astroviruses; rotaviruses; coronaviruses, such as human respiratory coronavirus; picornaviruses, such as human rhinovirus and enterovirus; ebola virus; human herpesvirus (*e.g.*, HSV-1-9); human adenovirus; hantaviruses; for animal, the animal counterpart to any above listed human virus, animal retroviruses, such as simian immunodeficiency virus, avian immunodeficiency virus, bovine immunodeficiency virus, feline immunodeficiency virus, equine infectious anemia virus, caprine arthritis encephalitis virus, arenaviruses, arvoviruses, tickborne virus or visna virus.

A protein inhibiting amount of the composition can be readily determined, such as by administering varying amounts to cells or to a subject and then adjusting the effective amount for inhibiting the protein according to the volume of blood or weight of the subject. Compositions that bind to the protein can be readily determined by running the putatively bound protein on a protein gel and observing an alteration in the protein's migration through the gel. Inhibition of the protein can be determined by any desired means such as adding the inhibitor to complete media used to maintain persistently infected cells and observing the cells' viability. The composition can comprise, for example, an antibody that specifically binds the serum protein. Specific binding by an antibody means that the antibody can be used to selectively remove the factor from serum or inhibit the factor's biological activity and can readily be determined by radio immune assay (RIA), bioassay, or enzyme-linked immunosorbant (ELISA) technology. The composition can comprise, for example, an antisense RNA that specifically binds an RNA encoded by the gene encoding the serum protein. Antisense RNAs can be synthesized and used by standard methods (*e.g.*, *Antisense RNA and DNA*, D. A. Melton, Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1988)).

The present methods provide a method of screening a compound for effectiveness in treating or preventing a viral infection, comprising administering the compound to a cell containing a cellular gene functionally encoding a gene product necessary for reproduction of the virus in the cell but not necessary for survival of the cell and detecting the level and/or activity (i.e. function) of the gene product produced, a decrease or elimination of the gene product and/or the gene product activity indicating a compound for treating or preventing the viral infection. The cellular gene can be, for example, a nucleic acid set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ

ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82; SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, or SEQ ID NO:127 (herein sometimes referred to as SEQ LIST 2, for brevity), any homolog thereof, or any other gene obtained using the methods provided herein for obtaining such genes. It is understood that the cellular gene can be present naturally in the cell being screened, or it can be introduced into the cell in a suitable expression vector, as are well known in the art. The level of the gene product can be measured by any standard means, such as by detection with an antibody specific for the protein. The level of gene product can be compared to the level of the gene product in a control cell not contacted with the compound. The level of gene product can be compared to the level of the gene product in the same cell prior to addition of the compound. Activity, or function, can be measured by any standard means, such as by enzymatic assays that measure the conversion of a substrate to a product or binding

assays that measure the binding of a protein to a nucleic acid, for example. Examples of gene products disclosed herein whose activity/function can be measured include tristetraprolin (human ZFP-36), 6-pyruvoyl-tetrahydropterin synthase, a eukaryotic DnaJ-like protein, ID3 (inhibitor of DNA binding 3), N-acetylglucos-aminyltransferase I (mGAT-1), cleavage stimulation factor (CSTF2), TAK1 binding protein, human zinc transcription factor ZPF207, Dlx2, Smad7 (Mad-related protein), and P-glycoprotein (mdr1b). The activity can be compared to the activity in a control cell not contacted with the compound or in the same cell prior to addition of the compound. Relatedly, the regulatory region of the gene can be functionally linked to a reporter gene and compounds can be screened for inhibition of the reporter gene. Such reporter constructs are described herein.

The present invention also provides a method of screening a compound for effectiveness in treating or preventing a viral infection comprising contacting the compound with the gene product of a cellular gene comprising a nucleic acid of SEQ LIST 2, or any homolog thereof, and detecting the function of the gene product, a decrease or elimination of the function indicating a compound effective for treating or preventing viral infection. Examples of gene products disclosed herein that can be utilized in this method include tristetraprolin (human ZFP-36), 6-pyruvoyl-tetrahydropterin synthase, a eukaryotic DnaJ-like protein, ID3 (inhibitor of DNA binding 3), N-acetylglucos-aminyltransferase I (mGAT-1), cleavage stimulation factor (CSTF2), TAK1 binding protein, human zinc transcription factor ZPF207, Dlx2, Smad7 (Mad-related protein), and P-glycoprotein (mdr1b).

The present invention provides a method of selectively eliminating cells persistently infected with a virus from an animal cell culture capable of surviving for a first period of time in the absence of serum, comprising propagating the cell culture in the absence of serum for a second time period during which a persistently infected cell cannot survive without serum, thereby selectively eliminating from the cell culture cells persistently infected with the virus. The second time period should be shorter than the first time period. Thus one can simply eliminate serum from a standard culture medium composition for a period of time (*e.g.* by removing serum containing medium from the culture container, rinsing the cells, and adding serum-free medium back to the container), then, after a time of serum starvation, return serum to the culture medium. Alternatively, one can inhibit a serum survival factor from the culture in place of the step of serum starvation. Furthermore, one can instead interfere with the virus-factor interaction. Such a

viral elimination method can periodically be performed for cultured cells to ensure that they remain virus-free. The time period of serum removal can greatly vary, with a typical range being about 1 to about 30 days; a preferable period can be about 3 to about 10 days, and a more preferable period can be about 5 days to about 7 days. This time period can be selected based upon ability of a specific cell to survive without serum as well as the life cycle of the target virus, *e.g.*, for reovirus, which has a life cycle of about 24 hours, 3 days' starvation of cells provides dramatic results.

Furthermore, the time period can be shortened by also passaging the cells during the starvation; in general, increasing the number of passages can decrease the time of serum starvation (or serum factor inhibition) needed to get full clearance of the virus from the culture. While passaging, the cells typically are exposed briefly to serum (typically for about 3 to about 24 hours). This exposure both stops the action of the trypsin used to dislodge the cells and stimulates the cells into another cycle of growth, thus aiding in this selection process. Thus a starvation/serum cycle can be repeated to optimize the selective effect. Other standard culture parameters, such as confluency of the cultures, pH, temperature, etc. can be varied to alter the needed time period of serum starvation (or serum survival factor inhibition). This time period can readily be determined for any given viral infection by simply removing the serum for various periods of time, then testing the cultures for the presence of the infected cells (*e.g.*, by ability to survive in the absence of serum and confirmed by quantitating virus in cells by standard virus titration and immunohistochemical techniques) at each tested time period, and then detecting at which time periods of serum deprivation the virally infected cells were eliminated. It is preferable that shorter time periods of serum deprivation that still provide elimination of the persistently infected cells be used. Furthermore, the cycle of starvation, then adding back serum and determining amount of virus remaining in the culture can be repeated until no virtually infected cells remain in the culture.

Thus, the present method can further comprise passaging the cells, *i.e.*, transferring the cell culture from a first container to a second container. Such transfer can facilitate the selective lack of survival of virally infected cells. Transfer can be repeated several times. Transfer is achieved by standard methods of tissue culture (*see, e.g.*, Freshney, *Culture of Animal Cells, A Manual of Basic Technique*, 2nd Ed. Alan R. Liss, Inc., New York, 1987).

The present method further provides a method of selectively eliminating from a cell culture cells persistently infected with a virus, comprising propagating the cell culture

in the absence of a functional form of the serum protein having a molecular weight of between about 50 kD and 100 kD which resists inactivation in low pH and resists inactivation by chloroform extraction, which inactivates when boiled and inactivates in low ionic strength solution, and which when removed from a cell culture comprising cells persistently infected with reovirus substantially prevents survival of cells persistently infected with reovirus. The absence of the functional form can be achieved by any of several standard means, such as by binding the protein to an antibody selective for it (binding the antibody in serum either before or after the serum is added to the cells; if before, the serum protein can be removed from the serum by, *e.g.*, binding the antibody to a column and passing the serum over the column and then administering the survival protein-free serum to the cells), by administering a compound that inactivates the protein, or by administering a compound that interferes with the interaction between the virus and the protein.

Thus, the present invention provides a method of selectively eliminating from a cell culture propagated in serum-containing medium cells persistently infected with a virus, comprising inhibiting in the serum the protein having a molecular weight of between about 50 kD and 100 kD which resists inactivation in low pH and resists inactivation by chloroform extraction, which inactivates when boiled and inactivates in low ionic strength solution, and which when removed from a cell culture comprising cells persistently infected with reovirus substantially prevents survival of cells persistently infected with reovirus. Alternatively, the interaction between the virus and the serum protein can be disrupted to selectively eliminate cells persistently infected with the virus.

Any virus capable of some form of persistent infection may be eliminated from a cell culture utilizing the present elimination methods, including removing, inhibiting or otherwise interfering with a serum protein, such as the one exemplified herein, and also including removing, inhibiting or otherwise interfering with a gene product from any cellular gene found by the present method to be necessary for viral growth yet nonessential to the cell. For example, DNA viruses or RNA viruses can be targeted. One can readily determine whether cells infected with a selected virus can be selectively removed from a culture through removal of serum by starving cells permissive to the virus of serum (or inhibiting the serum survival factor), adding the selected virus to the cells, adding serum to the culture, and observing whether infected cells die (*i.e.*, by titering levels of virus in the surviving cells with an antibody specific for the virus).

A culture of any animal cell (*i.e.*, any cell that is typically grown and maintained in culture in serum) that can be maintained for a period of time in the absence of serum, can be purified from viral infection utilizing the present method. For example, primary cultures as well as established cultures and cell lines can be used. Furthermore, cultures of cells from any animal and any tissue or cell type within that animal that can be cultured and that can be maintained for a period of time in the absence of serum can be used. For example, cultures of cells from tissues typically infected, and particularly persistently infected, by an infectious virus could be used.

As used in the claims "in the absence of serum" means at a level at which persistently virally infected cells do not survive. Typically, the threshold level is about 1% serum in the media. Therefore, about 1% serum or less can be used, such as about 1%, 0.75%, 0.50%. 0.25% 0.1% or no serum can be used.

As used herein, "selectively eliminating" cells persistently infected with a virus means that substantially all of the cells persistently infected with the virus are killed such that the presence of virally infected cells cannot be detected in the culture immediately after the elimination procedure has been performed. Furthermore, "selectively eliminating" includes that cells not infected with the virus are generally not killed by the method. Some surviving cells may still produce virus but at a lower level, and some may be defective in pathways that lead to death by the virus. Typically, for cells persistently infected with virus to be substantially all killed, more than about 90% of the cells, and more preferably more than about 95%, 98%, 99%, or 99.99% of virus-containing cells in the culture are killed.

The present method also provides a nucleic acid comprising the regulatory region of any of the genes. Such regulatory regions can be isolated from the genomic sequences isolated and sequenced as described above and identified by any characteristics observed that are characteristic for regulatory regions of the species and by their relation to the start codon for the coding region of the gene. The present invention also provides a construct comprising the regulatory region functionally linked to a reporter gene. Such constructs are made by routine subcloning methods, and many vectors are available into which regulatory regions can be subcloned upstream of a marker gene. Marker genes can be chosen for ease of detection of marker gene product.

The present method therefore also provides a method of screening a compound for treating a viral infection, comprising administering the compound to a cell containing any

of the above-described constructs, comprising a regulatory region of one of the genes comprising any of the nucleotide sequences set forth in SEQ LIST 2, or any homologs thereof, whose inhibition or reduction in expression causes inhibition of viral replication wherein the region is functionally linked to a reporter gene, and detecting the level of the reporter gene product produced, a decrease or elimination of the reporter gene product indicating a compound for treating the viral infection. Compounds detected by this method would inhibit transcription of the gene from which the regulatory region was isolated, and thus, in treating a subject, would inhibit the production of the gene product produced by the gene, and thus treat the viral infection.

Some genes when disrupted by the present method of retrovirus insertion, resulted in over expression of the gene product, and this overexpression inhibited viral replication. Thus the present invention provides a method of screening a compound for effectiveness in treating a viral infection, comprising administering the compound to a cell containing a cellular gene functionally encoding a gene product whose overexpression inhibits reproduction of the virus but does not prevent survival of the cell and detecting the level of the gene product produced, an increase in the gene product indicating a compound effective for treating the viral infection. Typically, an increase will be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 300%, 400%, 500% or higher increase over gene product produced when the compound is not present.

The present invention additionally provides a method of reducing or inhibiting a viral infection in a subject, comprising administering to the subject an amount of a composition that inhibits expression or functioning of a gene product encoded by a gene comprising the nucleic acid set forth in any of SEQ LIST 2, or a homolog thereof, thereby treating the viral infection. Reducing or inhibiting viral infection naturally can include both the initial infection of the subject and the infection of uninfected cells within an already infected subject, e.g. inhibiting viral replication in cells of the subject. The composition can comprise, for example, an antibody that binds a protein encoded by the gene. The composition can also comprise an antibody that binds a receptor for a protein encoded by the gene. Such an antibody can be raised against the selected protein by standard methods as set forth above, and can be either polyclonal or monoclonal, though monoclonal is preferred. Alternatively, the composition can comprise an antisense RNA that binds an RNA encoded by the gene, as described above. Examples of antisense RNA useful therapeutically include the fragments of the nucleic acids described above.

Furthermore, the composition can comprise a nucleic acid functionally encoding an antisense RNA that binds an RNA encoded by the gene. Other useful compositions will be readily apparent to the skilled artisan.

The present invention also provides a method of treating a viral infection in a subject comprising administering to the subject a treatment effective amount of a composition that increases expression of a gene whose over expression reduces or inhibits viral replication. Typically, an increase will be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 300%, 400%, 500% or higher increase over gene product produced when the composition is not present.

The present invention further provides a method of reducing or inhibiting a viral infection in a subject comprising mutating *ex vivo* in a selected cell, for example from the subject or from an allogenic source, an endogenous gene comprising a nucleic acid set forth in SEQ LIST 2 whose inhibition or reduction in expression causes inhibition of viral replication, or a homolog thereof, to a gene form incapable of producing a functional gene product of the gene or a gene form producing a reduced amount of a functional gene product of the gene, and placing (or replacing, in the case of the subject's own cells) the cell in the subject, thereby reducing viral infection of cells in the subject. The cell can be selected according to the typical target cell of the specific virus whose infection is to be reduced, prevented or inhibited. A preferred cell for several viruses is a hematopoietic cell. When the selected cell is a hematopoietic cell, viruses which can be reduced or inhibited from infection can include, for example, HIV, including HIV-1 and HIV-2. However, many other virus-cell combinations will be apparent to the skilled artisan.

The invention also includes a method of reducing or inhibiting viral infection in a subject comprising mutating *ex vivo* in a selected cell, for example from a subject or an allogenic source, an endogenous gene comprising a nucleic acid set forth in SEQ LIST 2 whose overexpression causes inhibition of viral replication, or a homolog thereof, to a gene form that expresses the gene at a higher level than the endogenous gene, and placing or replacing the cell in the subject. Typically, a higher level can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 300%, 400%, 500% or higher than the non-mutated, endogenous gene. The cell can be selected according to the typical target cell of the specific virus whose infection is to be reduced, prevented or inhibited. A preferred cell for several viruses is a hematopoietic cell. When the selected cell is a hematopoietic cell, viruses which can be reduced or inhibited from infection can

include, for example, HIV, including HIV-1 and HIV-2. However, many other virus-cell combinations will be apparent to the skilled artisan.

The present invention additionally provides a method of increasing viral infection resistance in a subject comprising mutating *ex vivo* in a selected cell, for example from the subject or from an allogenic source, an endogenous gene comprising a nucleic acid set forth in SEQ LIST 2, whose inhibition or reduction in expression increases viral infection resistance, said endogenous gene being mutated to a mutated gene form incapable of producing a functional gene product of the gene or a gene form producing a reduced amount of a functional gene product of the gene, and placing the cell in the subject, thereby increasing viral infection resistance of cells in the subject. The virus can be HIV, particularly when the cell is a hematopoietic cell. However, many other virus-cell combinations will be apparent to the skilled artisan.

Furthermore, the present invention provides a method for isolation of cellular genes utilized in tumor progression. The present invention provides a method of identifying a cellular gene that can suppress a malignant phenotype in a cell, comprising (a) transferring into a cell culture incapable of growing well in soft agar or Matrigel a vector encoding a selective marker gene lacking a functional promoter, (b) selecting cells expressing the marker gene, and (c) isolating from selected cells which are capable of growing in soft agar or Matrigel a cellular gene within which the marker gene is inserted, thereby identifying a gene that can suppress a malignant phenotype in a cell. This method can be performed using any selected non-transformed cell line, of which many are known in the art.

The present invention additionally provides a method of identifying a cellular gene that can suppress a malignant phenotype in a cell, comprising (a) transferring into a cell culture of non-transformed cells a vector encoding a selective marker gene lacking a functional promoter, (b) selecting cells expressing the marker gene, and (c) isolating from selected and transformed cells a cellular gene within which the marker gene is inserted, thereby identifying a gene that can suppress a malignant phenotype in a cell. A non-transformed phenotype can be determined by any of several standard methods in the art, such as the exemplified inability to grow in soft agar, or inability to grow in Matrigel.

The present invention further provides a method of screening for a compound for suppressing a malignant phenotype in a cell comprising administering the compound to a cell containing a cellular gene functionally encoding a gene product involved in

establishment of a malignant phenotype in the cell and detecting the level of the gene product produced, a decrease, inhibition or elimination of the gene product indicating a compound effective for suppressing the malignant phenotype. Detection of the level, or amount, of gene product produced can be measured, directly or indirectly, by any of several methods standard in the art (*e.g.*, protein gel, antibody-based assay, detecting labeled RNA) for assaying protein levels or amounts, and selected based upon the specific gene product.

The present invention also provides a method of screening for a compound for suppressing a malignant phenotype in a cell comprising administering the compound to a cell containing a cellular gene functionally encoding a gene product whose overexpression is involved in suppressing a malignant phenotype in the cell and detecting the level of the gene product produced, an increase in the gene product indicating a compound effective for suppressing the malignant phenotype.

The present invention further provides a method of suppressing a malignant phenotype in a cell in a subject, comprising administering to the subject an amount of a composition that inhibits expression or functioning of a gene product encoded by a gene comprising the nucleic acid set forth in SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:36 or SEQ ID NO:94, or a homolog thereof, or any gene whose overexpression is found by the present method to be involved in suppressing a malignant phenotype in the cell (e.g., any clone designated herein with an "x") thereby suppressing a malignant phenotype. The composition can, for example, comprise an antibody that binds a protein encoded by the gene. The composition can, as another example, comprise an antibody that binds a receptor for a protein encoded by the gene. The composition can comprise an antisense RNA that binds an RNA encoded by the gene. Further, the composition can comprise a nucleic acid functionally encoding an antisense RNA that binds an RNA encoded by the gene.

The present invention further provides a method of suppressing a malignant phenotype in a cell in a subject, comprising administering to the subject an amount of a composition that increases expression of a gene product whose overexpression is involved in suppressing a malignant phenotype in the cell. The gene product can be the product of a gene wherein disruption of an upstream gene by the present vector resulted in overexpression of the downstream gene, and the overexpression of the downstream gene

demonstrated a transformed phenotype. The composition can be, for example, an inhibitor, such as a small molecule inhibitor, of the COX 2 enzyme.

Diagnostic or therapeutic agents of the present invention can be administered to a subject or an animal model by any of many standard means for administering therapeutics or diagnostics to that selected site or standard for administering that type of functional entity. For example, an agent can be administered orally, parenterally (e.g., intravenously), by intramuscular injection, by intraperitoneal injection, topically, transdermally, or the like. Agents can be administered, *e.g.*, as a complex with cationic liposomes, or encapsulated in anionic liposomes. Compositions can include various amounts of the selected agent in combination with a pharmaceutically acceptable carrier and, in addition, if desired, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc. Parental administration, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Depending upon the mode of administration, the agent can be optimized to avoid degradation in the subject, such as by encapsulation, etc.

Dosages will depend upon the mode of administration, the disease or condition to be treated, and the individual subject's condition, but will be that dosage typical for and used in administration of antiviral or anticancer agents. Dosages will also depend upon the composition being administered, *e.g.*, a protein or a nucleic acid. Such dosages are known in the art. Furthermore, the dosage can be adjusted according to the typical dosage for the specific disease or condition to be treated. Furthermore, viral titers in culture cells of the target cell type can be used to optimize the dosage for the target cells *in vivo*, and transformation from varying dosages achieved in culture cells of the same type as the target cell type can be monitored. Often a single dose can be sufficient; however, the dose can be repeated if desirable. The dosage should not be so large as to cause adverse side effects. Generally, the dosage will vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art. The dosage can also be adjusted by the individual physician in the event of any complication.

For administration to a cell in a subject, the composition, once in the subject, will of course adjust to the subject's body temperature. For *ex vivo* administration, the composition can be administered by any standard methods that would maintain viability of the cells, such as by adding it to culture medium (appropriate for the target cells) and

adding this medium directly to the cells. As is known in the art, any medium used in this method can be aqueous and non-toxic so as not to render the cells non-viable. In addition, it can contain standard nutrients for maintaining viability of cells, if desired. For *in vivo* administration, the complex can be added to, for example, a blood sample or a tissue sample from the patient, or to a pharmaceutically acceptable carrier, e.g., saline and buffered saline, and administered by any of several means known in the art. Examples of administration include parenteral administration, e.g., by intravenous injection including regional perfusion through a blood vessel supplying the tissues(s) or organ(s) having the target cell(s), or by inhalation of an aerosol, subcutaneous or intramuscular injection, topical administration such as to skin wounds and lesions, direct transfection into, e.g., bone marrow cells prepared for transplantation and subsequent transplantation into the subject, and direct transfection into an organ that is subsequently transplanted into the subject. Further administration methods include oral administration, particularly when the composition is encapsulated, or rectal administration, particularly when the composition is in suppository form. A pharmaceutically acceptable carrier includes any material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected complex without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

Specifically, if a particular cell type *in vivo* is to be targeted, for example, by regional perfusion of an organ or tumor, cells from the target tissue can be biopsied and optimal dosages for import of the complex into that tissue can be determined *in vitro*, as described herein and as known in the art, to optimize the *in vivo* dosage, including concentration and time length. Alternatively, cultured cells of the same cell type can also be used to optimize the dosage for the target cells *in vivo*.

For either *ex vivo* or *in vivo* use, the complex can be administered at any effective concentration. An effective concentration is that amount that results in reduction, inhibition or prevention of the viral infection or in reduction or inhibition of the transformed phenotype of the cells.

A nucleic acid can be administered in any of several means, which can be selected according to the vector utilized, the organ or tissue, if any, to be targeted, and the characteristics of the subject. The nucleic acids, if desired in a pharmaceutically acceptable carrier such as physiological saline, can be administered systemically, such as

intravenously, intraarterially, orally, parenterally, subcutaneously. The nucleic acids can also be administered by direct injection into an organ or by injection into the blood vessel supplying a target tissue. For an infection of cells of the lungs or trachea, it can be administered intratracheally. The nucleic acids can additionally be administered topically, transdermally, etc.

The nucleic acid or protein can be administered in a composition. For example, the composition can comprise other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc. Furthermore, the composition can comprise, in addition to the vector, lipids such as liposomes, such as cationic liposomes (e.g., DOTMA, DOPE, DC-cholesterol) or anionic liposomes. Liposomes can further comprise proteins to facilitate targeting a particular cell, if desired. Administration of a composition comprising a vector and a cationic liposome can be administered to the blood afferent to a target organ or inhaled into the respiratory tract to target cells of the respiratory tract. Regarding liposomes, see, e.g., Brigham et al. *Am. J. Resp. Cell. Mol. Biol.* 1:95-100 (1989); Felgner et al. *Proc. Natl. Acad. Sci USA* 84:7413-7417 (1987); U.S. Pat. No.4,897,355.

For a viral vector comprising a nucleic acid, the composition can comprise a pharmaceutically acceptable carrier such as phosphate buffered saline or saline. The viral vector can be selected according to the target cell, as known in the art. For example, adenoviral vectors, in particular replication-deficient adenoviral vectors, can be utilized to target any of a number of cells, because of its broad host range. Many other viral vectors are available, and their target cells are known.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

EXAMPLES

Selective elimination of virally infected cells from a cell culture

Rat intestinal cell line-1 cells (RIE-1 cells) were standardly grown in Dulbecco's modified Eagle's medium, high glucose, supplemented with 10% fetal bovine serum. To

begin the experiment, cells persistently infected with reovirus were grown to near confluence, then serum was removed from the growth medium by removing the medium, washing the cells in PBS, and returning to the flask medium not supplemented with serum. Typically, the serum content was reduced to 1% or less. The cells are starved for serum for several days, or as long as about a month, to bring them to quiescence or growth arrest. Media containing 10% serum is then added to the quiescent cells to stimulate growth of the cells. Surviving cells are found to not be persistently infected cells by immunohistochemical techniques used to establish whether cells contain any infectious virus (sensitivity to 1 infectious virus per ml of homogenized cells).

Cellular Genomic DNA Isolation

Gene Trap Libraries: The libraries are generated by infecting the RIE-1 cells with a retrovirus vector (U3 gene-trap) at a ratio of less than one retrovirus for every ten cells. When a U3 gene trap retrovirus integrates within an actively transcribed gene, the neomycin resistance gene that the U3 gene trap retrovirus encodes is also transcribed, thus conferring resistance to the cell to the antibiotic neomycin. Cells with gene trap events are able to survive exposure to neomycin while cells without a gene trap event die. The various cells that survive neomycin selection are then propagated as a library of gene trap events. Such libraries can be generated with any retrovirus vector that has the properties of expressing a reporter gene from a transcriptionally active cellular promoter that tags the gene for later identification.

Reovirus selection: Reovirus infection is typically lethal to RIE-1 cells but can result in the development of persistently infected cells. These cells continue to grow while producing infective reovirus particles. For the identification of gene trap events that confer reovirus resistance to cells, the persistently infected cells must be eliminated or they will be scored as false positives. We have found that RIE-1 cells persistently infected with reovirus are very poorly tolerant to serum starvation, passaging and plating at low density. Thus, we have developed protocols for the screening of the RIE-1 gene trap libraries that select against both reovirus sensitive cells and cells that are persistently infected with reovirus.

1. RIE-1 library cells are grown to near confluence and then the serum is removed from the media. The cells are starved for serum for several days to bring them to quiescent or growth arrest.

2. The library cells are infected with reovirus at a titer of greater than ten reovirus per cell and the serum starvation is continued for several more days.
3. The infected cells are passaged, (a process in which they are exposed to serum for three to six hours) and then starved for serum for several more days.
4. The surviving cells are then allowed to grow in the presence of serum until visible colonies develop at which point they are cloned by limiting dilution.

MEDIA: DULBECCO'S MODIFIED EAGLE'S MEDIUM, HIGH GLUCOSE (DME/HIGH) Hyclone Laboratories cat. no. SH30003.02.

NEOMYCIN: The antibiotic used to select against the cells that did not have a U3 gene trap retrovirus, e.g. GENETICIN, from Sigma. [cat. no. G9516].

RAT INTESTINAL CELL LINE-1 CELLS (RIE-1 CELLS): These cells are from the laboratory of Dr. Ray Dubois (VAMC). They are typically cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal calf serum.

REOVIRUS: Laboratory strains of either serotype 1 or serotype 3 are used. They were originally obtained from the laboratories of Bernard N. Fields (deceased). These viruses have been described in detail.

RETROVIRUS: The U3 gene trap retrovirus used here were developed by Dr. Earl Ruley (VAMC) and the libraries were produced using a general protocol suggested by him.

SERUM: FETAL BOVINE SERUM Hyclone Laboratories cat. no. A-1115-L.

Identification Tags for Isolated Nucleic Acids

Genomic sequences, tagged with a vector, such as the U3 gene trap vector, are given a number corresponding to the genomic library of mutant cells from which the sequence was isolated., and a letter indicating a unique member of the library. More than one sequence with the same number and letter indicates multiple, unique sequences obtained from the genome surrounding the vector insert that "tagged" the gene. Such genomic sequences are obtained using vector-based primers, from which sequencing occurs 3' to 5' or 5' to 3'. In the former case, to recover the orientation of the gene into which the vector inserted, the sequence derived from the vector primer must be reversed and complemented. Such reverse complement sequences are designated "rE". In the case of genome sequencing from a primer that occurs 5' to 3' (i.e. the primer is at the 3' end of the vector), no changes are needed, since the derived sequence is the sequence as it appears

in the gene disrupted. Such sequences are designated "B4". Homologies indicated below each genomic sequence are in the positive direction, unless explicitly noted to be on the negative strand. As an example, SEQ ID NO. 27 comprises a nucleic acid sequence encoding a novel polypeptide on the positive strand, while the negative strand encodes ferritin.

SEQ ID NO:	Lab Designation
1	32-3-2#1E/-rE
2	L191B2E#1-RE
3	L191B2E#3+-rE
4	21-5-9E-RE

homology to: emb/AL021154/HS15005 human DNA sequence

5	14A14E-rE
6	4cx-b4
7	5a-b4
8	6BSA12-B4
9	X7B/B4
10	x27b4f_1
11	12C#A-rE
12	10-3b(5/2/96)/-rE
13	10_4B_4-rE
14	6BE60-rE

homology to: alpha-trophomyosin

15	19D3E-rE
16	L19D16E-rE
17	2b_rE
18	14_24_#6-rE
19	7A7'-rE

homology to: annexin II/dynein I

20	L12cx#6-rE

homology to: gb:X51760 human zinc finger protein ZFP-36

21	L12cx#11-rE

22 19D5E-rE
homology to: 6-pyruvoyl-tetrahydropterin synthase (gb/M77850/RAT6PTHS)

23 12_3b#7-rE

24 12_3B#8-RE
homology to: gb/AA871174/vq32a08.r1 Barskad bowel MPLRBg Mus musculus cDNA clone 10959265'

25 9B27-2-E
homology to: RAT LOCUS RNU53922 04-MAY-1996; Rattus norvegicus DnaJ-like protein (RDJ1) mRNA, complete Cds, ACCESSION U53922 (on negative strand)

26 x15-rE

27 X11-rE
homology to: ferritin H (on the negative strand)

28 X20-rE
homology to: LOCUS RATGL5A Rat NICER element (GL5-14)5' long terminal repeat, Acc.No. M59028 M33535N1D

29 X4-rE

30 14A7E-rE
homology to: MMSMAD7 3681 bp mRNA ROD 31-JUL-1998 DEFINITION Mus musculus mRNA for Mad-related protein Smad7 ,149 bases

31 14A13E-rE

32 14_7#2E-rE

homology to: N-acetylglucosaminyltransferase I

33 12CX#6-rE
homology to: gb|AA522204|AA522204 vf98g09_r1 Soares mouse mammary gland NbMMG Mus musculus cDNA clone 851872; also 5' similar to gb X51760 zinc finger protein ZFP-36 (HUMAN), gb L20450 Mus musculus DNA-binding protein mRNA, complete cds (MOUSE); Length = 442, 925 bases (shares homology with SEQ ID NO:20)

34 12C_2B#9E-rE

35 12CX#11E-rE

36 x5-rE

37 8C5_11-rE

38 191E2E-rE

39 19_7AE-rE

40 19_9BE-rE
homology to: LOCUS HS347M6 56583 bp DNA PRI 14-JAN-1998 Human DNA sequence from PAC 347M6 on chromosome Xq22, CSTF2 (Cleavage Stimulation Factor, CF-1, Polyadenylation Factor) 64 kD subunit gene

41 191E9E-rE

42 191E8E-rE

43 14C_2E/-rE
homology to: gb/H31084/EST104778 Rattus sp. cDNA - 5' end similar to signal recognition particle subunit(19kDa) (on negative strand)

44 14H1E-rE

45 14G3E-rE

46 14G_2E-rE

47 6_3_6_2E/-rE
homology to: Rattus norvegicus cis-golgi gp130 (on negative strand); and a HUMAN EST (on positive strand) AI127398; qb70g11.x1 Soares fetal heart NbHH19W Homo sapiens cDNA clone (1705508 3' mRNA sequence)

48 14H4E/-rE

49 18A_8_4E-rE

50 18A_8_1E-rE

51 SCB2_19E-rE

52 L197B3E-rE

53 L195C5E-rE
homology to: H. pylori and C.jeuni

54 21_5_7E-rE
homology to: id3 gene; emb|AL021154|HS150O5 Human DNA sequence from clone 150O5; HTGS phase 1 [Homo sapiens]; containing the E2F2 gene for transcription factor E2F-2 and the ID3 gene for Inhibitor of DNA binding 3 (dominant negative helix-loop-helix protein), 1R2, Length = 133667, 971 bases

55 L195B1E-rE
homology to: vK72b07.s1 Knowles Solter mouse 2 cell Mus musculus cDNA clone 960181 5'

56 L194c4E-rE

57 L193A1E#A-rE

58 L192A3E-rE

59 L1739E-rE

60 L192B3E#13-rE
contains sequence identical to: insulin growth factorII/mannose-6-phosphate receptor

61 3 2 4 rE
located in the same region of the genome as calcyclin, but the gene is "read" in the opposite direction

62 36 7 1 a-rE

63 36 5 1 4 a-rE

64 34 25 5a-rE
rat satellite DNA (RATRSSID 93 bp, ROD 12-MAR-1984)

65 34 24-126/rE
homology to:
HSU49928 (3096 bp mRNA) PRI 06-APR-1998, Homo sapiens TAK1 binding protein (TAB1) mRNA, complete cds, ACCESSION U49928 NID g1401125, and
HS333H23 (142274 bp DNA) HTG 17-JUL-1998 Human DNA sequence

66 34 23-1/rE

67 36 5 2-6/rE

68 36 5 2-196/rE

69 34 23-3/rE
homology to: gb|L16546|RATAP1X Rat P-glycoprotein (mdr1b) gene

70 34 25 23-rE

71 36 5 2-196/rE

72 31 3 9/rE
homology to: AA798638 568 bp mRNA EST 10-FEB-1998, vw34b06.r1 Soares mouse mammary gland NbMMG Mus musculus cDNA clone1245683 5, mRNA sequence, 824 bases.

73 31 3 6-2-rE

74 31 3 17-rE

75 31 3 5-rE
homology to: AF046001 2347 bp mRNA PRI 19-FEB-1998, Homo sapiens zinc finger transcription factor (ZNF207) mRNA, complete Cds, 833 bases.

76 31 3 15#1/rE

77 24 3 5#1/rE

78 31 4 4#1/rE

79 31 3 19#2/rE

80 31 4 5#1/rE

81 24 9 3#2/rE

82 L24_26_1-BL

homology to: AI045472 396 bp mRNA EST 06-JUL-1998, UI-R-C1-jz-h-09-0-UI.s2 UI-R-C1 Rattus norvegicus cDNA cloneUI-R-C1-jz-h-09-0-UI 3', mRNA sequence.

83 L24_26_1-B4

84 L22_5A1/rE

85 L24_3_2B/rE

86 L24 4-2/rE

87 L24 5-2/rE

88 L24 5-3/rE

89 (15-)L28AP/rE

90 L24 26-10/rE

homology to: LOCUS R06687 403 bp mRNA EST 03-APR-1995; yf10a10.r1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone 126426 5'

91 L24 26-2A/rE

92 L24 26-2B/rE

homology to: gb|AA590026|AA590026 vm22g03.r1 Knowles Solter mouse blastocyst B1 Mus musculus cDNA clone 990964 , 459 bases, 139A; and Rattus norvegicus Eker rat-associated intracisternal-A particle element

93 14 7#2E-rE

homology to: N-acetylglucosaminyltransferase I; this sequence shares homology with SEQ ID NO:32.

94 x18

95 31_3_9-rE

96 31_3_6_2-rE

97 31_3_17-rE

98 31_3_15#1-rE

99 24_3_5#1-rE

100 31_4_4#1-rE

101 31_3_19#2-rE

102 31_4_5#1-rE

103 24_9_3#2-rE

104 14XD#12E-rE

105 70A-rE

106 31-3-4-rE

107 3_6_9-NeoG-rE

108 31_4_2-rE

109 3_2_13-rE
homology to: calcyclin

110 3_2_4-E
homology to: pistlre-alpha 1 (with homology to calcyclin on negative strand)

111 L25-10/-rE
homology to: calcyclin

112 L24-4-3/-rE

113 L24-9-1-rE
rat id sequence

114 17-L25-27#7-rE
homology to: calcyclin

115 L21C1E-rE
homology to: calcyclin

116 L24-5-3BE-rE.
homology to:
LOCUS H32572 310 bp mRNA EST 08-SEP-1995 EST107805 Rat PC-12 cells, untreated Rattus sp cDNA 5' end, ACCESSION H32572, and
LOCUS AA858747 470 bp mRNA EST 10-MAR-1998 UI-R-A0-bb-e-01-0-UI.s1 UI-R-A0 Rattus norvegicus cDNA clone UI-R-A0-bb-e-01-0-UI, 3' similar to gb|AA473081|AA473081 vd44b07-r1 Barstead MPLRB1 Mus musculus cDNA clone 803413 5' mRNA sequence

117 L24-4-2BE-rE
homology to: LOCUS MMU51002 6495 bp DNA ROD 16-JAN-1997 Mus musculus Dlx-2 gene, complete cds, ACCESSION U51002 NID g1477589

118 17-3-3B-B4

119 L24-26-3/-rE
homology to: RNU23776, DNA ROD 10-AUG-1995, Rattus norvegicus Eker rat-associated intracisternal-A particle element

120 12_2B#2-rE

121 05-17-3-3He-1-T7

122 21_5_8E-rE
homology to: emb|AL021154|HS150O5 Human DNA sequence from clone 150O5; 1p36_13-36_22, contains the E2F2 gene for transcription factor E2F-2 and the ID3 gene for Inhibitor of DNA binding 3(dominant negative helix-loop-helix protein, 1R2, Length = 133667, 971 bases

123 X18H-t7

124	18A_8_4E-rE
125	L24-5-2BE-rE
126	L24-4-2AE-rE
127	L24-10-1BE-rE

Genes Necessary for Viral Infection

Some of the isolated sequences dislcosed here comprise sequence encoding the following proteins: tristetraprolin (human ZFP-36), 6-pyruvoyltetrahydropterin synthase, a eukaryotic DnaJ-like protein, ID3 (inhibitor of DNA binding 3), N-acetylglucosaminyltransferase I (mGAT-1), cleavage stimulation factor (CSTF2), TAK1 binding protein, human zinc transcription factor ZPF207, Dlx2, Smad7 (Mad-related protein), and P-glycoprotein (mdr1b).

Isolation of cellular genes that suppress a malignant phenotype

We have utilized a gene-trap method of selecting cell lines that have a transformed phenotype (are potentially tumor cells) from a population of cells (RIE-1 parentals) that are not transformed. The parental cell line, RIE-1 cells, does not have the capacity to grow in soft agar or to produce tumors in mice. Following gene-trapping, cells were screened for their capacity to grow in soft agar. These cells were cloned and genomic sequences were obtained 5' or 3' of the retrovirus vector, i.e. SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:36 or SEQ ID NO:94; sequences designated with an "x" in the clone name). All of the cell lines behave as if they are tumor cell lines, as they also induce tumors in mice.

Of the cell lines, two are associated with the enhanced expression of the prostaglandin synthetase gene II or COX 2. It has been shown that disruption of gene function by retroviral targeting of an upstream gene has lead to increased expression of a downstream gene product, COX 2. When a small molecule inhibitor of COX 2 enzyme was added, reversion of the transformed phenotype occurred. The COX 2 gene has been found to be increased in pre-malignant adenomas in humans and overexpressed in human colon cancer. Inhibitors of COX 2 expression also arrests the growth of the tumor. One of the cell lines, x18 (SEQ ID NO:94), has disrupted a gene that is now represented in the EST (dbest) database, but the gene is not known (not present in GenBank).

Each of the genes from which the provided nucleotide sequences is isolated (and all clones designated with an "x") represents a tumor suppressor gene. The mechanism by which the disrupted genes may suppress a transformed phenotype is at present unknown. However, each one represents a tumor suppressor gene that is potentially unique, as none of the genomic sequences correspond to a known gene. The capacity to select quickly tumor suppressor genes may provide unique targets in the process of treating or preventing (potential for diagnostic testing) cancer.

Isolation of entire genomic genes

An isolated nucleic acid of this invention (whose sequence is set forth in any of SEQ ID NO:1 through SEQ ID NO:127), or a smaller fragment thereof, is labeled by a detectable label and utilized as a probe to screen a rat genomic library (lambda phage or yeast artificial chromosome vector library) under high stringency conditions, *i.e.*, high salt and high temperatures to create hybridization and wash temperature 5-20°C. Clones are isolated and sequenced by standard Sanger dideoxynucleotide sequencing methods. Once the entire sequence of the new clone is determined, it is aligned with the probe sequence and its orientation relative to the probe sequence determined. A second and third probe is designed using sequences from either end of the combined genomic sequence, respectively. These probes are used to screen the library, isolate new clones, which are sequenced. These sequences are aligned with the previously obtained sequences and new probes designed corresponding to sequences at either end and the entire process repeated until the entire gene is isolated and mapped. When one end of the sequence cannot isolate any new clone, a new library can be screened. The complete sequence includes regulatory regions at the 5' end and a polyadenylation signal at the 3' end.

Isolation of cDNAs

An isolated nucleic acid (whose sequence is set forth in any of SEQ ID NO:1 through SEQ ID NO:127), or a smaller fragment thereof, or additional fragments obtained from the genomic library, that contain open reading frames, is labeled by a detectable label and utilized as a probe to screen a portions of the present fragments, to screen a cDNA library. A rat cDNA library obtains rat cDNA; a human cDNA library obtains a human cDNA. Repeated screens can be utilized as described above to obtain the complete coding sequence of the gene

from several clones if necessary. The isolates can then be sequenced to determine the nucleotide sequence by standard means such as dideoxynucleotide sequencing methods.

Serum survival factor isolation and characterization

The lack of tolerance to serum starvation is due to the acquired dependence of the persistently infected cells for a serum factor (survival factor) that is present in serum. The serum survival factor for persistently infected cells has a molecular weight between 50 and 100 kD and resists inactivation in low pH (pH2) and chloroform extraction. It is inactivated by boiling for 5 minutes [once fractionated from whole serum (50 to 100 kD fraction)], and in low ionic strength solution [10 to 50 mM].

The factor was isolated from serum by size fraction using centriprep molecular cut-off filters with excluding sizes of 30 and 100 kd (Millipore and Amnicon), and dialysis tubing with a molecular exclusion of 50 kd. Polyacrylamide gel electrophoresis and silver staining was used to determine that all of the resulting material was between 50 and 100 kd, confirming the validity of the initial isolation. Further purification was performed on using ion exchange chromatography, and heparin sulfate adsorption columns, followed by HPLC. Activity was determined following adjusting the pH of the serum fraction (30 to 100 kd fraction) to different pH conditions using HCl and readjusting the pH to pH 7.4 prior to assessment of biologic activity. Low ionic strength sensitivity was determined by dialyzing the fraction containing activity into low ionic strength solution for various lengths of time and readjusting ionic strength to physiologic conditions prior to determining biologic activity by dialyzing the fraction against the media. The biologic activity was maintained in the aqueous solution following chloroform extraction, indicating the factor is not a lipid. The biologic activity was lost after the 30 to 100 kd fraction was placed in a 100°C water bath for 5 minutes.

Isolated nucleic acids

Tagged genomic DNAS isolated were sequenced by standard methods using Sanger dideoxynucleotide sequencing. The sequences were run through computer databanks in a homology search. These genes can be therapy targets particularly because disruption of one or both alleles results in a viable cell.

What is claimed:

1. An isolated nucleic acid comprising a nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, and SEQ ID NO:127.

2. A nucleic acid comprising at least 20 consecutive nucleotides of a nucleotide sequence of claim 1.

3. A nucleic acid comprising at least 30 consecutive nucleotides of a nucleotide sequence of claim 1.

4. A nucleic acid comprising at least 40 consecutive nucleotides of a nucleotide sequence of claim 1.

5. An isolated nucleic acid encoding the protein encoded by the gene comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5,

SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, and SEQ ID NO:127, or a homolog thereof.

6. A host cell containing the nucleic acid of claim 1 or 5.

7. A nucleic acid comprising a nucleic acid that selectively hybridizes under stringent conditions with the nucleic acid of claim 1 or 5.

8. A nucleic acid having a region within an exon wherein the region has at least 50 % homology with a nucleic acid of claim 1 or 5.

9. A nucleic acid having a region within an exon wherein the region has at least 60 % homology with a nucleic acid of claim 1 or 5.

10. A nucleic acid having a region within an exon wherein the region has at least 70 % homology with a nucleic acid of claim 1 or 5.

11. A nucleic acid having a region within an exon wherein the region has at least 80 % homology with a nucleic acid of claim 1 or 5.

12. A nucleic acid having a region within an exon wherein the region has at least 90 % homology with a nucleic acid of claim 1 or 5.

13. A nucleic acid having a region within an exon wherein the region has at least 95 % homology with a nucleic acid of claim 1 or 5.

14. A polypeptide comprising the amino acid sequence encoded by the nucleic acid of claims 1 or 5.

15. A nucleic acid comprising a regulatory region of a gene comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:112, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, and SEQ ID NO:127, or a homolog thereof.

16. A construct comprising a regulatory region of claim 15, wherein the regulatory region is functionally linked to a reporter gene.

17. A method of reducing or inhibiting a viral infection in a subject, comprising administering to the subject an amount of a composition that inhibits expression or functioning of a gene product encoded by a gene comprising the nucleic acid set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82; SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, or SEQ ID NO:127 or a homolog thereof, thereby treating the viral infection.

18. The method of claim 17, wherein the gene is selected from a nucleic acid encoding a gene product from the group consisting or, or the gene product is selected from the group

consisting of: tristetraprolin (human ZFP-36), 6-pyruvoyltetrahydropterin synthase, a eukaryotic DnaJ-like protein, ID3 (inhibitor of DNA binding 3), N-acetylglucosaminyltransferase I (mGAT-1), cleavage stimulation factor (CSTF2), TAK1 binding protein, human zinc transcription factor ZPF207, Dlx2, Smad7 (Mad-related protein), and P-glycoprotein (mdr1b).

19. The method of claim 17, wherein the subject is a human.

20. A method of reducing or inhibiting a viral infection in a subject comprising mutating *ex vivo* in a selected cell an endogenous gene comprising the nucleic acid set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82; SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, or SEQ ID NO:127 or a homolog thereof, to a mutated gene

incapable of producing a functional gene product of the gene or to a mutated gene producing a reduced amount of a functional gene product of the gene, and placing the cell in the subject, thereby reducing viral infection of cells in the subject.

21. The method of claim 20, wherein the cell is a hematopoietic cell.

22. The method of claim 20, wherein the subject is a human.

23. The method of claim 20, wherein the cell is from the subject.

24. A method of screening a compound for effectiveness in treating or preventing a viral infection, comprising administering the compound to a cell containing a cellular gene comprising the nucleic acid set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82; SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117,

SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, or SEQ ID NO:127, or a homolog thereof, and functionally encoding a gene product necessary for reproduction of the virus in the cell but not necessary for survival of the cell and detecting the level and/or activity of the gene product produced, a decrease or elimination of the gene product and/or gene product activity indicating a compound effective for treating or preventing the viral infection.

25. A method of screening a compound for reducing or inhibiting a viral infection, comprising administering the compound to a cell containing the construct of claim 16 and detecting the level of the reporter gene product produced, a decrease or elimination of the reporter gene product indicating a compound for reducing or inhibiting the viral infection.

26. A method of screening a compound for effectiveness in treating or preventing a viral infection comprising contacting the compound with the gene product of a cellular gene comprising nucleic acid set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82; SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID

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27. A method of suppressing a malignant phenotype in a cell in a subject, comprising administering to the subject an amount of a composition that inhibits expression or functioning of a gene product encoded by a gene comprising the nucleic acid set forth in SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:36 or SEQ ID NO:94, or a homolog thereof, thereby suppressing a malignant phenotype.

28. A method of screening a compound for effectiveness in treating a viral infection, comprising administering the compound to a cell containing a cellular gene functionally encoding a gene product whose overexpression inhibits reproduction of the virus but does not prevent survival of the cell and detecting the level of the gene product produced, an increase in the gene product indicating a compound effective for treating the viral infection.

29. A method of screening for a compound that can suppress a malignant phenotype in a cell comprising administering the compound to a cell containing a nucleic acid functionally encoding a gene product encoded by a gene comprising the nucleic acid set forth in SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:36 or SEQ ID NO:94, or a homolog thereof, and detecting the level of the gene product produced, an increase in the gene product indicating a compound effective for suppressing the malignant phenotype.

SEQUENCE LISTING

<110> Rubin, Donald H.
Organ, Edward L.
DuBois, Raymond N.

<120> Mammalian Genes Involved in Viral Infection and Tumor Suppression

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cgaatctgtc ccacgtgcct caggtagcgt tccaaacagc aaagattcta gtgaagaaaa 720
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ccattcctct ggggaaggtg gggggggcgg tgtaatgcag ctctcaagaa gaaggtattt 840
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<210> 2
<211> 554
<212> DNA
<213> Rattus norvegicus

<400> 2
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ttgggaagag gaggaccgtg gttnataaat aacagaaagc ccagagggac gtanccatcc 180
gggatggaga gaggtaggga atccagntgt aagtcccaaa ctgccaccac cttcatnaga 240
actgcttcgt gtaaggtcac gcaccgggcc agctgtccng agtggcggtc ctggcgtgtt 300
aagttagcta aagtnactgc aactccgnct gtgcagactg ntcgtaaatt ctctctgtcc 360
gccaaattct ccctcctatt aaacttttca cttcctttca cttagtttcc tnacttcttt 420
caaacggaag ctgtaactga gcctgccacc cnganacntt gtggttgcca tttttatgct 480
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attataactc tgcc 554

<210> 3
<211> 891
<212> DNA
<213> Rattus norvegicus

<400> 3
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ntggtngggg ggggagggac ncccacagan tcatgnggtg gttngggngg ngggcatcgt 180
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catctctgtg acttccagac cggcntcgcc agagcaagtt ccaggccacc cagatgagat 840
gctcacagag gggacctttt tntgatgacc aacgnagnat gcaagtaagg a 891

<210> 4
<211> 974
<212> DNA
<213> Rattus norvegicus

<400> 4
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nttattgccg ncntttcccc cccgctnttg cncccctttа cttngagant ngtgntncna 180
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accggtntgg gttncnantt nnttgnancc nccnattggg gtttccgntt accngggttt 300
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gggttcttgg gngcagggcc tttttttcnt tggnngcaan cncataaatn ttaccagntt 480
gattgctaag gaagtancca tggttgngaa ccccccttn ttntctccca gatggaaccc 540
aggattttgg aactgcagag gcttcagggt cttgggaagc ggaggcagnn aaagattgga 600
gtgcactgtc cttttgcaat atggggtttg cctgcctgct ggctcntctc ctgctntntc 660
agatggtgac tgaggctact tcngcaggac tnggaataat catgtccagg tggctgccct 720
tccgagcaga aagggacaga cgtggggcga tgaagttgct atcgtttntt ttttttctg 780
cacagactgc aaagtgtgca gagggaggga ggctgtgcaa aaaaaaaaaa aaaaaaaaaa 840
aaaaaaaaaa ccgaggacgc agaagttaga ctgctgaccc atttggtgca tgtgtgccca 900
tggagggagg ggaccttntt taaagggttc acgcggcacg cantgggnaa nngnnccttnt 960
acgnnnctcc caga 974

<210> 5
<211> 850
<212> DNA
<213> Rattus norvegicus

<400> 5
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gttaggggga cccgnnggaa aattttaaaa ccnngngggc tttttcgaat taaggggaaa 180
ngcggtttng gtnnntgaag ggcgggnggt tggagtcnna gtccagagtt gatttccacc 240
cacaaatntg ggaggtgncg gggaatgntg ncnttttctt gngatgaggg ntgccgtncc 300
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cngttcgang ganccagatt tangngntgg agnaaggatt nggcagataa angcntgaga 420
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ngccttnana antgntcaga gaaccancag tggntanggg ntgcccnnnn naccagggaa 600
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atgntcnccg agtacnagan angatcntcc aacccggaat ncggtgctcc ngtcgtccga 720
tgnaatgagt cgnccggnaa cctcatatcc aagaaacnat acagcagtgg nntccgagtc 780
tcgtatantc nttgcgggng gaggctatnt tcagaggnca agattaccgt tagcgggana 840
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<210> 6

<211> 531
<212> DNA
<213> Rattus norvegicus

<400> 6
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ngtctnntgt ctgtgtngtg cccctgtccn catctctcac nccagggaga gagatgtgag 120
ananacatca gagatctctn gnacagtgtt tcacaagagt ctatcncana gagcacatct 180
gcccggggng anacacaact ctaaatgtgt ctcanntgat ctctctnttg tgtctctnac 240
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cacacacaca cacacacaca cacncttctc tctggcacag ggntatggca nagcacatnt 360
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gcnnatatag gggggngnnc tctngggctc tcttnggnaa tntgngggng agtctgcnca 480
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<210> 7
<211> 572
<212> DNA
<213> Rattus norvegicus

<400> 7
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gagacancgg nnacacagag gttttgngnn tattgngagt ctctgcgcac nccananttt 120
aaccncgggg nctcntgttt tattttaaaa aaaaagagtc ncatgtntat ttctctnatg 180
tgaaaatcnc attcanagtt ntggggtttc ccntgaggag anatagagtt tcacactctt 240
ctctccgagg ggtcntcnca tgtntctccc caatgtgngn ggnacacaca tgnggccccn 300
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gngacangtt agnncncccc atnttcnccc ccctttcaca ctgccccnag agagagaaan 480
tctnggcccc ctctanannt ntttttaaat cncccccnnac cacaggtntt cccagggtat 540
gngacntcnc cnnccccncn aaagatntgc nc 572

<210> 8
<211> 906
<212> DNA
<213> Rattus norvegicus

<400> 8
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gcgagaanac tctgtnnant ngtctccccc cncnccnaca gngtganant caaaacctct 120
agagcccccc agaaancccc tntctcaaan aaagagaaag agaagancga gnagnagaga 180
gananagaga gagagagtgt gganctntnt cctcngancc ccannnanan ngtgnggcnc 240
actcncnngt gnngngnacc ccnggggatt tncgcgtgtc cccttgngct ctgtntanga 300
gananatatg tntagtctct ctntcgcccc ctccgntgtc acgtgtgcgg ggcccnngag 360
acacagacac ntctctcang gggaacacat anngactcnc acntgtgttt atattcnccc 420
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gtacanattt antctnggcc anacccctct cngaagngng ggcanngtaa accccgcccc 540
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<210> 9
<211> 914
<212> DNA
<213> Rattus norvegicus

<400> 9
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gactcccatc tctntntntn cccccaganc tggngaacgg ngtgtggnga nccntntctg 120
ttctcnantc tctaaaagng cnaaaagcgc ananacacgn gcctctctat anatctcacg 180

tgtcccnngn nctctcngac ccctnntctg tntgagagac accctntctc aaaatatagt 240
gtacacgngc tttgnggctc tccccttttc tctccactnt tgagngngaa acgcggngtt 300
ntctctgaga tgtaganagn gtcccctnct cnatatatgt gttncccact ccnnagggng 360
tctcataaaa atcncntntc tcaacaccac cncctcnacc ccccncacga gaacacntcn 420
ccaccncnan gacacaaana naaggngtnn anaaccccan aaaaactnng ntntcngntt 480
tacacacaca cacacncacn ctcncncaca cccccacnna aatgggagaa aaaacagaga 540
ggngtgggtg ttngnntcaa caccntntta cctctctgnt gnnanttgag aaaatatttc 600
tntncttacc cctctccccc ctctgtgtgt ngannatatc ngntctagat gtcctnaccc 660
tccccaaacc tttctcnggn agagacntct ctntnttttt cccccncttc catttgaaan 720
anangagaag gnccaaaaag gngggngtct tctcgggaat ncnccctttt ggccccccaa 780
cctgggtttt tttccccctt ccttttaatn antttttcna nacaaanctt tnngngtttn 840
ggaaaangcc tttnnctgnn nnttttttcc cttccccttt tnnangggnt tccccccccc 900
ccngaatttt tttt 914

<210> 10
<211> 400
<212> DNA
<213> Rattus norvegicus

<400> 10
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acagtttatg aatattatta catatttcac aagactttat attgttataa tatgcctcat 120
gtgagatata tgtgattctg tggtggtgtt ctcagagggg gtttgggtta ttggggataa 180
tagtttgccc ctcgcggggt ctatatttat atatgtgaca caatatatta gagagatttt 240
tggttatata tatttccctt cgcgggggtg gagatttatc acaggggggag agcttttccc 300
ttgttagcaa aagtccctgg tctcgtcccc catctcccaa aaaaaaaaaa atgtgaaaaa 360
aaaaaaaaaa agggcccctc ttgagtgatg tccccttctt 400

<210> 11
<211> 880
<212> DNA
<213> Rattus norvegicus

<400> 11
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tcgctcncac ccccaagcct cccnttctta ncagcttttt tatangaaaa aagatgataa 120
cgaaatttta aaaaccgtcg ttagaggaaa tgaaggttca gccgaccatt acctganagt 180
aatgaaggtn ttccggaggg ttgccttcca atcccagatg gatttgagtt tcaggatcaa 240
ttcagttacc gntgaccatc caccnncctc cngtataatc attngatgag gatgaatggt 300
gagtgagtga tgatgatgat gatgatgatg aagggatgag aagnacacta tgataacaag 360
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cttttcnnac acaattaata gtntcttant ccttcccatc ttctctgccc cattctgttt 480
tccaccacag gtctgcagcg ggctacagct tccagtctcc aagcaaatac cagaactgga 540
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ccatctctct ctctaacctg aaatccttag gattctatta tttcaccgga ccagagctgt 780
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gcgaaagncc ccacaaagnn tttggcaagt agaaaagncg 880

<210> 12
<211> 909
<212> DNA
<213> Rattus norvegicus

<400> 12
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nagacggtgc nngggggga ggggcaggag nggnagagag gcangagngg agnggggaca 180
agcnnaaanc gaggaggnan gangngangg nnggngngnc gaaggcgcnn aagnnggtcg 240
gngagcggna gnggnnaaac tggggaacga gacagacggc cccnncggng gcangnggga 300
gagnnncgcc agngagagna gncagnanca gancanggga ggggggggan ncacnggcgg 360
gagggncgan gacggnnngn annggnnaga ggcannnnnc gccnanagng ngaagngagg 420
cangagtgnc gcnngagnag acaggcccgc gcnccggggg cagacnnngg ncaccaccga 480

gggtgggngg ggcncggaga naagaccaga ggnnngaggg cganggcnng ggtnngcccg 540
ggccncccna aaaaaanncc gaaaaaaaan aaggggcgcn gcngggcngg ggaggagcgc 600
ntnncgtang tngantgacg gaggccngna atngggccgn gccanncnag ggcgnagagg 660
cccaagngcg gnaggngnaa gnanagancc ngnnggtngg gagnganagn gcnnggnncc 720
naccccngn gttganggcn cccacgncgg ngcaggccgn nnaaagngag tccccnaaaa 780
nntcgnggtn tnacancgnc ccggggncgc cgcngngtcc cgncacacng gannncggag 840
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gaaaaagnc 909

<210> 13
<211> 927
<212> DNA
<213> Rattus norvegicus

<400> 13
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tttnaaaaag ggcgnccnat ataaangacn ttcgggggggg tttgaanagg gccggaancn 180
tcgacgggtt tccgggnggg ganaaggana agggnacgca cgggatttct tnccctttt 240
tngcaaattg cngcaggana ccaccgggtg gggnggtttt gttttccgtn aagaaagcgg 300
gngtggaaaa acanggataa acgggaagan ggggttattt nggttagnaa ttgnttccag 360
nggngccagg aaattggcct gtccaaaatt cttttcccng cttttaagac aggcaggtat 420
tatttggcag caggttatta cnataggnaa gtaaataaca atgggtaagt gcctggcaca 480
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aanacaagna anaaaggctg gtctcacata tcccaaagct ttatcttcnt aggtgcccca 600
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gaatcagtgn tcagagactc caggggcacc cctgattccc tttgctgtca cacagacact 720
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ggaagatttg gcaagntaag gaagntc 927

<210> 14
<211> 848
<212> DNA
<213> Rattus norvegicus

<400> 14
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tnatttnaan gggngtagtt tctggtnggt tcattccttn aaaaaaaaac aaaacaaaac 180
aaaccgnagc ttctgcattg gccaccngtt gnggcaccaa cccttnangc attgcccttt 240
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antgaagtac aaggccatca gcgaggagct ggaccacgct ctcaacgata tgacttccat 420
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agatgacctg gactccgaat gggctctgag tatntccttt taaaacctta aaccagantc 720
aagtaaagtt aggaagccat gaggcagtgg tgcaggaagt taggaagaaa naccgggttg 780
ttggtttcct gggnctgggg tgagggacca ttgatagacc tttacgaaan ganccgcang 840
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<210> 15
<211> 896
<212> DNA
<213> Rattus norvegicus

<400> 15
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agangnanaa agaananant nngagattac gaantcgggg agagngaaag gaaacaaagn 120
nggnggnaaa gagnnnanttn tttcaagggt ccgnaacaaa aagttgagng angattccna 180
acaagggntn nccacccaan ctgntaaagg gangatttgg ncaaacanaa accngtattg 240

gggagttaaa aagagtcacc aaatagggaa aaaaagttng ggggagggnn aacnacnggg 300
taaaggttcc aggaccagag ngttcagnac caagtttcag tattcaggag gacagagttc 360
aggatcnntt tggaacattg gggtttgggt agcntggnaa cacgaaccct tttgttcata 420
aaaaggaagg gaaaagaaag ggnngaagag tnttcccaga tgnattntga gcagagaatg 480
cccgaccccc cgaatacgta gttccaaaat gggattgnac ctgtttcacc tcaaatttca 540
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gttctgtggt tgccggtgga tgntctgcag ctgtntaccc caccgaaaac gaatggatgg 660
gatgtcactc ccaggcagta gggggcgcac gcgcattgtg ttntagagag anttccccag 720
cctccccngg aannacaaca cgttntcttc ttcttaaggt ggtggtgggg gggggggga 780
agacctattg ctttccgaga ggatcggacc aaacagcaga ttntgctcaa ggcccttgaa 840
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<210> 16
<211> 858
<212> DNA
<213> Rattus norvegicus

<400> 16
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gagggnggaa ngtnggtnaa agagttttaa tgttcttggg atcgcaanta ttttcctggt 120
tcgcgncttg tacattatga gggttgataa cngctgtttt tngattttgg ttaacanggg 180
ngggngcntt tttnggntga cctntagtnc ntcngngccg ggcattttgg ntacctttt 240
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tatattttat taaatatata cttagattca ntctttgcct aagcctggat gttgttggtn 360
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cttccacaca aacatgtcca cacacgggca aaggtgtatg cacagatatg gacataacac 480
acacagagaa gaatnacaaa caaacaaaca aaatatttcn gacagaaaca antaaataca 540
tccagaaggt agaatattct acaaggcatc aaatctgttc taaagaaaaa gttataataa 600
agaaaaacat tgaaaggcag gtgaaggaga ttgaaggcca taggggccac aaaaaggttt 660
aaacagcaaa gcaccaacgt agatatccgg aacgtgctaa atatggcaca cacaggatat 720
ccgggaacga tgagtcagcc agcggcacat ataaccaacg atgtaatctg ttatgtaact 780
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accagaagcc attgcctt 858

<210> 17
<211> 551
<212> DNA
<213> Rattus norvegicus

<400> 17
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ccnccncana anaaatatct ctctcccccc cttgttgntt gtcncccnnc ccaaaantgt 120
gngatctntc tctctgtgca cgaganattt tagaggggga tatccccggg gtgtngccng 180
tgtctntcct ctcgcgaata tctttangag nctctctctc tcgancccccc agngtaggnn 240
gagngganaa catttttntg tggnggcccc ccacaananc acnaacaana tattttcgag 300
aancncatgn ganaatcggg gggggggggg ccngtgttna cacnatancc ngggngatna 360
nanagacacn nnatatntct gggntgtgna aanataanac aagancanac atgnggagan 420
natgtgagan tgtgcacacc ctgttgtgac atgtgaggtg gggggctgat gatncctncc 480
ttctacgtnn tntcttctcc tccncantga tagacnccac ctgctggagt gnctagctan 540
ctggggtcgg t 551

<210> 18
<211> 888
<212> DNA
<213> Rattus norvegicus

<400> 18
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<210> 19
<211> 867
<212> DNA
<213> Rattus norvegicus

<400> 19
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ttagcttagc gttctaagga cacagat 867

<210> 20
<211> 897
<212> DNA
<213> Rattus norvegicus

<400> 20
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aaagttagga tntggttgga tccnacccac aaggaatttg ttnttaattt tttaaaggna 120
aatttgggca cttcnattgg gaaggttaaa acccaggcaa gtgntaccgg gntatgcaag 180
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<210> 21
<211> 435
<212> DNA
<213> Rattus norvegicus

<400> 21
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gcagagtata cactggttgg gtaaatgaag aggagagaca gagtgggaag tcggcttagt 180
ggatatggac ttcaaatttg atgaacaagc aattcaaatg agtatcgtgg gcttgantgg 240
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gagagagaga gagagagnaa gagagagagn gtgtgttgtt gttgttgttg ttgttgttta 360
ttggttnata acaanatnta cctttgggcn ctttngaaag actntncaca aaggagcttg 420
ncaagctaga aaggt 435

<210> 22
<211> 894
<212> DNA
<213> Rattus norvegicus

<400> 22
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ctagaggana accggccnat aggngggggn agnatggaag gattttccag agaggaatca 180
gtttggngag agaatttgat aaggagttcc ttggaaccaa ccnggagggg gttttggttt 240
nngggattna tcangatggt tgtccttggg aagcataagg ntggtttatt attttggtta 300
aaggggatga agtaccntgt gttgcacttg gtagcccaat gtcctgtcat tgtgctttgg 360
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ttttcttggt gaggccccat agtgggantc cgcacttcac catttctttt ccgcccgccc 480
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gcgcgtggca cttttcggtc cacctggagg caacactggc gccntttcct gtttcagtct 840
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<210> 23
<211> 594
<212> DNA
<213> Rattus norvegicus

<400> 23
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nagagtaatt tcaaaagccc cagntttgtg gaatcanttt ttgaanatat gaaaaggccc 180
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<210> 24
<211> 586
<212> DNA
<213> Rattus norvegicus

<400> 24
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aactccacnt tcaaggtatc cgctccgggt tagcagcccg ccaaacgccc tgctggnttc 540
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<210> 25
<211> 909
<212> DNA
<213> Rattus norvegicus

<400> 25
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gggggatccc tnggttccgg aagggccgcc ttagttnttc ttttcctcca cctatgaaag 120
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taaaggagt 909

<210> 26
<211> 576
<212> DNA
<213> Rattus norvegicus

<400> 26
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gtnggggget ccaagggggn nggggaganc tnaagntcnt caannntagag agggggaagc 120
tccccactct acatctgttg tcggagcacc cccccaccca gagggcgctg tcagtcatag 180
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gggctatgaa gaaagtgggg aagggaggag gggaga 576

<210> 27
<211> 853
<212> DNA
<213> Rattus norvegicus

<400> 27
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taaaangggn tanangtntt taangggcna aaagnttggt ttnantccca ggngggtccc 120
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tggaaccagc cgtactacag aggcattctg ggtcccagag agtatcgata aggttgattt 840
ttaagtccca ccg 853

<210> 28
<211> 825
<212> DNA
<213> Rattus norvegicus

<400> 28
ggnttncagg ggnacccccc ccccncttnn antttgtcca cgnaanattn nngccnnnna 60

agganggggn ngggaagttt nagggcaang aaaagggaaa agtttngttt ggacaaacct 120
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tgggcgcttg ggactcctcc tgagggaaag tcctctctgg ggtct 825

<210> 29
<211> 861
<212> DNA
<213> Rattus norvegicus

<400> 29
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cccngagnan naaaattgag tcagtngggg gnaaccgacg nananaggaa caggtttccc 180
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gcagtccgcc ccnaggacga naggagacca ggggcccang ctgnagtaac naatcaacta 780
ccctnacnag atgnancaga gagagagagn accgtatant nantgnaaga gaggtcccgg 840
tttcnagttc ccagnacgga a 861

<210> 30
<211> 149
<212> DNA
<213> Rattus norvegicus

<400> 30
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gaggcttttc ctcccttcag taggtcagc 149

<210> 31
<211> 857
<212> DNA
<213> Rattus norvegicus

<400> 31
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tgacnagggg gganaccccn taccgngggn cnancggaan tnttggncac cgnaaaaaat 120
ttccaggngn acangaacgg gtgcggnggg antaggggga aangtttgga gtgngccaaa 180
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<210> 32
<211> 1630
<212> DNA
<213> Rattus norvegicus

<400> 32
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gaagagcctg 1630

<210> 33
<211> 883
<212> DNA
<213> Rattus norvegicus

<400> 33
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<210> 34
<211> 913
<212> DNA

<213> Rattus norvegicus

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ccngtnaaag attttcccat ggcgcaccat gtacgggttg cgaggngtat taggcggnaa 240
cggtttttna gtgggcctaa tacggnanat aggaggacga tttgtnttgg tttgtngagc 300
cagtaccttn gnaaagagtt gtagttttga tccggcaacc aaccacngtt gtagcgnggt 360
tttttgttga agcagcanta acgcgcagaa aaaaggatnt caggagatcc tttgattttt 420
cttcgggttc ngacgttatg ttgtgtggat tgtgagcgga taacaatttc acacagattc 480
cgatngtagt ccaatttgtt aaagacagga tatntttccc ttcaaagaaa acagaaaaat 540
acagaaacgt taattttcaa atctcnaatc tttcnttctc tcttcnntca ttcattcntt 600
cnttctttct tctttctttc tntctttctn nagaggaggc atgctagggt aacagtagct 660
cattttaaaa tctggcacct ggaattaatt tagggacaaa acacctttat gcaaaaaaaa 720
gtttatgttt ttccatggaa cacagtaaaa tcaaaattaa aagaatataa caaaggcttt 780
ggtgatttgg taggattttt tttttcctgg aggggaaaac agatgacttg gaaagtgtta 840
ggaacatatc aagccccagg gaaagaaaaa cgtttgattg gtattaatta aaacactgct 900
aatatattct aat 913

<210> 35
<211> 320
<212> DNA
<213> Rattus norvegicus

<400> 35
tatgcaccca tgacacaaga tcacagaagt acaggcctgg accatggcag agtatacact 60
ggttgggtaa atgaagagga gagacagagt gggaagtcgg cttagtggat atggacttca 120
aatttgatga acaagcaatt caaatgagta tcgtgggctt gactggtatg aagacccgtt 180
tgcaaagcag tgntcataag agagaaaaga gagagagaga gagagagaga gagagagaga 240
gagaaagaga gagagtgtgt gttgttgttg ttgttgttgt tgtttattgg tttataacaa 300
gatntacntt tggtaacttt 320

<210> 36
<211> 389
<212> DNA
<213> Rattus norvegicus

<400> 36
ggggggngc naaaagggtc tttcttttna naaaaatcnn gganggaggc cncnanacgg 60
ctnttanann tnttcngggt gtncctcncc gntgtgggga atganatntc gntctcgaca 120
tcaggggatt ggagattntc tgngctcncc nctcacnacc cagaagaagc gcacagagan 180
cagagtanca catcatacac acctnttcag ctacagagcg antnctctan aaggggactc 240
ggggganaac acaaccctcc tcctcttctg actgngagng ccgcntgtag gntctgtcta 300
cccancaagn cttgtgcagn ntgngaacct ctctntgggg tagagtgtgt tgngggagca 360
gggcgtantg ttccaggnct agnctttca 389

<210> 37
<211> 882
<212> DNA
<213> Rattus norvegicus

<400> 37
agnaacgcgg ncggnggnnc tcncccngcg gagcnggncc nccccnngn ncccagaana 60
gnagcgctcg gngannnccc acgngnagac nnnggctgcc ccncgngncc anggcnttnn 120
nccnnccccc cgnatccggn ncnccccccc ctccctnggg gngcgggggt cccngngccg 180
nggngatacc nggcganncn ttgtgccccc gcnnggggggg naggaccccc ggcaccggcc 240
cngacccana ncagnngctt ngtgggggggc ccccccgcca nagaacgaat tncgccnccg 300
gccgcggcca tcggaacncn cctagcagng cgtcntgcta ggcnggnnna cgggnatccg 360
caancccncc cttngtaccg ggacagccgn gggnccgtat gggctgngcg ntnggccgta 420
gccanntncc tttngaaang acncggnagc tnttcatccg cctcacaaac cncngggncn 480
gnggggggctn tntcntgngc cgcccgccgc gtgngcgcan aaaaaaaaaa aanncggccn 540
tccnccccctc ttttggccng ggtnccccgc ncaccccgtg ccgagtnccn nnccccccac 600
aacctcacac cgatcccngt gggttcccnn ngggagtcgc ncgngcnnag cnggnttctc 660

cccatnncgc gnngcttnag cgngccnnnn cacngtttgt nngngnntgc ctccccttcn 720
tccttgaggc aaaagcccgn acngtntctg tggaccacnn tgctgaggng ctgggcgccn 780
cgntctctct ctctctcnct ctctctctct ctctatctct ctttctctct ctggggcccc 840
tcccttgntg nngccanaag nnngcnnacc cgtaaagtaa gt 882

<210> 38
<211> 975
<212> DNA
<213> Rattus norvegicus

<400> 38
aatttngnca ataanggccc ttcccctgag tgnggggganc ncncntgttc anaaggtacg 60
tttagcgngg ttctcnagtt natggtaacc nagtacttaa ttggcncnct tgataaatgc 120
tngatcctna naatttcaac aaccgcagga ccatttttga acttggcggn ngtttaccct 180
tnatgnnctt tccnnaaaat ggcttccttt gncatcnaat agtgntgccc ctaacccctn 240
ggttccggag gatgcatnng tggntgtgng tttgnccttg agcatgcngt tccgtnacgg 300
gancaagntt ntcaatgttc cntcacncca tacttnggct tggggtacaa nttgtatatc 360
ttcgggatta tatnagttta tgtctgnttt tcataaaatc acttgtggat ttggctttaa 420
ngttaggaca acttnccaca gtttcttgga tctccntcaa catgttaacg ccattttgtt 480
cttgtatact aaagtgacat gtcnttntng acactaacaa tcacaaatta ggagtaccaa 540
tcaactttga gaaaatttaa aagatgcccc atctcttgta tcagcaagta ttcagccagg 600
atttaattct ttatgtaaaa attagcaagc atttctatnt cattcacgtg caaattttct 660
ttgattgtta attaagattg aagtgatatg tatggcccaa ataagtctca ctttaaaaaa 720
tatttcttta tgaattatta tccatgaatg tttgatctgt atagctattt tatataagta 780
tatgcaagga ttgctaaaac aatttttgag tgaaaaaaga tcctaggtag aaaatgttta 840
agactaccta taccgtcatt aaaaactcct caccagcatt tactatggtt ggactttcag 900
agatctcaat caactctttc ccacccagtc tactgaaagn ttccacctgt agcggcccaa 960
gcaaactgag atntt 975

<210> 39
<211> 850
<212> DNA
<213> Rattus norvegicus

<400> 39
ggggaaaccc acggtnaagg gnngganaac naggtanctn tttctccggg ttccaanaat 60
ngaangcctt ccngagggcc ngaaaancat tncttcngga gccgttcaag ccagnaggtg 120
ggtttcaaac aatgcttaag ttgtggggag aacnagncag tccgttccng acccngttta 180
tcntaaagga gacggnggtt aaaggttagg gggttngaca gtcctgctgg tgttcaagga 240
ggaggagaca agttgncatc caggngngca ggaanacctg ttaaattcct gaccnaccgg 300
atgnttggag agcnaaggcg gattcttccg gcagtggcca gatttcaacc caggtcccgc 360
ccngcttttc ttggttaggc aagcaggcct tagtccgnga ggacgcccct tggtggccag 420
ggtatcacgg ccccccctngg gtttccattt gcagtttgta ttggaccatg gatcactgct 480
tccttntgcc ggaagttcca gattccaaac tgtgngantc ccatntgcaa ctcccatgtt 540
tgccgntggg acttttttnta atatcntggt acccgcttcc catttcccca cccccntgnt 600
cccttcggga ggaatcaccg cccagtgtgt cacttcctgt aggnacttcc aaggntagat 660
gagtgagtgg caggcctcac nttggcccag ttantcagtg cccacagagt agctttttg 720
agacgntagt aaggtcttag gggaaggaat gtagtcgatc cttctccttg gtggccctca 780
gcactgtgag tagaccccac acatcagggc tgtgtcgtta ggatctctgg gagggttgaa 840
agtttcgagg 850

<210> 40
<211> 889
<212> DNA
<213> Rattus norvegicus

<400> 40
ggggtttcca aaaatttggg gntttggana aaccttcggg gaataaaaca acngnnnaaa 60
attaaggggg gccgggggaa aaaggagatt nattaaancn ccacccgaat tnaaacnccc 120
nccgggaccg naaccgtttt tggccnaaan ncgagaagtg ccttccnggc aaagtagggg 180
accaaaggtn gggggagaga attggggttt gtncagngtt ccggttcnac ggaaggagcc 240
ggttgttggg attgtttcca aggagngngt ttgngaccgg agcacctcng gggngaccat 300
ggggnttgcc tgttagagac cngcgngatg ttttgggttc gnattcgggg agggatttcg 360
ggggcctcag acnggggagg agtcccntgc gttcccnatg ggaccggttg tcgggcgggt 420

gcagtttcgc tgctgtcctt tggcaatgng cntgggnatt ngtgggcaga ngagattccc 480
cngccccgc natttccccn gttccagttc ntaggnacca gaggttttcc gcagtgtgat 540
tcagggagnt agantntagc gtctgtnttn tntgcgtttt ccccttcatg attctcagtt 600
atttttagg agaaaaggtg cgtggaaaca gagcgtccct gttccgtgct gtttctcnta 660
gcccaaaata cagatttaat tctgaagcca tcgaccccca tatccacttc ccgccctctc 720
ataaacgtgt aatatggctt gctttttcct tgtaacgttt catccaacca tagtggtagc 780
ggccacctgg catcttgagg tgggttgcga atgagtgaat gaatgagtga gtgaatgaat 840
gaatgaatga atgaatgaag caagcttcag ggagattttc agagaagtg 889

<210> 41
<211> 929
<212> DNA
<213> Rattus norvegicus

<400> 41
aatgcccntn aggggnnttt ccccgnattt naaaatgggn tncnngnttc caaagtttcc 60
taaaaatttn cantttccgt ttttaccngg tttatggttt ncagcctact cctgttcgan 120
ttccaaatcg gtttaantgg ncccnccgaa ncnttntttn tttggcagaa ggtgaanttc 180
nttggggccc ttgtttaagg gttttnagcc ttaaattgnt tgntnagnnt ctccntaatt 240
agttcattcc tttgaccatc ttttgnccct ccatcttgta aacanttaag tctattgcat 300
tccactttnc tntcagttnc cgtttnaccc tcctnagcag aacccgnttc tcagctntgg 360
atggttccaa anggtttccc aacctatgct caataccaca ggcagcttgc aggagggaga 420
antggtatgt atttaacagc attttgaccc aaacttttag gagcagagag gactttaccc 480
aggacaggaa ggcaaaagac ttgaatctta aacaaaggat taagaacagg atgtcatctg 540
tgagcctgtc acagtgggtt tgcagagcag gagaacacag acaggattag ctataaagtt 600
gttacattag ttattntatt ggagcataca atacttaaat agttctaggg caagagaaat 660
gaacagaaat gaccttataa gagccagagc tgtagccaca gctttctttg tgcttagttt 720
gctagttcac tctttccagg gcagtctggt ggattacacc aaattgctta gaaaatgcta 780
gctctactgt ccctgtctat tgtcagcttt gcaatgtgca tagtgacagg agttgcctgg 840
gaagcttggg gcttatgttt tgcagatcca ttgtaattaa aaaagaattg taaggagatg 900
gaggcacggg gtgagggtga gggtgagtg 929

<210> 42
<211> 943
<212> DNA
<213> Rattus norvegicus

<400> 42
ttggaaaccc caacctggaa aangngtntt nccgggaaat tcaacctgcg ggcnaatggt 60
gtaaaagggc ctaccttggc ttngaaggga atntcctgaa ggnnnaatcc caannttgtg 120
natcccaatt aaggntnaac nggtttaatt tgtnntccnc ntaccnaccn ggtttnccgt 180
tatactaaag ggctaacaat taaatgctca naagggaccc ccaatcctng gcnagaactt 240
gggttaaggn ttccattagg atttgccatc ctntaccgtg atcctgaaca tntnttgaac 300
tgntttgcca aggaacngaa ggttttncct naagntagca cacagcagng accaaggatt 360
ggaacccagc nagtgcttgg aggtaaaaga tcacttccnt ntcccttagt caggancntt 420
agggagtgga ggcatcaccc acacattccc cagtttgnac gtaggtttca gccagcaanc 480
cgtccactaa agctgcctcc aattcaaact ggattgagtg acaagtggct tgggtgtctc 540
tcaaagattt ataggtggca atggccactc ctctgtgtaa ttaccctnta tgcacgtctt 600
tttnttctct cccactccat cccccacccc tctttgtttc ttcntccntt cctntccctc 660
ctgttgactt tttctctccc tgcaaacagt tccaggcacc gnttagcatn tgccactctg 720
gctntagaaa gctttgcttc ccctctgctc cctggctggc tggaactcag cctccggtgt 780
gggcagactg gctcatcctc tgtgtttctc tgagtgtgga ctgctgcctt ccacacagac 840
tctctgaagt caaggagccg caccagcact tcagttgtgg gccataatca agncangact 900
gaaagttgcc acctgtagng gccgcaagca aactgagatn ttg 943

<210> 43
<211> 867
<212> DNA
<213> Rattus norvegicus

<400> 43
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accctcaagn cggggggggt taaanaagga atcggattcg ggctttgnac aaataaagga 120
gttttgngng nattttcccc ntggtcgttt tntgnacgat ccacggttga ccgacgacgn 180

acggaccgac aaccaanacg taaaggggaa ttgtggaggg gttggaagtt tagatgcccc 240
gacccaggac gtgcggccan cttccggaga cccacctttc ttgtnggccg ggnccggcgg 300
cagcgnagcc atttccaccg gatccctata gcnggccagc ctagcaggcn gaacaccagc 360
gggaagttga ntnggacctc ggagagcgcc cgcccttccg gcggaagtnc taattccaaa 420
gcggcccgcg gcngagtttc ccatacaggt tggttccgtc tcggagtgac gtggcttgaa 480
ggacggtctt cgcgcgagaa gagtaccctg cctttcaggt gcgggagtta cntcagcctg 540
ctgcacaccc ggctgtgcgc antcttctgg tgtggccggg acggttcacc cagaggagtc 600
tctgtagttc ggagcaagat gtcggttaaa tctggcagga aaatgccttc tatgctcatn 660
tatatattcc tgcttccctc agcttgcttt cgacttagta aggtaacatt tcagagcggt 720
gcacttagta ctttttggca ctgtgctgta taaatataaa tgttccacac ttaacatctt 780
agatgttata tctaaagata tgcatcttta aacttcgaaa gcgcataccc taaaatttca 840
tatttttgca tacattggtc agctgtg 867

<210> 44
<211> 303
<212> DNA
<213> Rattus norvegicus

<400> 44
ggaaatgatt agtccaagaa atatttgagc agaagggagt tagggttttc aaattaggaa 60
agtggaatcc acagagttcc cttgacagag aatataaaaa ggactctggg gtgtcagaat 120
ggtgggcatt aacctgatct tccacttgag ggtaagggaa atgattagtc caagaaatat 180
ttgagcagaa gggagttagg gttttcaaat taggaaagtg gaatccacag agttcccttg 240
acagagaata taaaaaggac tctggggtgt cagaatggtg ggcattaacc tgatcttcca 300
ctt 303

<210> 45
<211> 840
<212> DNA
<213> Rattus norvegicus

<400> 45
aaaccggnng aanaaaaaan gaaannngang gcnnnaaaaa agttnngaca gaaaaaactt 60
tnggaaaaaa gganggggan aaggcaggng nccnactnaa aanggncttt tcnaagngng 120
anagagntgg naatnagnaa naggacattc ttnnaacctc cnanggnggn nggaannaat 180
ngggattgag cngccaccat tagggangaa gttngaattn nggggcccgn gngagttaaa 240
angattcccn ggtttttaa aacagagaat acctncaggn acagatnaac ccgagattgg 300
ttccctngaa aattnnngan aaagataaan gtaggagcat tcaaagtagn anggtaaaan 360
taatgggaga catagacacc aaaaaaagcc agttcagtgg gccccgaagg ngcattaagg 420
gaggaccagg aaacggcagc anagccacng gcagccgcct gccccnacac cagtnattcc 480
cgcacntaga tccaggcgnt gggggcgggg cggggcgcgc ntgngcagng aagntnngcg 540
gcaacaantt tgcntagacc ggntggaacc ggttagaacc ggccgcgccg gaccggccgc 600
ccgttccgga ttntgcgttc acaaagggag gcgggactca cgacntgngt atcnttgngg 660
tcccaacccc ggcccccnac cccnaccccc nttgtccctg tggcattcgc gttctttccg 720
ccgtctccct cgcgggccgn ttntctgcgc ctggtgatcc tttcgccatg gtcctntgga 780
gaaagaaaaa atctttaatt tnctagggac gtccttttcc tgtagtcgta attgtagaaa 840

<210> 46
<211> 893
<212> DNA
<213> Rattus norvegicus

<400> 46
gagaaggann aggnggggng agngaagana gaggagggaa gaaangaagg tggaganaag 60
tggannaaaa agagggagan ggagggagaa ntaaaganag ganaagagng gggaggaggg 120
gnagnatagg agaggaaaga aagganggan agaagagaaa agaanganga gagaaaggaa 180
agaggaaaga aagaggggag aagaggaaga aanagaggag gggangagag ggaggataag 240
agaggaaaga gggaganagg nttgaaaagg gaaagagaag gagaaaggna gnaggngngg 300
aagagaggna agggagaggg gganaanggt aagggggnaa agaangagaa gtatnggggg 360
aaaggaggag angaaagaag aaagaganga ggaggagagg gagagtgagg aataaagggg 420
agggaaaagg angagaaaga gagagaggga gagggaagaa nagagaagga tagnggggtg 480
gagaaggaga aaggagagaa ggagaaggng agaggagaan tgaagaagga gggagtaaga 540
aaggantgag naggaaagga ganagagagg tagagagaaa anaaagaggg aaanggaggg 600
gaggagggng nanaaggaat agagggngga aanangagag aggggaaang gggaaggaaa 660

ggaggaaaaa aagnagagaa gaagagnaat gggaaggang nagtagnaaa agaaaagnag 720
aggggagagg gggangangg ggganacggg ggggaanaga aaaagtgaag gaggcccccc 780
naccccccc ccccacacac acacacagcc ttttcgccgg cggaagtgca ggttggtcca 840
ggagcctgtg gtcaatccag tcagtagtgg gcgaggtgta acatctgtgt ccg 893

<210> 47
<211> 789
<212> DNA
<213> Rattus norvegicus

<400> 47
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tngggcgggc ancatcaatg gtanaaattt gggggggnng annaaaatca tnaanncaac 120
cgtttccana gncaaccatt ctgggngncc caaggttnga ngagntccgn tcaaggngaa 180
acctttttcaa gaccaattaa ctaggggatn agaggcgggn tggttnntga ggggcgggct 240
gctgagaaga ttcgttgggg gacccaggag tgaaggtttt tnacctgtgt ntntcgggaa 300
ggtcggatnt attatantcc tgctgttgga ggagttcggt ggttcaaggg ccggacccgg 360
agcgtttact ttttnttgnc cgcagccaat ttgttntgct tggtttcttc ngaatcccgg 420
ggcggggagg gggaagcggg gggcccaatc accacgatcc cggcagccac cgcgaaattg 480
ttccggcagn tacgantctt caacaagagc cagagaaggc gggtgcagag nttcattagg 540
acgntcggaa acccggcgtg acttactttn tccaagccca ttggttgatg agaatgatga 600
ctgacaggga ggcgtggtca cgctgtcgcg ggcgggagcg acgggtggag ttaacgacga 660
aagctgcgcg cgcagccatg acccctcaca gccacntatc ggagggaggg gcgggacagc 720
tttagcttgg tgcgtgcgca gccggacgtg aggcagttgg tggtcttcca tcgtcgattt 780
ctggttacc 789

<210> 48
<211> 872
<212> DNA
<213> Rattus norvegicus

<400> 48
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cggggaagga aaanggggct ctnaaaatan gttantggga tggngcctta agggggggcc 120
catgngccag gaangcagat tcaaaaatgt tccaagtgga aaaccanggt tggnanaggc 180
cctccnggnc gtnaaggagg agaggagaga tggagtttca ggtgtgtttc ccacccagtg 240
ttcccaggga acacaaaacg gataggtcac cntcaatgna caaggaatta aaagcttggg 300
tgtatnggga ggcctgcttc caaagccacc agaaaatccg gagagccggn ggatcntacn 360
cacccagagg ttcataggga gggcantatt aggggtgtgc ccttgtgaga ggaagtgtgg 420
cacngtgggg ctgggtttga gatntcagat gntcaagcca ggcccattnt ntctctctca 480
gtntctctcg gtctctttct cngtctctnt tcagtctntt cagtctctct cagactctct 540
ctctctctct ctctctctnt ctctctctct ctctctctct ctctcccngc tgcnttcaga 600
tatagacgta gaantctcnt ntatccagca ccatgtctgc ntgcatgctg ccattnttcc 660
caccangacg ataataggct aaacttntga actctaagcc agcctcaatt aaatttntan 720
gagtcaaacc agcctcaatt aaatgttttc atttctatga gtcacagtgg tcatggcatt 780
tctttacagc aatagaaacc ctaactaaga cttgccgaaa cctcaaccac aacttcagcc 840
ctcagaagcc caagagggaa aagaccttga at 872

<210> 49
<211> 785
<212> DNA
<213> Rattus norvegicus

<400> 49
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gtgacccata acttcggaaa ggttgtgttt tatccggcaa caaccacngt gtagcggtgt 180
tttttgtttg cagcagcaga taacgcgcag aaaaaggatn tcaggagatc ctttgatttt 240
ttnttcgggt tctgacgntc atgttgtgtg gaattgtgag cggataacaa tttcacacag 300
aattcaaagg agaggagcca atatagaggg ggaaaaaaaa agaaggggaa agcattagtt 360
taaaaagttg agagaacaaa gtatgttttg cttggatggg caaccaaaga agcntgccag 420
gaatggtcgg taaaaggtgt aagagtcatg aaacgtcttc tgtccaaccg ttaccggaaa 480
catgcaagga atttcttaga ctggccagga ttggattgtg ggaaaggtct cttcaagcnt 540
ccccttggct tttatggcaa gaaaatagtg cggactatag agagcgtcgt tctcaaagct 600

tgtccccaat agcagaaaag cattgtccta aattccttaa aaggcaccgt gaaataaata 660
ttacgaggac acgatggcac aagaaggagc tttcaactct gccaccagaa cagttatact 720
tcatagtaac catgttgccc tgttcaatga caaggcacgc tctccagcag aaagggaaaa 780
ggagc 785

<210> 50
<211> 889
<212> DNA
<213> Rattus norvegicus

<400> 50
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ggctttgggn gggntttcat anggnnntgn tttacccaat tcagtttttt attggtnttt 120
natgggcgca gggatagngn gttcnggntt cccacangaa tttgatttnt ggaatcacaa 180
gtnaccagtn gccgnaatca cgagtttgcc gctttntttc ctaccttana ttcataatan 240
gaatgagtan ttttttttta ttgagnaang ttttnacagg tttagtaaac atgaggacag 300
aggttttaag ttgangatta ggaaggagag ttccggggga cagaatgtgt gtattntcag 360
tcagtgcact acccggaaga gttgcagtca ggttgaggaa gggagcggat ttcctggagg 420
ttttaaccaa cagagagaaa aagcatttac tactgattaa gcacacaatc tctggattca 480
gagaagggtg tttaccttta tataaaatgt ctcctaactg cgtgactgtg tgactttgtt 540
gaagtcaact gagcactgac tgtgttgtgt gcaacatggt aagaggacca actttnttct 600
taaatttttat ttattattta tgtcacgtgn acacttgttg cttttgtttt tgttctaatt 660
ttatctgcat atatgtctgc ataccacgtg catttctgat gcntacagat gccagaaaag 720
gacaccgagt ttcccctggg antggagtta tagatggtta taagtctctg agtaggtact 780
gggaagtgaa cttcagtttc ctctggaagg gcagaaagcg cttttcaaat gctgggccat 840
gtatttcagc ccctacttaa tttataattt tattttagag gatgtgctc 889

<210> 51
<211> 947
<212> DNA
<213> Rattus norvegicus

<400> 51
anaaaaatng agaagangag accccagaga agaagnanga gaganaacag agaagaagag 60
agnaagggng anaaantaga gaaaggaaaa gntcttaaag aggcnanaaa ntancnatnn 120
aaggagaaga nggaaggnta acataggagn caagaatana aaganaaaaa gaggtagaga 180
anncagagaa cgagaaaaga tgaaanaaag antanaangg aagaaagang nccagnanaa 240
anaaggcaga aanaagatgn cgtaaaanaa gagagaagat aggnaaaata gaggagaagg 300
ccnaacagga ngggaagagc agcgaattnn agataaaacc ggagganagn nagagaaggn 360
agagntngnn aaggcaaaga cagnanngag nacggtacnt gccccagaag gnngaagaan 420
gncnagangg tgagggnngg cacngnccnt tccccttagg aggncgcccg cccagagatc 480
aggtttcnag gncaccgagt tggatacnag attatncacc naggcaggaa angantatng 540
caaaangatt cggggngggg tcacggggtg agaaataaan tcannaaana gaggacgngg 600
aggagggngg gaaactctng acagaaatng caagcangaa gccagccnca cccaagcccc 660
nacngaagca gcngagangt tgcanggcgg naggtccaaa tcancgnagt catggagnga 720
gcttcgggng ggcccnganc cantgaggaa gggcaggaaa ccatatcnag ccgagccnng 780
nganggntgc cctganacac ccggagaggt aatttttatt tnacgggaag cgtccagnca 840
agttcgtggg ccggaagaga cggtacttta gtatacancg ctnntgctnc gagttgtnng 900
nccttntnat gnnagatctc acaaangaag ctnanaagta gatatgt 947

<210> 52
<211> 860
<212> DNA
<213> Rattus norvegicus

<400> 52
aagggaattt ttaccccggt tnccttttgn cnggggggna aaaaaannaa aaaataattt 60
tttaaaatta aaggggnggg angtttttcc ggttctattn ngccnattcg gggttacact 120
tttatccanc ntttgntttt ttanccggcc gggttaaaaa tgggggggga ttagttcggg 180
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ggtntcacaa ttttnttaaa caggatttnc ttcaaccatg gattaataca tttccggtgc 300
agnttgcccg gtttgttttt tggntggata gggatgccag caggattcag ggatgcccat 360
tgtgnttagt ntctggccct ttaggagagc tttgggctaa ttatgtgacc gattttaaga 420
agtggtgttg ttgtggttcc agggactcac ggatcagcct ttattttata aggacactgt 480

ggaggagaga cagaggctga gctgcattct gatgtcattt gtgctgctgt ggaagttaaa 540
gaaaagctgc agaagtcagc aaaacagatg aataccaaga agggcagtgt gagtacagga 600
atggagagaa aagtcagagt ccagctttgg ttaactccct aggatcagac anttctgcgt 660
aaggacgggt ctacagttta acagaccaca gagcaangtc aaacagcaaa gtggtttcat 720
ggcaggcagg aaatggaaca tttaactgga aacactgaac ccacccatgg caaacttagc 780
aatgaagctg ggtgtggtgg cacatgcctt taattccaac actcagggga cagatntaat 840
gagtttgagg ctagactggt 860

<210> 53
<211> 191
<212> DNA
<213> Rattus norvegicus

<400> 53
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aattcctcag gatggggaac agccattggg cttttagtag aggagggaca ggccctttg 120
cagcaacagt tctcccctga atgttggatc tccacctata cacatggggt acttagcctt 180
atggatgccc c 191

<210> 54
<211> 988
<212> DNA
<213> Rattus norvegicus

<400> 54
ttnttggnna cgggtntccg nantatgaan ccnttcccgg ggtttttaaa aancccngga 60
tattcgggga tttgggtttt nnacggcctt tttttnagag gccaaatncc cntntnaang 120
ccttttatcc ttccntttnt gccccncttc naattaggaa gcntggtttg nccgantntt 180
aaggttttta gtcntccttc gttnntnttt cccttntttt ttccctnaag ttataaagcn 240
ggtatntggt ttgccaggnt tctnttgtac ccgtcatngc gggttncggn ttacccaggn 300
tttgttcctn ggccggtncc ttccaatttt ggantntccn ggtcnggngt ccnattncct 360
tgnaacngtt ccacacntna tgacaattaa ttgtttcctg tgtaatttgt ccccggactt 420
ntggattctt gngancaggg cctntgtttc atggaagcaa actcccttaa ntatttacca 480
ggttgattga ttaagaaagt antcatgntt gggaaaccca cntgttttnt tcccaggatg 540
gaancccagg attttggaac tgcagaggct tcagggtctg ggaagcggag gcaggcaaag 600
aatggagtgc actgtccttt tgcaatatgg ggtttgcctg cctgctggct cctctcntgc 660
tntctcagat ggtgactgag gctacttcag caggactagg aataatcatg tccaggtggc 720
tgcccttccg agcagaaagg gacagacgtg gggcgatgaa gttgctatcg ttttttttttt 780
tttctgcaca gactgcaaag tgtgcagagg gagggaggct gtgcaaaaaa aaaaaaaaaa 840
aaaaaaaaaa aaaaaaccga ggacgcagaa gttagactgc tgacccattt ggtgcatgtg 900
tgcccatgga gggaggggac cttctcaaaa gggttcacgc agcangcatt gaaagtnccc 960
cacntgtagg gncgcaagca actgagat 988

<210> 55
<211> 665
<212> DNA
<213> Rattus norvegicus

<400> 55
gaaaaagatt caggaanctt atttttntcg gttcgacttc agtnggggaa tgggcggana 60
catttcacac ggatttgtaa anacngtnac ngaaacttgg nggttcgtag atccactttt 120
ttnagacctg agagtagttt ttaaaatatt tnaattaaag gtttcctgca cccacttttt 180
tttttatccc taacttttca tccagtatgg tttttcaata tcacanttta atctaggact 240
ccttgcttaa agcaattaca agttaaatta aaagtaagag atggctnata gctctcatta 300
ctgggatgca ggtgtgaaac aagtgatttg tgtagaagct ggcaggatgg gtataaacaa 360
gaacacgtgc ccagaggatg tattgaaagt tggatttaag tctctgagta gtttatgcta 420
ggcggtagca ttgaacaaga tgaantctct gntcatagag gtagaaactn cccagattct 480
gaggaagtgt gagggagagc attagatgtt actgttgggg atttgggaag gccaggaaac 540
gttactccat gcccaaggag ggtaggagaa aggtttgggc ttagctttga ggacggaggg 600
aactggtggg tggatatgag gatggttatg ctaaaagcag agtggttttc aactattgtt 660
cttct 665

<210> 56
<211> 857

<212> DNA
<213> Rattus norvegicus

<400> 56
aaaaaaagaa aggaaagggg agananaaaa annangngan aaaanagana ganagaggna 60
agaggaagng agggngaaaa gagaggagan aaanaagagg aaggagaann gaggaaaang 120
aaaggaacaa aaganaagng anggaagana aagggagaaa aaanaagagg gagaaangga 180
ggagggaaan agagaanaga gggggagaga anncagagaa nagaanngag aaaaggngga 240
gacnaanana gagggaagaa aagngaggag aagagagggg agaanaaant tgaagaagaa 300
gaagangaga agangagnag aggaaganga ggggaagaag aagaggngga ggagaagaag 360
aggagaggag gaggaaggag aaggaggagg aagagaagga ggaggaagag gagaggagaa 420
ggaggaggat actanggagg ttgtttcaat aaaagagngg gatntaagat taananaagn 480
aataatgccg gtttntatct gttcgggggg ggtccttgtt ctccaaacac aganntgggc 540
cagtttntca aaattnaant gngaagattt cttggntnga gagcagntca gattnantng 600
nattnttttc tagttttnaa cacaanctt gtgntaacaa agagnganga ttcnaggana 660
actcgntttt ntttgggagg agactttgtt cctttcnatg aagatgcagg acgnggaaga 720
cgcagggtgt gaacaggaca cagnnacgct tnngtntntg tcngcntcag cngcgtggga 780
atgagtcaga gcagcacggg gaggtgcctg gatntaagct ttctggtagg gagaacagag 840
tgcaggcngc ggcccag 857

<210> 57
<211> 902
<212> DNA
<213> Rattus norvegicus

<400> 57
aaaggggggng ggaagaanga aaagggnaaa cnttngtttg gaagccnnca nnaaagnaan 60
gncgaattta anaaggggggt agggaaaaaa aaaacanaat attccntcct tagccatnaa 120
ccgaacttcc ngcaaggaaa aaaaatttgg ngggngtaaa gggcaccncn tcccacaaaa 180
ttttgntaan tttgggcgca aattcangca ggntttngtt ggaaaggngn ananaccaaa 240
gggatttngg ggatttnaaa atcngngttt nnggcaggnn atccngaagt tngaatcgga 300
cgncnaccct ttatttnagc agttatttan gggaacatgg gagggnacca tttcaaacca 360
nggatcgggc cnggagtntg agtgttcagc ccacngcctt cnaacantac cgggataagt 420
ttttccctgn gccagagacc catccangtt ccagcaaaag gntggtcatc tngggcnagc 480
tccnngagtc atcnngggtt tctcccagcc nggggccaat ggtcgaaggc aggttntttt 540
tgtctccagc ttgttcccna ccgngggagc ctgtcaaggc tgcacagnac cagantagtg 600
gtcatntcng gctagctccn ttagctccnt gtccagggga cttcctggca ctggattagt 660
ggnggactca ggcttgcttt tttttcagga gaggttagat tactaatcat tcagatgttc 720
ataagtcaga acactgagca aagcaatagn ttctcctcca cntactgant cacacgtgca 780
caacagccac acccgcaatg cttntaggag caggtccagn gnacttttgt tttaactatt 840
tntggctctt tattaatcag cacataaata cgcttcgttt ctccttttttc aatatgnatg 900
tg 902

<210> 58
<211> 852
<212> DNA
<213> Rattus norvegicus

<400> 58
acagaggggg ggggggngtg gaattttngg naggangttn tnggaaggcc nctaaaaaag 60
aaatgttccc agaccaaaag gggggggggna gtnnaattca nggatcctna ngaggnggaa 120
atttttnnnn tattnaggat caggataaat angaaaangg gnanattttn nnnangnggg 180
ttttttttttt ttttttttttt tttttnngng gnnnnnannan annnnnaaat ggcgncgggc 240
atggntaatg gggaanttgg gganaattac agagatttnt ttttcccatg ggnttccagg 300
atgaattcag ntaccaacca ggttggtacc agcattttaa cattcgagtt agacatcaat 360
ggttaggtcg ggagtgagag gttcggggcc ngacatatat tcntggtgaa cccagtgcac 420
cttntggttt ntacaaggag cttgaggtag tcgcccacca gtagctgtca ggcaggtggc 480
ttaagttcag aaccgnttcg tggaacccga gaagcagaaa aagacataag ttntgcngct 540
tcanaatcca ctcntgaata cananatctc ggccaaagaa gcacagccag tctttccgtt 600
nacangaggc cgggagcaac aantccacag ccagcccaag ganatacaaa ggacttgggt 660
cagttctgna ccagttggag tcagagatgg ggccctcaaa gtcccagcag tgaagggcat 720
ggtctccagc nnacagtgga acctttaaga ggtggggact tgtaggagga gttagataat 780
tggggtgtgc ctttgtcccc nacntcgttc tttccctctt tatggccttg atgtggacaa 840
gattgtttct gc 852

<210> 59
<211> 884
<212> DNA
<213> Rattus norvegicus

<400> 59
aaaaaaaatt ntttttccna ggnaaataac ccgngcttaa ccgggcgggg gagatcaatt 60
ntttgtngtt gtttcctcng aggcggagng tcaaaanaga acacnnctgg naaacccccc 120
ttaaaanaca aaaatttgan ggggnnggng ngttacaaaa agacaggatg ttttccgagt 180
cggattcaat cccaccacaa catggggttc acaccatngt aaggaatcgn tgccttttg 240
ggggtatcct agggggtana nttccaaata nngataanaa ttttttaaa aatttaattg 300
tanatattta ttanataatt taataaataa tatttggana nantnatgtt ctngcgcctt 360
gnggactggt agtttttttnt ccnnattnna actttcccag nactnggtag cctatgtgnt 420
tatgcaaccc nttagaagct gccttcanta ttnaactcat actgtttctc gataatcngg 480
ggagtagctc cagttngcta tgaagctgcg gaaaggtagg cggacatccc aggcttagac 540
agagttcagg ttatttggaa ctttnnaaca gaagtgtgtt cntgcacggc agcaagacna 600
tntgggtccc gtagttccgg tcgccaggag tagtgtattg cttaggacca ttctgggtgg 660
aatgcatctg gtgggtctta aannatgtca ggcagggcct ggcaccaggg tctggcggga 720
agcctcacat accgttntaa tgacttcatc tgcttagaat ttgtggggaa acgatgcaga 780
aaaatctaac cagggatgtt tctgggccag tcatgttggg gatgcctcag tcatgtaaaa 840
ttgagctccc cctggagcac accttaaaac atcttctgtt taat 884

<210> 60
<211> 955
<212> DNA
<213> Rattus norvegicus

<400> 60
cccntggaaa accnaanana atangnnnan anaaanactc cncccattga gggaacnttt 60
tagggnttcc nnntttcccc gganccgcca aatgngacac caaaannngac cgnantcttt 120
ggnngttgct tctcttggan cgcnttttgt tcgaccgggg tgactaaggn catgtngggg 180
acgantaatt gtttccgggg gcngntcggc accttccnan gngngngngg tttggttctg 240
gaagnccgaa nnggcatgtn ttaagatttg ccnatccatt tagggttcgt tcaacgcctt 300
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agtagggaga gagggaaggg agatagaccc ggagacagag aagggaggga ggaagggagg 420
gattatcctg taggatgtga gcccagacnt gtctgtggtn tctttccatg acacaagaga 480
ctttntgctt gtccctagaa tgcttcattt tntagtgtct caaacttaaa gggctagtgt 540
aaagttagac tgtgaacann tngtaaacac aggtgacagg aatgtntgtc agctgggccc 600
nttatatgcc acggcagagt ggtacgtgat gcccccacat gttatgtgga agttntcatg 660
cagggcttca gaacacagta gatggagatt gtgaaaatct gttgttnact taagagactg 720
gccccaagga tccatgtgat gntacttctg ttgcttgtgc tttaaaatct tatgtgatgt 780
tttgcagact ccnttcggga ccccagcaca cagctgagag tctgccctgc tggcactgct 840
gcctgtctgc tgaaggggaa cccaggcatt tgatgttggc cggcccaagg aggggctgaa 900
gctantgagc aaggacagtg atagacccac acagnagttt gcaagtaaat gagnc 955

<210> 61
<211> 1107
<212> DNA
<213> Rattus norvegicus

<400> 61
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nttcccntga ancctcctga ggggccaaan attgggggg gttnacaccc ccggggaaac 180
ccttcttgac cccnagaaan gcngtttagn ttcccnccca tgggntccct taccctgggn 240
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atccagtgca ttccaccatt gagccngcag aggttgatng gcaggaangg tttaaccctt 360
ngaccaggag tgacaaattt ngngggacnc cccagtgnga gctcacaaca ngtngacatt 420
gaggcnccaa aggattgttg aggggatgga ttgtgtcgca gtctggttgc ctttatagtg 480
ccagcatcgt tgagccccgc ccagggagtg ttggcacgcc caaaccccna cccagcgctt 540
gaggcaaggc aaacacactt cccagcccct taanttncna cgcctttgtt gcttggacgt 600
cccggantgg gagcaggatg aaggatttta gtgcaggaga agaccagtgc aagccggaga 660
catngagttc cctntaattc ggtgttcagt ttgccnttnt ggcacgtgac tcgtaactct 720
ggtatgtgtg ctgaaccntc taccagccag agatcagtgt ccttaaagtt cgaatcagtg 780

tgaggggac tgggaacaat actgatgctg ttgccctcta gtggcaaggt caactccaag 840
cgagagggga agcagtcagt ctaccgcatc ctctaagata gtggttctcg acctctctaa 900
tactgcggat taatacattc ttcatgttgt ggtgacgctc caaccataaa gtgattttcg 960
ttgctgcttc ataactatat ttttgctact gttatgaatc gtgacataaa tactgtgttt 1020
tcagatggtc tcaggcaatt cctgtgaaag gggtctccca caggtttgaa agtntcccac 1080
ctgtaggtgg gccaagctaa atgagat 1107

<210> 62
<211> 92
<212> DNA
<213> Rattus norvegicus

<400> 62
atggggcatc ttgtaacagg aggcctggat tgagtactgt aactgagntc ttgaaagact 60
ttacctgtag gtttggncng cttgaaagag at 92

<210> 63
<211> 209
<212> DNA
<213> Rattus norvegicus

<400> 63
aattccagcc catcctgaga cacacagtga ccctgtctca caaaaccagg gaaaagccag 60
gtgcggagtc tcacgccttt aatctcagtc tccggaaaca gaggcagngg gatctctgtg 120
agttcccagg cgaganttct ttgtacaggg nnccctctga annenectga aagatttcac 180
ctgtaggttg ggccnagctt aaaagagat 209

<210> 64
<211> 97
<212> DNA
<213> Rattus norvegicus

<400> 64
acagagaaac agtgtttccg ttccttaaaa cgttgctcta tcttgaataa caagcttatt 60
acatgcgaat cgtattggga acctactgaa ttccgat 97

<210> 65
<211> 1047
<212> DNA
<213> Rattus norvegicus

<400> 65
caaggtgaat tccanttggn gtttnnaaat ngtttttnaa aaanaaattt tntttggnna 60
ttgccttnaa ngtttgggnc ctgaattcaa aattccaant tacccaaaat ttcatgttcc 120
atccanaatt naattccgga aatttacaat aatttgaatt ntagttttcc caattntaat 180
ntcagtagtt tgnntttgtg tgccccnatt ntaanatcag acccgtccaa tcacccaatt 240
gnttttttnaa attgaatngt tttcccntgt accttccttg caangttgct ttaaattnga 300
atttcagaat ccccattgaa aagaatccgg gnnaaagcaa caccnttaag gaccccagga 360
aaccagaaat tngnagaaan ttggacgnag gganttnaca ttnttnccgc canaggatgn 420
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cagaagctgt tgtctttaga tggcagagtg cggacccctc gccccagagg ccntagggtg 720
cttgcagcgc gcgcaagacc ctttccagtc tagagcctcg cctagttctg cgcgtgcgcg 780
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caagccggaa agggacatgg cgccgccgag cgggccatcc ggagggcgga cacgactaat 900
aataaatcgc ccccccgccc ccgcttgtgt aaggcgcgct gtatctctgg cattgtgtgg 960
accgcctcac attcataagc ttcgtcagca gcagtagaga atggcttgaa agacnttnac 1020
ctgtaggttt ggcnagcttt aaaagat 1047

<210> 66
<211> 1063
<212> DNA

<213> Rattus norvegicus

<400> 66
catnggagtt cccaatggnt tccntnaann ggttntnttc aggttgggca ncntttagga 60
attgaaaatn ttnnttggga ttcccctaga atttgatccc attngggaaa ttttttattt 120
ccngaacagt ccantnttaa aattgggcct nttgggatta acggattcca aggttgcaac 180
anattggcaa gtttnnggac aggaggtttc aantggntaa agtggataaa tngtgaattt 240
tggagangga attgacttgg ttgggggcca aaantaggta gcattttgcc cggagggttg 300
attgcattct gttttgtgta aanatgaagn tacttgacag ctttgagata agaaggagac 360
ntaatttgct aaacatttta agtgttctat tctgccggag ttttggagag ggtatatgcc 420
ggtcaggaag ggagccagaa gccagtaaca ttgcaagtat ttcaacatgg aaagctttag 480
gttatctctt gtgcatctta tgctcggnta atgatgtaan ccaattgtaa ttctgggcac 540
agctttccca tgtgtctttg gaacagtctg ggtttgtggt tntaaaacaa catttgtatn 600
tagttggagg cttatctaag gagcttctta gcatttgggt tgtaatttat tttagtattg 660
tttcagctac ccattgctac atagtaaatg tacaaaaatt tagtggatta aaataatgat 720
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tgtcactttt ccaggtttct gtcttacagc atggtggctt ggttctgaag ggccatcact 960
ctaatggtgg ctgggttccc agcgagaacc agtgganccc aaggatagct tttggtgact 1020
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<210> 67
<211> 815
<212> DNA
<213> Rattus norvegicus

<400> 67
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ggggggggtt tccaaanatt ccnggggttt tttnnggggg taaagggntt naaaggtnaa 180
aaaatgttcc cggngccccc anacttccaa aggttttccc ttnnaaaatt ccnggccttc 240
cgggggnccn tntgtncccc ccnttccccn aaatnncntt nngaaaaggg ttnaanantg 300
ttnaaaancc cnaangttaa angggnnnat nnaaanggtt tccctnncnn ggggngggna 360
aaaaggtttc gcgcgganac cnntgatgcc caggttcagt ttccccggag cttggggcca 420
gacccgcggc gcgccntggg tgtggcggga gcgcgcgggc ttgcgcccgg acggcttctc 480
cccgcccccg actcccctcc gcggcggcgg gagtaggttc ttccggctcc ggtctgaggc 540
ggtgcctggc accttctgac caggatccgc gggtccccgt gctgtggtcc cgggaggcac 600
gcggggcctg cctgctatag cgggtttgca gggcgagcct ccctggagcg gtagggtcgg 660
tttgggtgtt gcacgctcgg tttgacgttt taatccggag gagttgtggg gttcctcgaa 720
tctcaaactg ccttcttccc ttttgagact tgaaaatacc cgaagcctgc cttgtactga 780
aagacnttac ctgtaggttt ggcagcttaa aagat 815

<210> 68
<211> 1034
<212> DNA
<213> Rattus norvegicus

<400> 68
aaaaaanagg tttccccngg angtccctng gggntcnttt tnnganentn cgttangggg 60
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gggttaagtn tttncccaaa agttggtttt tnnaaaaanc ccctttnncc cggacgtttn 180
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acaaacncaa aaacanaaac aancaaactg aaagactnta acctgtaggt tggncagctt 1020
gaaagagatn tttc 1034

<210> 69
<211> 186
<212> DNA
<213> Rattus norvegicus

<400> 69
agaccacctg ggtggaaact cctattctta caccaagctg cctctgtatc cacagatacc 60
aagaagtagc caccgttgtt ttacttaact catggtccac ggggtgagct gaggtctcct 120
tcctgagcaa gatggaaatt ttacttggtc tgttaactag cgtgcattga atggangaca 180
tatgat 186

<210> 70
<211> 1028
<212> DNA
<213> Rattus norvegicus

<400> 70
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cttaaattta ggnatttttg aatnatttca acccnttgca ggcagtttgt nccatgttnt 120
gggaaagttt taacaggatg gttatttnga caaaacaggt tttttcagac catttgtgna 180
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aaaagatc 1028

<210> 71
<211> 1034
<212> DNA
<213> Rattus norvegicus

<400> 71
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gaaagagatn tttc 1034

<210> 72
<211> 824
<212> DNA
<213> Rattus norvegicus

<400> 72
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ggcccttctc ggtgcccacg cacccccga tcgaacccga ggatgagcat agggtgtatt 660
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cactataaag gaggccaggg ccaaggactg gcctcctctt gctcacgagg tcagacgcga 780
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<210> 73
<211> 774
<212> DNA
<213> Rattus norvegicus

<400> 73
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antaggttnt catntggatt gccngngttc cngttggcat ccgggaaaan tgagactgtg 180
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ccttcccgaa ccggcccntg gcgtctccgc cttnggcact tgcacatntg gcggcccagg 300
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atggctcact gattaagaac actgactgct cttccagaag tcttgagttc aattccgagc 660
aagcacatgg tggctcacaa ccatctgtaa cagattctgg tttatgtnga gacaactaca 720
gtgtactcgt attgaaagnt ncccacctgt aggttnggca agctaaanga gatc 774

<210> 74
<211> 248
<212> DNA
<213> Rattus norvegicus

<400> 74
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tagctcaggc tggttttgaa atcaggatcc tgaccctcag gaatgttaaa gtgcctaaaa 180
gtggngacaa attattttac gtgcctttga aagacttcac ctgtaggttn ggcnagctag 240
aagagatc 248

<210> 75
<211> 833
<212> DNA
<213> Rattus norvegicus

<400> 75
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aattnttaag cntttgcatt aagtantaat gccaaaatga ccccaanata tngntccttg 120
antgtnntaa aaangaggat cttcnttgnc catanacgcc ntatatgaaa gcaactgaac 180
aagatttaaa attggacagg tcacaancgg gcgtgtgcct ttaatcccag cactcgntgg 240
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ntatatcagt agggctttgt agagaccnta tctcaaaaaa caaaagcaaa acaacagaga 360
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ctcgtaatct ttttctctct tcagtttgcg tacgggacag cagacctact cacaacccaa 480
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<210> 76
<211> 880
<212> DNA
<213> Rattus norvegicus

<400> 76
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ccggattaac tccaaggcca aaattccgag ggggaatcaa caacaaggac ccaaccggat 120
taaggcgggt tcaaacaaac ttggatttcc ngccctttgg ggcgggggaa atgggcacgg 180
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<210> 77
<211> 864
<212> DNA
<213> Rattus norvegicus

<400> 77
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gctcacttgt ggatttcctt taagcaagac ttcctctctg cttccaggac tcctgtcaaa 600
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tcaactggga cactcactct gagacaggga ggcaagggag aaacaggtca gaggtagaga 780
gagctcagtc ccagggactc acgttgaggt ccctaaggtg cgctagggag aggnttttac 840
attcggttng gcaagctaaa agag 864

<210> 78
<211> 874
<212> DNA
<213> Rattus norvegicus

<400> 78
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<210> 79
<211> 886
<212> DNA
<213> Rattus norvegicus

<400> 79
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aagtccaact tctgtttttt cttccttccc cgcaacatta ggaatgactt ctaagagngc 840
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<210> 80
<211> 865
<212> DNA
<213> Rattus norvegicus

<400> 80
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<210> 81
<211> 859
<212> DNA
<213> Rattus norvegicus

<400> 81
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gagaagaatc cataaagnnt gaagacatgc ttgtngtgnc tgaaggacnn tacntgtagn 840
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<210> 82
<211> 1021
<212> DNA
<213> Rattus norvegicus

<400> 82
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<210> 83
<211> 1013
<212> DNA
<213> Rattus norvegicus

<400> 83
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<210> 84

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<213> Rattus norvegicus

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<212> DNA
<213> Rattus norvegicus

<400> 85
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<210> 86
<211> 1039
<212> DNA
<213> Rattus norvegicus

<400> 86
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<210> 87
<211> 1058
<212> DNA
<213> Rattus norvegicus

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<210> 88
<211> 1043
<212> DNA
<213> Rattus norvegicus

<400> 88
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<210> 89
<211> 454
<212> DNA
<213> Rattus norvegicus

<400> 89
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<211> 873
<212> DNA
<213> Rattus norvegicus

<400> 90
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<211> 876
<212> DNA
<213> Rattus norvegicus

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<210> 92
<211> 459
<212> DNA
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<210> 93
<211> 3133
<212> DNA
<213> Rattus norvegicus

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<211> 2161
<212> DNA
<213> Rattus norvegicus

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<211> 824
<212> DNA
<213> Rattus norvegicus

<400> 95
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<210> 96
<211> 774
<212> DNA
<213> Rattus norvegicus

<400> 96
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aagcacatgg tggctcacaa ccatctgtaa cagattctgg tttatgtnga gacaactaca 720
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<210> 97
<211> 248
<212> DNA
<213> Rattus norvegicus

<400> 97
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aagagatc 248

<210> 98
<211> 880
<212> DNA
<213> Rattus norvegicus

<400> 98
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<210> 99
<211> 864
<212> DNA
<213> Rattus norvegicus

<400> 99
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attcggttng gcaagctaaa agag 864

<210> 100
<211> 874
<212> DNA
<213> Rattus norvegicus

<400> 100
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<210> 101
<211> 886
<212> DNA
<213> Rattus norvegicus

<400> 101
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aagtccaact tctgtttttt cttccttccc cgcaacatta ggaatgactt ctaagagngc 840
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<210> 102
<211> 865
<212> DNA
<213> Rattus norvegicus

<400> 102
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<210> 103
<211> 859
<212> DNA
<213> Rattus norvegicus

<400> 103
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<210> 104
<211> 883
<212> DNA
<213> Rattus norvegicus

<400> 104
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<210> 105
<211> 987
<212> DNA
<213> Rattus norvegicus

<400> 105

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<210> 106
<211> 1031
<212> DNA
<213> Rattus norvegicus

<400> 106
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<210> 107
<211> 1138
<212> DNA
<213> Rattus norvegicus

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<210> 108
<211> 1072
<212> DNA
<213> Rattus norvegicus

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<210> 109
<211> 1094
<212> DNA
<213> Rattus norvegicus

<400> 109
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tcgatgtctc cggcttgcac tggtcttctc ttgcactaga atcnttcatc ntgctcccag 780
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gctggccact ataaggccag ccagactgcg acacagtcca tcccctcgac cactcttttg 960
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gctaaaatga gatc 1094

<210> 110
<211> 1107
<212> DNA
<213> Rattus norvegicus

<400> 110
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tcacaggaat tgcctgagac catctgaaaa cacagtattt atgtcacgat tcataacagt 120

agcaaaaata tagttatgaa gcagcaacga aaatcacttt atggttggag cgtcaccaca 180
acatgaagaa tgtattaatc cgcagtatta gagaggtcga gaaccactat cttagaggat 240
gcggtagact gactgcttcc cctctcgctt ggagttgacc ttgccactag agggcaacag 300
catcagtatt gttcccagtc cccctcacac tgattcgaac tttaaggaca ctgatctctg 360
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gaacaccgaa ttanagggaa ctcnatgtct ccggcttgca ctggtcttct cctgcactaa 480
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tccctgggcg gggctcaacg atgctggcac tataaaggca accagactgc gacacaatcc 660
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atggnccngn ngnaccnttg nnntttg 1107

<210> 111
<211> 1069
<212> DNA
<213> Rattus norvegicus

<400> 111
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cttttaggat tggttcccct tntgtctccc tttttggaca tggntcttan ataggtggnt 240
caaaattcta cntnttggaa tcagcntatn tcatcaggat ttagcccagt gtgntnaacc 300
tgtggagacc cntttcacag ganttgcttg agaccatttg aaacacagta tttatgtcan 360
gattcataac agtagcaaaa atatagttat gaagcagcaa cgaaatcact ttatggttgg 420
agcgtcacca caacatgagg aatgtattaa tccgcagtat tagagaggtc gaganccact 480
atcttagagg atgcggtaga ctgattgctt cccntcttcg cttggagttg accttgccan 540
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acactgatct ctggctggta gagggttcag cacacatacc agagttacga gtcacgtgcc 660
agaagggcaa actgaacacg gaattagagg gaactcgatg tctccggctt gcactggtct 720
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ctctcactgg ggcgtccctc taagatctgt ccactcctgg tntaggggtt aagcctttcg 1020
tgccctgaaa gatttncacc tgtaggtggg gcaagctaaa agagangcc 1069

<210> 112
<211> 1058
<212> DNA
<213> Rattus norvegicus

<400> 112
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cgaccttcgg ttaccggtac ctgcccnctt tttcctttgg gagggtgggn tttttcatag 180
ctcagctgta gtatctcagt tcgtttagtc nttngnccaa gttggtttnt gcaggacccc 240
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ngattattgc cattggcagc agcaatgtaa caggttngca gagcgaggta tgtaggcggt 360
gtacngggtt cttgaagtgg tgccntaant tacggntaca ntngagggac agtatttggt 420
atttgcgctn ttgttgaagc cagttacttt nggaaaggag ttgntagttc ttnatccggc 480
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aaaaaagnat ctcaggaaga tcctttnatc ttttctttcg gggtctgacg ctcatgttgt 600
gtggaattgt gagcggataa caatttcaca cagaatttct cttagaaaaa tctgtccttc 660
agaaacttaa attctgctgt tccataacag aagtcagcaa gtgactcacc ctccagatac 720
aggtatatta cctccactcc catccacaga gacttaattc tagtcagctt catgatagtg 780
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tttttaaacg gtaacccagg gaccacatcc attaaaaaca ctggactgtt tgtgagagtg 900

tatattcctg agcattgcct atcccttaag gtactacaaa atttgggagt gaggctcagc 960
aaactatttt aacatgcctc tcccacccaa ctactcaaga ttccccgtgc acagttgaaa 1020
gntttnccac ctgnaggtgg ggccaagcta aaagagat 1058

<210> 113
<211> 1046
<212> DNA
<213> Rattus norvegicus

<400> 113
cannaaaann agttccaagg aantggntgc ccngaacaag gacccaaaac ntgnnnnana 60
angggggann naanggcana annnatggac gagagtnaan ancgcnangn agaagantna 120
aaantcncca nntggngccc caaatnncnc aattgancca aancnntaga ggnncccaag 180
acnaatgggc actntganna gancnggcca gaagncaagn gggggannnt catagnnaca 240
tggnanaaat aaagntntgt aaacccggan tggcaatnga aaccagcaaa gacccatgaa 300
cgtgagngan accagttgga aacaatgaan nnantgggtn antnacagga atgnggtnan 360
gacgcnnagt gancccaaan aggcaacncc attgaaagcc ttcnccncca tggaaatact 420
gtanntaaaa caaacaaaca aatnacaaaa anaaaaaacc caaagcttaa gtggagtgcc 480
cnttccagnt agccaccnnn taagaactgt aaatcgcacc ntcccangcc agatgcaggt 540
aaggnaggat tacaggnatn tcggagggct caggagggaa tgggtcncaa nntgagctga 600
ggcncnggtg anttncgcta cntcgnaaaa aangagaagt catgtgggac gnatgtgtgt 660
aagcacagct cntgtgangt caagtcagca acantatgcc atactctgaa gacagaggnc 720
cataatagna ttgttacang atncnngact tttanaaaan caaaatccta aatcctattc 780
tccgtgggcc cacacgaaac anccatccat caggatcatc tcacagttgc ctctgannnt 840
tngtnttctn ggaancntan gntntcggag ttggggaccg aactcagggc cgtgtgcttg 900
ctaggcaagc gctctaccag tgagctaaat ccncaacccc cacagntgcc tcntntgatt 960
gnaggtntcn tatcccnttc ttttgtggca agntcttctg ggcccccntga aagtgaannc 1020
acntaagngg ncgccagcta agnaga 1046

<210> 114
<211> 1083
<212> DNA
<213> Rattus norvegicus

<400> 114
ctcccnggcc ccaaaaattn ttttanaaan ttttttttttc gggnaaattt tnaaaatttt 60
aagnggggggg aannacaaag nnnnttntgg gntggnccaa tggggaaaat taagnnnann 120
ttgnntgggg tgaattcccg ccntngnttg gaggaggnaa ttatnttgta gaaatttatg 180
gttgtggggg atnttgttaa atcttttgaa tgtgttcccc ttntgtttcc cttttgggac 240
atggntctta ataggtggnc aaatttttacc ntnttggaat cagcctattt atcaagatta 300
gcccagtgtg ctcaaccttg tggaacccct ttaacaggat ttgcttggnc catntgaaac 360
acagtattta tgtcaggatt cataacagta gcaaaantat agttatgang cagcaagaaa 420
atcactttat ggttggagcg tcaccacaac atgaggaatg tattaatccg cagtattaga 480
gaggtcgaga accactatct tagaggatgc ggtagactga ttgcttccct tctcgcttgg 540
agttgacctt gccactagag ggcaacagca tcagtattgt tcccagtccc cctcacactg 600
attcgaactt taaggacact gatctctggc tggtagaggg ttcagcacac ataccagagt 660
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aaggccagcc agactgcgac acagtccatc ccctcgacca ctcttttggc gcttcattgt 960
cgacgtgtgg tgagctctca ctggggcgtc cctctaagat ctgtccactc ctggtttagg 1020
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ntt 1083

<210> 115
<211> 913
<212> DNA
<213> Rattus norvegicus

<400> 115
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taanataggt ggggnccnaa aancttgatt ttccctttttc cctttgantg nntaaagttg 120
cnaanttccc tttggacgcc ntttacaaga ttagccngtg tgtaaccttt gggcccttta 180

acaggattnc ttggccntnt gaaacacgta tttatgtcag gnttntaccg tngcaaantt 240
ngttttgagc agcaacgaaa tcactttatg gttggaggtc accacaactt gaggatgtat 300
taatccgcag tattagagag tcgagaacca ntatcttaga ggatcggtag actgatgttt 360
cccntttngc ttggagttgn cttnccacta gaggcaacag catcagtatt gttccccagt 420
ccccctcaca ttgattcgaa ctttaaggac actgatctct ggcttggtag agggttcagc 480
acacatacca gagttacgag tcacgtgcca gaaggcaaac tgaacacgga attagaggga 540
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ggcgcttcat tgtcgacgtg tggtgagctc tcactggggc gtccctctaa gatctgtcca 840
ctcctggtct agggnttaag cctttcctgc cctgaaagac cntacntgta ggttngncaa 900
gctaaatgag atc 913

<210> 116
<211> 1123
<212> DNA
<213> Rattus norvegicus

<400> 116
acgcnatntt ggtggaattt ggggggtaaa aattttnaac gaattaggna ncttagggna 60
cnaaatccga aatggggaat ngggntaaat ttcgaaccnt ttnggaggnn ntaaatntaa 120
aaatgaggnt aattggnttn gaaangcnta tcaggcattc caaattntta aatttccctt 180
ggccagagat tggggaaaat tttncccgga ntccagnttt aggttnnttg gaaaaacggn 240
gccccaggga ttgttgcacc nttcccaatn aaggnggttt tccntccaan gcctttnggg 300
gnaaacccag ggggggnttn aggggcccaa ttcaggaaaa ggggaccgga ntcgggtccc 360
ggaaggnttc ccggnggga atcaacccgg ttcccntccg gaggccgggg gggaccttta 420
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gttggcgcaa gggacttttg gcagccccgg ccggtttggc ggttggactc caagggggta 600
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gnangtgacc ccgcntttag gagtttgccc cngccnttag gccttgcccc cagaggtcgc 720
cccacntact agagtgtcgc ttggcgcgat gacgtangan gacgcaggcg cagtgagtag 780
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ccgtccatac ctgggtgtag tcagggacct ttatggtggc tgtcacgcag gcgatttgnc 1080
aattgaaaga ctttnncctg taggnanggg nagctaaaaa gat 1123

<210> 117
<211> 1116
<212> DNA
<213> Rattus norvegicus

<400> 117
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ccccccttgna anttttcccc gtaaataagg naatgntgna nttgtattta ncttgcccaa 120
aaaaaacnnt gttcttnaat gcaaggtant tgggggttat tattntgaaa ggcaactaat 180
tnttaatggt ggattnaaca attttgaagn ggattaaana aaanaaatna ttgntttcca 240
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gngggntccc cnttccccgg gaatnggntt gaaccggaaa ttgaacattt tgcacccttt 360
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gtggaagggg tttcagnttc cttcccaacc ccccccggc cgggagtccg gnggggcggt 480
ttntttcacc ttaagggcgg gcgtggantt aaattaagcg ccggggnggg ntcccaagcc 540
ntccggcccg gctttggttc cttntgggcg ccgggggcna acggccccng gggctttggg 600
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ggaatggtac actttgcacc tcacactctt ccagagggac agtccataca acactcagct 1020
tcgcttccca ctataggctt cacatgacca gctcttcagc gtcggaaagg acngtactga 1080

aagacttnac ctgtaggnng gncagctaaa aagatc 1116

<210> 118
<211> 900
<212> DNA
<213> Rattus norvegicus

<400> 118
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tgtgggggnt antntgtatc ccctnnnctc nctcgaganc ccnnntctcg anattttggn 120
gaccnggggc cggggcccag anactcncca ccccatatgg ngaccctnta taagtgtcnn 180
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acagacccnn attttttttt ataaagaccc ggggcatntt ctcngccccn tctcctcngc 300
tacangnnac ccacacacag tgtgtctcct ctcagccccc tggcacactt tntntngant 360
cngnggggat atgagattcn cnagactggg nccgcnntan tanncnnccc cntgtctcct 420
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gactctnccc nccntcngct ntgngacnca canctgnaaa tcccgnnncn caaaaagggc 540
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tccggggccc caaccccaaa atcccantnt tcttttntnt tggttggggt gtcaaaattc 780
ctnccccta antttgaac ccccttaat tccccccccc ggntnaaggc ccnacttccc 840
tnggntnttt tcnctaaaaa attttttgtn gccctccctg ggaaatcccc ggtattcctc 900

<210> 119
<211> 498
<212> DNA
<213> Rattus norvegicus

<400> 119
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attgaaagca tgtgcaaaga taaagatttg gggtagtagt agtggtcaaa agggacaagg 120
taataatggt aatatgcttt tgtgtatgtg ttcttttaga gttatgttaa aatctagaga 180
agcaaagtcg attctcatag atgcttttag tctttggacc ctgactagag acagtttaca 240
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gtgggagacg tcttgcctcc ttgctgctcc tattggagaa gtgcttattt ctggttctgg 420
gtttttagg taggntgtct gggtcccttt ggtntgaaag accttacctg taggtttggn 480
cgntngaaaa gatcntgg 498

<210> 120
<211> 380
<212> DNA
<213> Rattus norvegicus

<400> 120
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nccgggaacn tgnaaacatt gaccaanctt gttttaatta ccggtttggg gnaaaagggg 120
caaccccaaa ggggaaggga anggaangga aaatnaattn cctttnnaaa aaggagnaaa 180
tncgggtang gaaaattccg gtgnggggtt ttcaaaggtc ccccccgnn ggnntaaaaa 240
attgaagttn antcnnggggg gggaacccaa nagaatataa anaaaccggg gtttcccccn 300
gggagttcct tgggggtttn ccggttcgac ccgncgntta ccggaaacct ntcnccttttt 360
tcccttgggg nagggggggg 380

<210> 121
<211> 998
<212> DNA
<213> Rattus norvegicus

<400> 121
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tagcttcgcg tgcactacca ccctgcccaa cctggcactg tgcccattga cttcgggggg 120
ccgggggcag gaggtaccca cctccccacc ctcctcttcc ctcctctcag gagcttatct 180
atcggtgagc agcaagtagg aaaaggtaag ctgagaaaga gcacttggct ggctacagga 240

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acaagctnnt atgggcaagg gctttggttc nagnaagg 998

<210> 122
<211> 970
<212> DNA
<213> Rattus norvegicus

<400> 122
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tgggttttta acggcttttt ttanaaggcc nagataccct tttnatggcc tttattccct 120
tccgttttnt tccccccctt caatttggaa gtttggtttg ccgaanttta agttnttgtc 180
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aaggntnttn ttgaacccgt aatngcggnt ttccggttaa ccnagggttt gttcctnngc 300
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caactgagat 970

<210> 123
<211> 884
<212> DNA
<213> Rattus norvegicus

<400> 123
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agaagcaatt tagtgtcctn tgtcctctga cctccacaag tgctgtggca tggggacaca 120
ggactgtaca cacacacaca cacacacaca cacacacaca cacacacgca cgcacacaca 180
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<210> 124
<211> 855
<212> DNA
<213> Rattus norvegicus

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<210> 125
<211> 1059
<212> DNA
<213> Rattus norvegicus

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<210> 126
<211> 1042
<212> DNA
<213> Rattus norvegicus

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gtcttcagta acaaagcact aaacagaaag gggttgaaga gacttggtca gtggcatgag 660
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tagagaaata ggcagcacag gcctaacagc ccatantgtg tgctattcta tcaatagtgc 960

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<210> 127
<211> 960
<212> DNA
<213> Rattus norvegicus

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