



(86) Date de dépôt PCT/PCT Filing Date: 2005/08/05
(87) Date publication PCT/PCT Publication Date: 2006/02/23
(85) Entrée phase nationale/National Entry: 2007/01/25
(86) N° demande PCT/PCT Application No.: US 2005/027658
(87) N° publication PCT/PCT Publication No.: 2006/020480
(30) Priorité/Priority: 2004/08/09 (US60/600,328)

(51) Cl.Int./Int.Cl. *C12N 15/00* (2006.01),
A61K 39/12 (2006.01), *A61K 49/00* (2006.01),
C12N 7/00 (2006.01)
(71) Demandeur/Applicant:
MERCK & CO., INC., US
(72) Inventeurs/Inventors:
EMINI, EMILIO A., US;
SHIVER, JOHN W., US;
CASIMIRO, DANILO R., US;
BETT, ANDREW J., US
(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : COMPOSITIONS DE VECTEURS ADENOVIRAUX
(54) Title: ADENOVIRAL VECTOR COMPOSITIONS

(57) **Abrégé/Abstract:**

Applicants disclose herein novel methods, vectors, and vector compositions for improving the efficiency of adenoviral vectors in the delivery and expression of heterologous nucleic acid encoding a polypeptide(s) (e.g, a protein or antigen) of interest. Adenoviral infection is quite common in the general population, and a large percentage of people have neutralizing antibodies to the more prevalent adenoviral serotypes. Such pre-existing anti-adenoviral immunity can dampen or possibly abrogate the effectiveness of this virus for the delivery and expression of heterologous proteins or antigens. The method taught herein functions to offset pre-existing immunity through the delivery of the protein or antigen by a cocktail of at least two adenoviral serotypes. Utilizing a composition of at least two adenoviral serotypes in this manner has been found to increase the effectiveness of adenoviral administration. Adenoviral vectors of utility in the elicitation of an immune response against Human Immunodeficiency Virus ("HIV") are also disclosed.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 February 2006 (23.02.2006)

PCT

(10) International Publication Number
WO 2006/020480 A3

(51) International Patent Classification:

C12N 15/00 (2006.01) *A61K 49/00* (2006.01)
C12N 7/00 (2006.01) *A61K 39/12* (2006.01)

(21) International Application Number:

PCT/US2005/027658

(22) International Filing Date: 5 August 2005 (05.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/600,328 9 August 2004 (09.08.2004) US

(71) Applicant (*for all designated States except US*): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **EMINI, Emilio, A.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **SHIVER, John, W.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **CASIMIRO, Danilo, R.** [PH/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **BETT, Andrew, J.** [CA/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
23 November 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ADENOVIRAL VECTOR COMPOSITIONS

(57) Abstract: Applicants disclose herein novel methods, vectors, and vector compositions for improving the efficiency of adenoviral vectors in the delivery and expression of heterologous nucleic acid encoding a polypeptide(s) (e.g., a protein or antigen) of interest. Adenoviral infection is quite common in the general population, and a large percentage of people have neutralizing antibodies to the more prevalent adenoviral serotypes. Such pre-existing anti-adenoviral immunity can dampen or possibly abrogate the effectiveness of this virus for the delivery and expression of heterologous proteins or antigens. The method taught herein functions to offset pre-existing immunity through the delivery of the protein or antigen by a cocktail of at least two adenoviral serotypes. Utilizing a composition of at least two adenoviral serotypes in this manner has been found to increase the effectiveness of adenoviral administration. Adenoviral vectors of utility in the elicitation of an immune response against Human Immunodeficiency Virus ("HIV") are also disclosed.

WO 2006/020480 A3

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

WO 2006/020480

PCT/US2005/027658

TITLE OF THE INVENTION

ADENOVIRAL VECTOR COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 The present application claims the benefit of U.S. Provisional Application No. 60/600,328 filed August 9, 2004, which is hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

10 Adenoviruses are nonenveloped, icosahedral viruses that have been identified in several avian and mammalian hosts; Horne *et al.*, 1959 *J. Mol. Biol.* 1:84-86; Horwitz, 1990 In *Virology*, eds. B.N. Fields and D.M. Knipe, pps. 1679-1721. The first human adenoviruses (Ads) were isolated over four decades ago. Since then, over 100 distinct adenoviral serotypes have been isolated which infect various mammalian species, 51 of which are of human origin; Straus, 1984, In *The Adenoviruses*, ed. H. Ginsberg, pps. 451-498, New York:Plenus Press; Hierholzer *et al.*, 1988 *J. Infect. Dis.* 158:804-813; 15 Schnurr and Dondero, 1993, *Intervirology*; 36:79-83; De Jong *et al.*, 1999 *J Clin Microbiol.*, 37:3940-5. The human serotypes have been categorized into six subgenera (A-F) based on a number of biological, chemical, immunological and structural criteria which include hemagglutination properties of rat and rhesus monkey erythrocytes, DNA homology, restriction enzyme cleavage patterns, percentage G+C content and oncogenicity; Straus, *supra*; Horwitz, *supra*.

20 Adenoviruses are attractive targets for the delivery and expression of heterologous genes. Adenoviruses are able to infect a wide variety of cells (dividing and non-dividing), and are extremely efficient in introducing their DNA into infected host cells. Adenoviruses have not been found to be associated with severe human pathology in immuno-competent individuals. The viruses can be produced at high virus titers in large quantities. The adenovirus genome is very well characterized, consisting of a 25 linear double-stranded DNA molecule of approximately 30,000-45,000 base pairs (Adenovirus serotype 5 ("Ad5"), for instance, is ~36,000 base pairs). Furthermore, despite the existence of several distinct serotypes, there is some general conservation found amongst the various serotypes.

 The safety of adenoviruses as gene delivery vehicles is enhanced by rendering the viruses replication-defective through deletion/modification of the essential early-region 1 ("E1") of the 30 viral genomes, rendering the viruses devoid (or essentially devoid) of E1 activity and, thus, incapable of replication in the intended host/vaccinee; *see, e.g.*, Brody *et al*, 1994 *Ann N Y Acad Sci.*, 716:90-101. Deletion of adenoviral genes other than E1 (*e.g.*, in E2, E3 and/or E4), furthermore, creates adenoviral vectors with greater capacity for heterologous gene inclusion. Presently, two well-characterized adenovirus serotypes of subgroup C, serotypes 5 ("Ad5") and 2 ("Ad2") form the basis of the most 35 widely used gene delivery vectors.

 One concern surrounding the use of adenovectors relates to any cellular and humoral immune response elicited by the virus (Chirmule *et al.*, 1999 *Gene Ther.* 6:1574-1583). Although an

WO 2006/020480

PCT/US2005/027658

immune response associated with the initial administration of a vector may be advantageous (Zhang *et al.*, 2001 *Mol. Ther.* 3:697-707), the generation of systemic levels of adenovirus-specific neutralizing antibody may cause poor transduction when the vectors are readministered (booster immunizations; Kass-Eisler *et al.*, 1996 *Gene Ther.* 3:154-162; Chirmule *et al.*, 1999 *J. Immunol.* 163:448-455). The scientific literature and data from our own epidemiological studies suggest that most North Americans have anti-Ad5 neutralizing antibody titers, and about one third have relatively high titers (>200). Other parts of the world typically exhibit higher frequencies and levels of anti-Ad5 antibodies. Serospecific antibodies to these and other adenoviral serotypes resulting from such natural adenovirus infections in humans may affect the extent of response to the administration of heterologous polypeptides by adenovectors; Chirmule *et al.*, 1999 *Gene Ther.* 6:1574-1583.

The instant invention offers vector compositions and methods for evading such host immunity.

SUMMARY OF THE INVENTION

The present invention relates to novel methods and compositions for improving the efficiency of adenoviral vectors in the delivery and expression of heterologous polypeptides. Adenoviral infection is relatively common in the general population, and a large percentage of people have neutralizing antibodies to the more prevalent adenoviral serotypes largely found in group C. Such pre-existing anti-adenoviral immunity can dampen or possibly abrogate the effectiveness of these viruses for the delivery and expression of heterologous proteins or antigens. The methods taught herein function to offset pre-existing immunity through the delivery and expression of heterologous polypeptides by a cocktail of at least two adenoviral serotypes. Utilizing at least two adenoviral serotypes in accordance with the methods and compositions disclosed herein has been found to increase the effectiveness of adenoviral administration. Adenoviral vectors of utility in the elicitation of an immune response against Human Immunodeficiency Virus ("HIV") are also disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the nucleotide sequence of a codon optimized version of full-length p55 gag (SEQ ID NO: 2).

Figures 2A-1 through 2A-2 illustrate a codon optimized wt-pol sequence, wherein sequences encoding protease (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and RNase H activity) and IN integrase activity (SEQ ID NO: 3). The open reading frame starts at an initiating Met residue at nucleotides 10-12 and ends at a termination codon at nucleotides 2560-2562.

Figures 3A-1 through 3A-2 illustrate the open reading frame (SEQ ID NO: 4) of the wild type pol construct disclosed as SEQ ID NO: 3.

WO 2006/020480

PCT/US2005/027658

Figures 4A-1 through 4A-3 illustrate the nucleotide (SEQ ID NO: 5) and amino acid sequence (SEQ ID NO: 6) of IA-Pol. Underlined codons and amino acids denote mutations, as listed in Table 1 herein.

Figure 5 illustrates a codon optimized version of HIV-1 jrf1 nef (SEQ ID NO: 7). The open reading frame starts at an initiating methionine residue at nucleotides 12-14 and ends at a "TAA" stop codon at nucleotides 660-662.

Figure 6 illustrates the open reading frame (SEQ ID NO: 8) of codon optimized HIV jrf1 Nef.

Figures 7A-1 through 7A-2 illustrate a nucleotide sequence comparison between wild type nef (jrf1) and codon-optimized nef. The wild type nef gene from the jrf1 isolate consists of 648 nucleotides capable of encoding a 216 amino acid polypeptide. WT, wild type sequence (SEQ ID NO: 11); opt, codon-optimized sequence (contained within SEQ ID NO: 7). The Nef amino acid sequence is shown in one-letter code (SEQ ID NO: 8).

Figure 8 illustrates nucleic acid (herein, "opt nef (G2A, LLAA)"; SEQ ID NO: 9) which encodes optimized HIV-1 Nef wherein the open reading frame encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. The open reading frame starts at an initiating methionine residue at nucleotides 12-14 and ends at a "TAA" stop codon at nucleotides 660-662.

Figure 9 illustrates the open reading frame (SEQ ID NO: 10) of opt nef (G2A, LLAA).

Figure 10 illustrates nucleic acid (herein, "opt nef (G2A)"; SEQ ID NO: 12) which encodes optimized HIV-1 Nef wherein the open reading frame encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2). The open reading frame starts at an initiating methionine residue at nucleotides 12-14 and ends at a "TAA" stop codon at nucleotides 660-662.

Figure 11 illustrates the open reading frame (SEQ ID NO: 13) of opt nef (G2A).

Figure 12 illustrates a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

Figure 13 illustrates, in tabular format, the seroprevalence of Adenovirus subtypes 5 and 6. Brazilian and Thai subjects were selected for high risk behavior for HIV infection.

* = Thai subjects were primarily high risk for HIV infection.

Figure 14 illustrates, diagrammatically, the construction of the pre-adenovirus plasmid construct, MRKAd5Pol.

Figure 15 illustrates, diagrammatically, the construction of the pre-adenovirus plasmid construct, MRKAd5Nef.

Figure 16 illustrates the homologous recombination protocol utilized to recover pMRKAd6E1-.

WO 2006/020480

PCT/US2005/027658

Figure 17 illustrates MRKAd5gagnef, a modification of a prototype Group C Adenovirus serotype 5 vector in which the E1 region (nucleotides 451-3510) is deleted and replaced by nef and gag expression cassettes.

Figures 18A-1 through 18A-12 illustrate a nucleic acid sequence (SEQ ID NO: 16) for MRKAd5gagnef.

Figure 19 illustrates key steps involved in the construction of adenovirus vector MRKAd5gagnef.

Figure 20 illustrates MRKAd6gagnef, a modification of a prototype Group C Adenovirus serotype 6 vector in which the E1 region (nucleotides 451-3507) was deleted and replaced by nef and gag expression cassettes.

Figures 21A-1 through 21A-12 illustrate a nucleic acid sequence (SEQ ID NO: 17) for MRKAd6gagnef.

Figure 22 illustrates key steps involved in the construction of adenovirus vector MRKAd6gagnef.

Figure 23 illustrates MRKAd5gagpol, a modification of a prototype Group C Adenovirus serotype 5 vector in which the E1 region (nucleotides 451-3510) is deleted and replaced by a gagpol fusion expression cassette.

Figures 24A-1 through 24A-11 illustrate a nucleic acid sequence (SEQ ID NO: 18) for MRKAd5gagpol.

Figure 25 illustrates key steps involved in the construction of adenovirus vector MRKAd5gagpol.

Figure 26 illustrates the PCR strategy for generating the gagpol fusion fragment for use in MRKAd5gagpol.

Figure 27 illustrates MRKAd5nef-gagpol, a modification of a prototype Group C Adenovirus serotype 5 vector in which the E1 region (nucleotides 451-3510) is deleted and replaced by nef and gagpol expression cassettes.

Figures 28A-1 through 28A-12 illustrate a nucleic acid sequence (SEQ ID NO: 19) for MRKAd5nef-gagpol.

Figure 29 illustrates key steps involved in the construction of adenovirus vector MRKAd5nef-gagpol.

Figure 30 illustrates MRKAd5gagpolnef, a modification of a prototype Group C Adenovirus serotype 5 vector in which the E1 region (nucleotides 451-3510) is deleted and replaced by a gagpolnef expression cassette.

Figures 31A-1 through 31A-12 illustrate a nucleic acid sequence (SEQ ID NO: 20) for MRKAd5gagpolnef.

Figure 32 illustrates key steps involved in the construction of adenovirus shuttle plasmid pMRKAd5gagpolnef.

WO 2006/020480

PCT/US2005/027658

Figure 33 illustrates the PCR strategy for generating the polnef fusion fragment for use in MRKAd5gagpolnef.

Figure 34 illustrates key steps involved in the construction of adenovirus vector MRKAd5gagpolnef.

5 Figure 35 illustrates MRKAd6nef-gagpol, a modification of a prototype Group C Adenovirus serotype 6 vector in which the E1 region (nucleotides 451-3507) is deleted and replaced by nef and gagpol expression cassettes.

Figures 36A-1 through 36A-12 illustrate a nucleic acid sequence (SEQ ID NO: 21) for MRKAd6nef-gagpol.

10 Figure 37 illustrates key steps involved in the construction of adenovirus vector MRKAd6nef-gagpol.

Figure 38 illustrates MRKAd6gagpolnef, a modification of a prototype Group C Adenovirus serotype 6 vector in which the E1 region (nucleotides 451-3507) is deleted and replaced by a gagpolnef expression cassette.

15 Figures 39A-1 through 39A-11 illustrate a nucleic acid sequence (SEQ ID NO: 22) for MRKAd6gagpolnef.

Figure 40 illustrates key steps involved in the construction of adenovirus vector MRKAd6gagpolnef.

20 Figure 41 illustrates, in tabular format, the levels of Nef-specific T cells during the course of immunization. Values reflect the mock-subtracted numbers of IFN- γ secreting cells per million PBMC; wk, week. The bold numbers (the final row of each group) are the cohort geometric means in SFC/10⁶ PBMC.

25 Figure 42 illustrates, in tabular format, the effect of pre-existing Ad5-specific immunity on the efficacy of MRKAd5gag and a cocktail of MRKAd5gag +MRKAd6gag. The first two cohorts have Ad5-specific neutralization titers averaging 1300-1400 prior to immunization with the gag-expressing vectors. The third cohort had no detectable pre-existing neutralization titers. Shown are the SFC/10⁶ PBMC values for each animal at week 4 and week 8 against the entire gag peptide pool and mock control. In bold are the cohort geometric means for the T cell responses.

30 Figure 43 illustrates, in tabular format, the levels of Gag, Pol, and Nef-specific T cells in rhesus macaques immunized with 10¹⁰ vp/vector of one of the following vaccines: (1) MRKAd5gag + MRKAd5pol + MRKAd5nef; (2) MRKAd5hCMVnefmCMVgag + MRKAd5pol; (3) MRKAd5hCMVnefmCMVgagpol; and (4) MRKAd5hCMVgagpolnef. Cytokine secretion was induced using entire nef, gag, and pol peptide pools consisting of 15-aa peptides with 11-aa overlaps. Shown are the mock-corrected SFC/10⁶ PBMC values for each animal at week 4 and week 8. In bold are the cohort
35 geometric means for the T cell responses to each of the antigens.

Figure 44 illustrates, in tabular format, the levels of Gag, Pol, and Nef-specific T cells in rhesus macaques immunized with 10⁸ vp/vector of one of the following vaccines: (1) MRKAd5gag +

WO 2006/020480

PCT/US2005/027658

MRKAd5pol + MRKAd5nef; (2) MRKAd5hCMVnefmCMVgag + MRKAd5pol; (3) MRKAd5hCMVnefmCMVgagpol; and (4) MRKAd5hCMVgagpolnef. Cytokine secretion was induced using entire nef, gag, and pol peptide pools consisting of 15-aa peptides with 11-aa overlaps. Shown are the mock-corrected SFC/10⁶ PBMC values for each animal at week 4 and week 8. In bold are the cohort geometric means for the T cell responses to each of the antigens.

Figure 45 illustrates, in tabular format, the levels of Gag, Pol, and Nef-specific T cells in rhesus macaques immunized with 10¹⁰ vp /vector of one of the following vaccines: (1) MRKAd5nefgagpol; (2) MRKAd6nefgagpol; (3) MRKAd5nefgagpol + MRKAd6nefgagpol. Cytokine secretion was induced using entire nef, gag and pol peptide pools consisting of 15-aa peptides with 11-aa overlaps. Shown are the mock-corrected SFC/10⁶ PBMC values for each animal at week 4 and week 8. In bold are the cohort geometric means for the T cell responses to each of the antigens.

Figure 46 illustrates, in tabular format, the levels of Gag, Pol, and Nef-specific T cells in rhesus macaques immunized with 10⁸ vp /vector of one of the following vaccines: (1) MRKAd5nefgagpol; (2) MRKAd6nefgagpol; (3) MRKAd5nefgagpol + MRKAd6nefgagpol. Cytokine secretion was induced using entire nef, gag and pol peptide pools consisting of 15-aa peptides with 11-aa overlaps. Shown are the mock-corrected SFC/10⁶ PBMC values for each animal at week 4 and week 8. In bold are the cohort geometric means for the T cell responses to each of the antigens.

DETAILED DESCRIPTION OF THE INVENTION

Applicants disclose herein novel methods and compositions for circumventing pre-existing anti-adenoviral immunity through administration of desired nucleic acid encoding a polypeptide(s) of interest via at least two adenoviral serotypes. This method is based on results of experiments conducted by Applicants employing serotypes of high homology and same group classification, contemporaneously, in the delivery and expression of nucleic acid of interest, and the favorable comparison of such delivery methodology to single serotype administrations utilizing the individual serotypes of the contemporaneous administration.

Administration of a nucleic acid of interest by at least two adenoviral serotypes proved effective in both evading pre-existing host immunity and effectuating the delivery and expression of a polypeptide of interest. The expression effected was sufficient to elicit a host immune response to the expressed polypeptide that was comparable to that effectuated by single serotype administration where pre-existing immunity did not present a challenge. Pre-existing immunity did not have any apparent detrimental effect on the induced immunity. In contrast, pre-existing immunity had a measurable impact on single serotype administration in situations where the serotype utilized was that to which pre-existing immunity was directed towards. Importantly, the cellular immune response was found to be comparable to that of the individual serotype administration that was not challenged by pre-existing immunity.

In accordance with these and other findings disclosed herein, Applicants submit that the disclosed methods and vector compositions should improve the breadth of patient coverage in gene

WO 2006/020480

PCT/US2005/027658

therapy and/or vaccination protocols by overcoming potential pre-existing immunity to single serotype delivery. Consequently, the disclosed methods and compositions form a viable prospect for mass administration in the face of pre-existing immunity, even to the more prevalent (group C) adenoviral serotypes.

5 The present invention, therefore, relates to methods for effecting the delivery and expression of heterologous nucleic acid encoding a polypeptide(s) of interest, which comprises contemporaneously administering purified replication-defective adenovirus particles of at least two different serotypes, wherein said replication-defective adenovirus particles comprise heterologous nucleic acid encoding at least one common polypeptide. The polypeptide can be any protein or antigen
10 which one desires to have expressed in a particular cell, tissue, or subject of interest. Administration can be either within the same composition or in separate formulations administered contemporaneously; "contemporaneous" as defined herein meaning within the same period of time. More specifically, contemporaneous administration refers to the administration of viral particles of alternative serotypes either simultaneously (whether in the same or separate formulations) or with some period of time
15 between the administrations of the two or more different serotypes. This period of time can be of any duration, generally extending from simultaneous administration to a period of eighteen ("18") weeks between the administrations. Preferably, the period of time between the administrations does not exceed a period of more than 18 weeks. More preferably, the period of time between administrations is significantly less than 18 weeks. Most preferably, the period of time between administrations is, in an
20 increasing order of preference, less than four weeks, less than two weeks, less than one week, less than two days, less than one day, less than one hour, within five minutes ("simultaneous" administration). The result sought by contemporaneous administration is not that of a "prime-boost" effect but rather the effect of a single administration (albeit alternative administrations can be present), whether that administration be in the form of a prime (or primes employing the at least two serotypes), in the form of a
25 boost (employing the at least two serotypes), or involving prime and boost administrations (the administrations of which independently both comprise the at least two serotypes). The present invention contemplates as well the contemporaneous administration of at least two adenoviral serotypes encoding at least one common polypeptide in a sole administration not dependent on a prime/boost regimen.

 The present invention also relates to compositions comprising the at least two adenoviral
30 serotypes; said at least two adenoviral serotypes comprising heterologous nucleic acid encoding at least one common polypeptide. The methods in accordance with the present invention utilize (and compositions in accordance with the present invention comprise) purified replication-defective adenovirus particles of at least two different serotypes. There are over 100 distinct adenoviral serotypes identified to date that can be utilized in the methods/compositions of the present invention; 51 of which
35 are of human origin and numerous that infect various different species, including various mammalian species; Straus, 1984, In *The Adenoviruses*, ed. H. Ginsberg, pps. 451-498, New York:Plenus Press; Hierholzer *et al.*, 1988 *J. Infect. Dis.* 158:804-813; Schnurr and Dondero, 1993, *Intervirology*; 36:79-83;

WO 2006/020480

PCT/US2005/027658

De Jong *et al.*, 1999 *J Clin Microbiol.*, 37:3940-5; and Wadell *et al.*, 1999 In *Manual of Clinical Microbiology*, 7th ed. American Society for Microbiology, pp. 970-982. One of skill in the art can readily identify and develop adenoviruses of alternative and distinct serotype (including, but not limited to, the foregoing) for purposes consistent with the methods and compositions of the present invention. Those of
 5 skill in the art are readily familiar with the various adenoviral serotypes including, but not limited to, (1) the numerous serotypes of subgenera A-F discussed above, (2) unclassified adenovirus serotypes, (3) non-human serotypes (including but not limited to primate adenoviruses (*see, e.g.*, Fitzgerald *et al.*, 2003 *J. Immunol.* 170(3):1416-1422; Xiang *et al.*, 2002 *J. Virol.* 76(6):2667-2675)), and equivalents, modifications, or derivatives of the foregoing. Adenoviruses can readily be obtained from the American
 10 Type Culture Collection ("ATCC") or other publicly available/private source; and adenoviral sequences can be discerned from both the published literature and widely accessible public databases, where not obtained elsewhere.

The specific combination of serotypes suitable for use in the methods and compositions disclosed herein is limitless. There are numerous means by which one can choose a candidate
 15 combination of serotypes. One means by which to evaluate a candidate pairing of serotypes is to evaluate the seroprevalence of the vectors in combination (*i.e.*, determine whether the population tends to be more/less/equally infected by all of the serotypes of the combination). Preferably, the effective neutralizing antisera titer to the combination of serotype components is lower than that exhibited to an individual serotype (particularly to a serotype(s) of real interest) or, in the alternative, the percentage of
 20 individuals with serotype-specific neutralizing antisera titers to all the serotype components is less than that with titers to an individual serotype tested (again, particularly to the serotype(s) of real interest). The effective neutralizing antisera titer against a candidate composition (*i.e.*, the combination of serotype components) is the lower of the titers tested since that component of the vector will therefore be more potent. For purposes of comparison, arbitrary ranges can, but need not be, established as a qualitative
 25 reference for the potency of a determined serum towards specific serotypes (for example, ranges used herein for Ad5 were as follows: very low or undetectable [<18], low [$18-200$], medium [$201-1000$], and high [>1000]).

Evaluation of serotype-specific neutralizing antisera as a means of selecting an appropriate serotype adenovector is well understood and appreciated in the art, and the practice thereof is
 30 well within the realm of one of ordinary skill in the art; Aste-Amézaga, 2004 *Hum. Gene Ther.* 15:293-304; Piedra *et al.*, 1998 *Pediatrics* 101(6): 1013-1019; Sanchez *et al.*, 2001 *J. Med. Virol.* 65:710-718; Sprangers *et al.*, 2003 *J. Clin. Microbiol.* 41(11):5046-5052; and Nwanegbo *et al.*, 2004 *Clin. Diagn. Lab. Immunol.* 11(2):351-357. Additionally, several methods are available for determining type-specific antibodies to adenovirus (Ad) serotypes. Several different assay formats can be used such as, for
 35 example, end point dilution assays, or any available assays designed to evaluate gene expression. The basic principle behind such assays is to ascertain the specificity/existence of any preexisting antisera in the subject population. In the present studies, serum neutralization studies were utilized to evaluate the

WO 2006/020480

PCT/US2005/027658

preexisting antisera of the candidate population; *see* Example 1. Serum neutralization assays generally involve incubating serum (from a candidate(s)) along with virus of the serotype of interest and cells to ascertain whether the serum contains antibodies specific for the virus sufficient to inhibit infection of the cells. Infection can be detected by a number of methods, the most frequently utilized being cell viability or transgene expression; Sprangers *et al.*, *supra*.

As a substitute for, or a complement to, the various assays discussed above, various epidemiological studies are available for reference as well for use in determining the prevalence of neutralizing antibodies to a specific serotype(s) in a given population; *see, e.g.*, Nwanegbo *et al. supra*. As one of ordinary skill in the art will appreciate, the present invention certainly contemplates as one embodiment hereof administration of a serotype of adenovirus which is appreciated in the art as prevalent/moderately prevalent in a given population with one appreciated in the art as not as prevalent in the population, without the obligation of undergoing a specific study on an individualized basis as discussed above. Combinations of adenovirus for contemporaneous administration can, therefore, be constructed based on existing knowledge.

One of skill in the art can envision the various possibilities made possible by the present disclosure. If one serotype is known or found not to be prevalent in a population of individuals, that serotype can be utilized with one or more that is a bit more prevalent to support the administration in the event that neutralizing antisera to the prevalent adenovirus poses a threat/challenge. In an alternative scenario, rare serotypes can be administered contemporaneously. Additionally, as evidenced herein, two or more relatively prevalent serotypes can be administered contemporaneously, particularly where the effective neutralizing antisera titer to the combination of serotype components is lower than that exhibited to an individual serotype (particularly to a serotype(s) of real interest) or, in the alternative, the percentage of individuals with serotype-specific neutralizing antisera titers to the combination of serotype components is less than that with titers to an individual serotype tested (again, particularly to the serotype(s) of real interest). Accordingly, the present invention encompasses and is exemplified herein by contemporaneous administration of adenovirus serotypes 5 and 6, both encoding at least one common polypeptide of interest. Adenovirus serotypes 5 and 6 are well known in the art (American Type Culture Collection ("ATCC") Deposit Nos. VR-5 and VR-6, respectively, and sequences therefore have been published; *see* Chroboczek *et al.*, 1992 *J. Virol.* 186:280, and PCT/US02/32512, published April 17, 2003, respectively). Despite the relatively high percentage of individuals exhibiting neutralizing antisera titers to both serotypes on a population-wide basis, Applicants found that the percentage of individuals with relatively high titers of neutralizing antibodies to both was significantly lower. Furthermore, while employing the two relatively prevalent group C adenoviral serotypes as vectors for the delivery and expression of a heterologous polypeptide, Applicants discovered that pre-existing immunity did not have any apparent detrimental impact on their contemporaneous delivery. By contrast, pre-existing immunity had a measurable impact on administration using one of the serotypes for which pre-existing immunity was present. The cocktail was, furthermore, effectively able to express sufficient amounts of the

WO 2006/020480

PCT/US2005/027658

polypeptide to elicit a cellular immune response which was comparable to that of the individual serotype of the cocktail that was not effected by pre-existing immunity.

Another embodiment of the present invention involves the combination/contemporaneous administration of human serotypes of adenovirus with serotypes that naturally infect other species. For purposes of exemplification, this could entail administering, contemporaneously, a human adenovirus and an adenovirus that naturally infects primates, including but not limited to chimpanzees.

One of skill in the art can readily identify adenoviruses of alternative and distinct serotype (*e.g.*, the various serotypes found in subgenera A-F discussed above; including but not limited to those on deposit with widely accessible public depositories such as the American Type Culture Collection ("ATCC") and those for whom the sequence is known and/or published in the scientific literature and widely available public sequence databases). As is taught herein, any combination of these adenoviral serotypes is suitable for use in the present invention, provided that neutralizing antisera does not present a hindrance to administration of a desired combination of serotypes. As stated, this can be determined very readily by one of skill in the pertinent art from published literature concerning the relative prevalence of the various serotypes in specific populations, from actual experiments conducted, or from the various assays discussed above which are available to identify the existence of/quantify immunity to the serotype/classification group of interest.

Adenoviral serotypes administered via the methods and compositions of the present invention should be replication-impaired in the intended host; unless the replication thereof in the intended host is determined not to pose a safety issue. Preferably, the vectors are at least partially deleted/mutated in E1 such that any resultant virus is devoid (or essentially devoid) of E1 activity, rendering the vector incapable of replication in the intended host. Preferably, the E1 region is completely deleted or inactivated. Specific embodiments of the present invention employ adenoviral vectors as described in PCT/US01/28861, published March 21, 2002. Said vectors are at least partially deleted in E1 and comprise several adenoviral packaging repeats (*i.e.*, the E1 deletion does not start until approximately base pairs 450-458, with base pair numbers assigned corresponding to a wildtype Ad5 sequence). The adenoviruses may contain additional deletions in E3, and other early regions, albeit in certain situations where E2 and/or E4 is deleted, E2 and/or E4 complementing cell lines may be required to generate recombinant, replication-defective adenoviral vectors. Vectors devoid of adenoviral protein-coding regions ("guttled vectors") are also feasible for use herein. Such vectors typically require the presence of helper virus for the propagation and development thereof.

Adenoviral vectors can be constructed using well known techniques, such as those reviewed in Graham & Prevec, 1991 *In Methods in Molecular Biology: Gene Transfer and Expression Protocols*, (Ed. Murray, E.J.), p. 109; and Hitt *et al.*, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206. Example 2 details the construction of several adenoviral vector constructs suitable for use herein.

WO 2006/020480

PCT/US2005/027658

E1-complementing cell lines used for the propagation and rescue of recombinant adenovirus should provide elements essential for the viruses to replicate, whether the elements are encoded in the cell's genetic material or provided *in trans*. It is, furthermore, preferable that the E1-complementing cell line and the vector not contain overlapping elements which could enable homologous recombination between the nucleic acid of the vector and the nucleic acid of the cell line potentially leading to replication competent virus (or replication competent adenovirus "RCA"). Often, propagation cells are human cells derived from the retina or kidney, although any cell line capable of expressing the appropriate E1 and any other critical deleted region(s) can be utilized to generate adenovirus suitable for use in the methods of the present invention. Embryonal cells such as amniocytes have been shown to be particularly suited for the generation of E1 complementing cell lines. Several cell lines are available and include but are not limited to the known cell lines PER.C6® (ECACC deposit number 96022940), 911, 293, and E1 A549. PER.C6® cell lines are described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908. PER.C6® is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. 293 cells are described in Graham *et al.*, 1977 *J. Gen. Virol.* 36:59-72. For the propagation and rescue of non-group C adenoviral vectors, a cell line expressing an E1 region which is complementary to the E1 region deleted in the virus being propagated can be utilized. Alternatively, a cell line expressing regions of E1 and E4 derived from the same serotype can be employed; *see, e.g.*, U.S. Patent No. 6,270,996. Another alternative would be to propagate non-group C adenovirus in available E1-expressing cell lines (*e.g.*, PER.C6®, A549 or 293). This latter method involves the incorporation of a critical E4 region into the adenovirus to be propagated. The critical E4 region is native to a virus of the same or highly similar serotype as that of the E1 gene product(s) (particularly the E1B 55K region) of the complementing cell line, and comprises typically, at a minimum, E4 open reading frame 6 ("ORF6"); *see*, PCT/US2003/026145, published March 4, 2004. One of skill in the art can readily appreciate and carry out numerous other methods suitable for the production of recombinant, replication-defective adenoviruses suitable for use in the methods of the present invention. Following viral production in whatever means employed, viruses may be purified, formulated and stored prior to host administration.

The methods and compositions described herein are well suited to effectuate the expression of heterologous polypeptides, especially in situations where pre-existing immunity prevents administration or readministration of at least one of the adenoviral serotypes employed. Accordingly, specific embodiments of the present invention comprise methods for effecting the delivery and expression of heterologous nucleic acid encoding a polypeptide(s) of interest, which comprises contemporaneously administering purified replication-defective adenovirus particles of at least two different serotypes, wherein said replication-defective adenovirus particles comprise heterologous nucleic acid encoding at least one common polypeptide. Additional embodiments of the present invention are compositions comprising purified replication-defective adenovirus particles of at least two

WO 2006/020480

PCT/US2005/027658

different serotypes, wherein said replication-defective adenovirus particles comprise heterologous nucleic acid encoding at least one common polypeptide. The expressed nucleic acid can be DNA and/or RNA, and can be double or single stranded. The nucleic acid can be inserted in an E1 parallel (transcribed 5' to 3' relative to the vector backbone) or anti-parallel (transcribed 3' to 5' relative to the vector backbone) orientation. The nucleic acid can be codon-optimized for expression in the desired host (e.g., a mammalian host). The heterologous nucleic acid can be in the form of an expression cassette. A gene expression cassette can contain (a) nucleic acid encoding a protein or antigen of interest; (b) a heterologous promoter operatively linked to the nucleic acid encoding the protein/antigen; and (c) a transcription termination signal.

In specific embodiments, the heterologous promoter is recognized by a eukaryotic RNA polymerase. One example of a promoter suitable for use in the present invention is the immediate early human cytomegalovirus promoter (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986). Further examples of promoters that can be used in the present invention are the strong immunoglobulin promoter, the EF1 alpha promoter, the murine CMV promoter, the Rous Sarcoma Virus promoter, the SV40 early/late promoters and the beta actin promoter, albeit those of skill in the art can appreciate that any promoter capable of effecting expression of the heterologous nucleic acid in the intended host can be used in accordance with the methods of the present invention. The promoter may comprise a regulatable sequence such as the Tet operator sequence. Sequences such as these that offer the potential for regulation of transcription and expression are useful in circumstances where repression/modulation of gene transcription is sought. The adenoviral gene expression cassette may comprise a transcription termination sequence; specific embodiments of which are the bovine growth hormone termination/polyadenylation signal (bGHpA) or the short synthetic polyA signal (SPA) of 50 nucleotides in length defined as follows:

AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTG (SEQ ID NO: 1). A leader or signal peptide may also be incorporated into the transgene. In specific embodiments, the leader is derived from the tissue-specific plasminogen activator protein, tPA.

Heterologous nucleic acids of interest typically encode immunogenic and/or therapeutic proteins. Preferred therapeutic proteins are those which elicit some measurable therapeutic benefit in the individual host upon administration. Preferred immunogenic proteins are those proteins which are capable of eliciting a protective and/or beneficial immune response in an individual. A specific embodiment of the instant invention, illustrated herein, is the delivery of nucleic acid encoding representative immunogenic proteins (HIV Gag, Nef and/or Pol) by the methods and compositions disclosed, albeit any gene encoding a therapeutic or immunogenic protein can be used in accordance with the methods disclosed herein and form important embodiments hereof. The methods and compositions disclosed in the present invention do not hinge upon any specific heterologous nucleic acid. Accordingly, the methods and compositions of the instant invention can be used to effectuate the delivery of any polypeptide whose presence/function brings about a desired effect in a given host, particularly a

WO 2006/020480

PCT/US2005/027658

therapeutic/immunogenic effect useful in the treatment/alteration/modification of various conditions associated with, caused by, effected by (positively or negatively), exacerbated by, or modified by the presence or absence of a particular nucleic acid, protein, antigen, fragment, or activity associated with any of the foregoing.

5 One aspect of the present invention, as indicated above, relates to methods and compositions employing adenoviral vectors carrying heterologous nucleic acid encoding an HIV antigen(s)/protein(s). Human Immunodeficiency Virus ("HIV") is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV is an RNA virus of the Retroviridae family and exhibits the 5'LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains flanking sequences known as long terminal repeats (LTRs).

Heterologous nucleic acid encoding an HIV antigen/protein may be derived from any HIV strain, including but not limited to HIV-1 and HIV-2, strains A, B, C, D, E, F, G, H, I, O, IIB, LAV, SF2, CM235, and US4; *see, e.g.*, Myers *et al.*, eds. "Human Retroviruses and AIDS: 1995 (Los Alamos National Laboratory, Los Alamos NM 97545). Another HIV strain suitable for use in the methods disclosed herein is HIV-1 strain CAM-1; Myers *et al.*, eds. "Human Retroviruses and AIDS": 1995, IIA3-IIA19. This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. HIV gene sequence(s) may be based on various clades of HIV-1; specific examples of which are Clades A, B, and C. Sequences for genes of many HIV strains are publicly available from GenBank and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland.

HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef). The *gag* gene encodes a 55-kilodalton (kDa) precursor protein (p55) which is expressed from the unspliced viral mRNA and is proteolytically processed by the HIV protease, a product of the *pol* gene. The mature p55 protein products are p17 (matrix), p24 (capsid), p9 (nucleocapsid) and p6. The *pol* gene encodes proteins necessary for virus replication - protease (Pro, P10), reverse transcriptase (RT, P50), integrase (IN, p31) and RNase H (RNase, p15) activities. These viral proteins are expressed as a Gag or Gag-Pol fusion protein which is generated by a ribosomal frame shift. The 55 kDa gag and 160 kDa gagpol precursor proteins are then proteolytically processed by the virally encoded protease into their mature products. The *nef* gene encodes an early accessory HIV protein (Nef) which has been shown to possess several activities such as down regulating CD4 expression, disturbing T-cell activation and stimulating HIV infectivity. The *env* gene encodes the viral envelope glycoprotein that is translated as a 160-kilodalton (kDa) precursor (gp160) and then cleaved by a cellular protease to yield the external 120-kDa envelope glycoprotein (gp120) and the transmembrane

WO 2006/020480

PCT/US2005/027658

41-kDa envelope glycoprotein (gp41). Gp120 and gp41 remain associated and are displayed on the viral particles and the surface of HIV-infected cells. The *tat* gene encodes a long form and a short form of the Tat protein, a RNA binding protein which is a transcriptional transactivator essential for HIV replication. The *rev* gene encodes the 13 kDa Rev protein, a RNA binding protein. The Rev protein binds to a region of the viral RNA termed the Rev response element (RRE). The Rev protein promotes transfer of unspliced viral RNA from the nucleus to the cytoplasm. The Rev protein is required for HIV late gene expression and in turn, HIV replication.

Nucleic acid encoding any HIV antigen may be utilized in the methods and compositions of the present invention (specific examples of which include but are not limited to the aforementioned genes, nucleic acid encoding active and/or immunogenic fragments thereof, and/or modifications/derivatives of any of the foregoing). The present invention contemplates as well the various codon-optimized forms of nucleic acid encoding HIV antigens, including codon-optimized HIV gag (including but by no means limited to p55 versions of codon-optimized full length ("FL") Gag and tPA-Gag fusion proteins), HIV pol, HIV nef, HIV env, HIV tat, HIV rev, and modifications/derivatives of immunological relevance. Embodiments exemplified herein employ nucleic acid encoding codon-optimized Nef antigens; codon-optimized p55 Gag antigens; and codon-optimized Pol antigens. Codon-optimized HIV-1 gag genes are disclosed in PCT International Application PCT/US00/18332, published January 11, 2001 (WO 01/02607). Codon-optimized HIV-1 env genes are disclosed in PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997 (WO 97/48370), respectively. Codon-optimized HIV-1 pol genes are disclosed in U.S. Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000. Codon-optimized HIV-1 nef genes are disclosed in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000. It is well within the purview of the skilled artisan to choose an appropriate nucleotide sequence including but not limited to those cited above which encodes a specific HIV antigen, or immunologically relevant portion or modification/derivative thereof. "Immunologically relevant" or "antigenic" as defined herein means (1) with regard to a viral antigen, that the protein is capable, upon administration, of eliciting a measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce/contain viral load within the individual; or (2) with regards to a nucleotide sequence, that the sequence is capable of encoding for a protein capable of the above. One of skill in the art can, furthermore, appreciate that any nucleic acid encoding for a protein, antigen, derivative or fragment capable of effectuating a desired result (sequences that may or may not be codon-optimized) is of use in the methods and compositions of the instant invention.

A codon-optimized gag gene that can be utilized in the methods and compositions of the present invention is that disclosed in PCT/US00/18332, published January 11, 2001 (*see* Figure 1; SEQ ID NO: 2). The sequence is derived from HIV-1 strain CAM-1 and encodes full-length p55 gag. The

WO 2006/020480

PCT/US2005/027658

gag gene of HIV-1 strain CAM-1 was selected as it closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence (Los Alamos HIV database). The sequence was designed to incorporate human preferred ("humanized") codons in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12).

5 Open reading frames for various synthetic *pol* genes contemplated herein and disclosed in PCT/US00/34724 comprise coding sequences for reverse transcriptase (or RT which consists of a polymerase and RNase H activity) and integrase (IN). The protein sequence is based on that of Hxb2r, a clonal isolate of IIIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber, et al., 1998, *Human retroviruses and AIDS*, Los
10 Alamos National Laboratory, Los Alamos, New Mexico).

A particular embodiment of this portion of the invention comprises methods and compositions comprising codon optimized nucleotide sequences which encode wt-pol constructs (herein, "wt-pol" or "wt-pol (codon optimized)") wherein sequences encoding the protease (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and
15 RNase H activity) and IN integrase activity. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO :3 (Figures 2A-1 to 2A-2), the open reading frame being contained from an initiating Met residue at nucleotides 10-12 to a termination codon from nucleotides 2560-2562. The open reading frame of the wild type pol construct (SEQ ID NO: 4; Figures 3A-1 to 3A-2) contains 850 amino acids.

20 Alternative specific embodiments relate to methods and compositions utilizing adenoviral vector constructs which comprise codon optimized HIV-1 pol wherein, in addition to deletion of the portion of the wild type sequence encoding the protease activity, a combination of active site residue mutations are introduced which are deleterious to HIV-1 pol (RT-RH-IN) activity of the expressed protein. Therefore, the present invention relates to methods and compositions employing an
25 adenoviral construct comprising HIV-1 pol wherein the construct is devoid of sequences encoding any PR activity, as well as containing a mutation(s) which at least partially, and preferably substantially, abolishes RT, RNase and/or IN activity. One type of HIV-1 pol mutant which is part and parcel of an adenoviral vector construct of use in the methods and compositions disclosed herein may include but is not limited to a mutated nucleic acid molecule comprising at least one nucleotide substitution which
30 results in a point mutation which effectively alters an active site within the RT, RNase and/or IN regions of the expressed protein, resulting in at least substantially decreased enzymatic activity for the RT, RNase H and/or IN functions of HIV-1 Pol. In a specific embodiment of this portion of the invention, a HIV-1 DNA pol construct contains a mutation (or mutations) within the Pol coding region which effectively abolishes RT, RNase H and IN activity. A specific HIV-1 pol-containing construct contains
35 at least one point mutation which alters the active site of the RT, RNase H and IN domains of Pol, such that each activity is at least substantially abolished. Such a HIV-1 Pol mutant will most likely comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN

WO 2006/020480

PCT/US2005/027658

activity, respectfully. To this end, specific embodiments relate to methods and compositions utilizing HIV-1 pol wherein the encoding nucleic acid comprises nine codon substitution mutations which result in an inactivated Pol protein (IA Pol: SEQ ID NO: 6, Figures 4A-1 to 4A-3) which has no PR, RT, RNase or IN activity, wherein three such point mutations reside within each of the RT, RNase and IN catalytic domains. Therefore, one exemplification contemplated employs an adenoviral vector construct which comprises, in an appropriate fashion, a nucleic acid molecule which encodes IA-Pol, which contains all nine mutations as shown below in Table 1. An additional amino acid residue for substitution is Asp551, localized within the RNase domain of Pol. Any combination of the mutations disclosed herein may be suitable and therefore may be utilized in the vectors, methods and compositions of the present invention. While addition and deletion mutations are contemplated and within the scope of the invention, the preferred mutation is a point mutation resulting in a substitution of the wild type amino acid with an alternative amino acid residue.

Table 1

	<u>wt aa</u>	<u>aa residue</u>	<u>mutant aa</u>	<u>enzyme function</u>
15	Asp	112	Ala	RT
	Asp	187	Ala	RT
	Asp	188	Ala	RT
	Asp	445	Ala	RNase H
20	Glu	480	Ala	RNase H
	Asp	500	Ala	RNase H
	Asp	626	Ala	IN
	Asp	678	Ala	IN
	Glu	714	Ala	IN

25

It is preferred that point mutations be incorporated into the IAPol mutant adenoviral vector constructs of the present invention so as to lessen the possibility of altering epitopes in and around the active site(s) of HIV-1 Pol. To this end, SEQ ID NO: 5 (Figures 4A-1 to 4A-3) discloses the nucleotide sequence which codes for a codon optimized pol in addition to the nine mutations shown in Table 1 and referred to herein as "IAPol".

30

To produce adenoviral constructs comprising IA-pol for use in the vectors, methods and compositions of the present invention, inactivation of the enzymatic functions was achieved by replacing a total of nine active site residues from the enzyme subunits with alanine side-chains. As shown in Table 1, all residues that comprise the catalytic triad of the polymerase, namely Asp112, Asp187, and Asp188, were substituted with alanine (Ala) residues (Larder, et al., *Nature* 1987, 327: 716-717; Larder, et al., 1989, *Proc. Natl. Acad. Sci.* 1989, 86: 4803-4807). Three additional mutations were introduced at Asp445, Glu480 and Asp500 to abolish RNase H activity (Asp551 was left unchanged in this IA Pol

35

WO 2006/020480

PCT/US2005/027658

construct), with each residue being substituted for an Ala residue, respectively (Davies, et al., 1991, Science 252:, 88-95; Schatz, et al., 1989, *FEBS Lett.* 257: 311-314; Mizrahi, et al., 1990, Nucl. Acids. Res. 18: pp. 5359-5353). HIV pol integrase function was abolished through three mutations at Asp626, Asp678 and Glu714. Again, each of these residues was substituted with an Ala residue (Wiskerchen, et al., 1995, J. Virol. 69: 376-386; Leavitt, et al., 1993, *J. Biol. Chem.* 268: 2113-2119). Amino acid residue Pro3 of SEQ ID NO: 6 marks the start of the RT gene. The complete amino acid sequence of IA-Pol is disclosed herein as SEQ ID NO: 6 and shown in Figures 4A-1 to 4A-3.

As noted above, it will be understood that any combination of the mutations disclosed above may be suitable and therefore be utilized in adenoviral HIV constructs, methods and compositions of the present invention, either when administered alone, with other heterologous genes, in a combined modality regime and/or as part of a prime-boost regimen. For example, it may be possible to mutate only 2 of the 3 residues within the respective reverse transcriptase, RNase H, and integrase coding regions while still abolishing these enzymatic activities.

Another aspect of this portion of the invention are methods, vectors and compositions employing adenoviral vector constructs comprising codon optimized HIV-1 Pol comprising a eukaryotic trafficking signal peptide or a leader peptide such as is found in highly expressed mammalian proteins such as immunoglobulin leader peptides. Any functional leader peptide may be tested for efficacy. The respective DNA may be modified by known recombinant DNA methodology. In the alternative, as noted above, a nucleotide sequence which encodes a leader/signal peptide may be inserted into a DNA vector housing the open reading frame for the Pol protein of interest. Regardless of the cloning strategy, the end result is a vector construct which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Pol protein of interest, including but not limited to a HIV-1 Pol protein which contains a leader peptide.

The design of gene sequences disclosed herein incorporates the use of human preferred ("humanized") codons for each amino acid residue in the sequence in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12). As can be discerned by inspecting the codon usage in SEQ ID NOs: 3 and 5, the following codon usage for mammalian optimization is preferred: Met (ATG), Gly (GGC), Lys (AAG), Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG); Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG), Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian (human) codon optimization, see WO 97/31115 (PCT/US97/02294). It is intended that the skilled artisan may use alternative versions of codon optimization or may omit this step when generating HIV vaccine constructs within the scope of the present invention. Therefore, the present invention also relates to vectors, methods and compositions comprising/utilizing non-codon optimized or partially codon optimized versions of nucleic acid molecules and associated recombinant adenoviral HIV constructs which encode the various wild type and modified forms of the HIV proteins. However, codon optimization of these constructs constitutes a preferred embodiment of this invention.

WO 2006/020480

PCT/US2005/027658

Codon optimized versions of HIV-1 nef and HIV-1 nef modifications of use in specific embodiments of the present invention can be found in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000. Particular codon optimized nef and nef modifications relate to nucleic acid encoding HIV-1 Nef from the HIV-1 jrfl isolate wherein the codons are optimized for expression in a mammalian system such as a human. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO: 7 (Figure 5), while the expressed open reading frame is disclosed herein as SEQ ID NO: 8. Figures 7A-1 to 7A-2 illustrate a comparison of wild type vs. codon optimized nucleotides comprising the open reading frame of HIV-nef. The open reading frame for SEQ ID NO: 7 comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The open reading frame of SEQ ID NO: 7 provides for a 216 amino acid HIV-1 Nef protein expressed through utilization of a codon optimized DNA vaccine vector. The 216 amino acid HIV-1 Nef (jrfl) protein is disclosed herein as SEQ ID NO: 8; Figure 6. Another modified nef optimized coding region relates to a nucleic acid molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein described as opt nef (G2A, LLAA). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO: 9, while the expressed open reading frame is disclosed herein as SEQ ID NO: 10. Yet another modified nef optimized coding region relates to a nucleic acid molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2), herein described as opt nef (G2A). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO: 12, while the expressed open reading frame is disclosed herein as SEQ ID NO: 13.

HIV-1 Nef is a 216 amino acid cytosolic protein which associates with the inner surface of the host cell plasma membrane through myristylation of Gly-2 (Franchini et al., 1986, *Virology* 155: 593-599). While not all possible Nef functions have been elucidated, it has become clear that correct trafficking of Nef to the inner plasma membrane promotes viral replication by altering the host intracellular environment to facilitate the early phase of the HIV-1 life cycle and by increasing the infectivity of progeny viral particles. In one aspect of the invention, the methods, vectors and compositions of the present invention employ an adenoviral vector(s) comprising codon-optimized nef sequence modified to contain a nucleotide sequence which encodes a heterologous leader peptide such that the amino terminal region of the expressed protein will contain the leader peptide. The diversity of function that typifies eukaryotic cells depends upon the structural differentiation of their membrane boundaries. To generate and maintain these structures, proteins must be transported from their site of synthesis in the endoplasmic reticulum to predetermined destinations throughout the cell. This requires that the trafficking proteins display sorting signals that are recognized by the molecular machinery responsible for route selection located at the access points to the main trafficking pathways. Sorting decisions for most proteins need to be made only once as they traverse their biosynthetic pathways since

WO 2006/020480

PCT/US2005/027658

their final destination, the cellular location at which they perform their function, becomes their permanent residence. Maintenance of intracellular integrity depends in part on the selective sorting and accurate transport of proteins to their correct destinations. Defined sequence motifs exist in proteins which can act as 'address labels'. A number of sorting signals have been found associated with the cytoplasmic domains of membrane proteins. An effective induction of CTL responses often required sustained, high level endogenous expression of an antigen. As membrane-association via myristylation is an essential requirement for most of Nef's function, mutants lacking myristylation, by glycine-to-alanine change, change of the dileucine motif and/or by substitution with a leader sequence, will be functionally defective, and therefore will have improved safety profile compared to wild-type Nef for use as an HIV-1 vaccine component.

In specific embodiments, therefore, the nucleotide sequence is modified to include a leader or signal peptide of interest. This may be accomplished by known recombinant DNA methodology. In the alternative, as noted above, insertion of a nucleotide sequence may be inserted into a DNA vector housing the open reading frame for the Nef protein of interest.

It has been shown that myristylation of Gly-2 in conjunction with a dileucine motif in the carboxy region of the protein is essential for Nef-induced down regulation of CD4 (Aiken et al., 1994, *Cell* 76: 853-864) via endocytosis. It has also been shown that Nef expression promotes down regulation of MHCI (Schwartz et al., 1996, *Nature Medicine* 2(3): 338-342) via endocytosis. The present invention contemplates adenoviral vectors which comprise sequence encoding a modified Nef protein altered in trafficking and/or functional properties and the use thereof in the methods and compositions of the present invention. The modifications introduced into the adenoviral vector HIV constructs of the present invention include but are not limited to additions, deletions or substitutions to the nef open reading frame which results in the expression of a modified Nef protein which includes an amino terminal leader peptide, modification or deletion of the amino terminal myristylation site, and modification or deletion of the dileucine motif within the Nef protein and which alter function within the infected host cell.

A recombinant adenoviral construct of use in accordance with the methods and compositions disclosed herein can comprise sequence encoding optimized HIV-1 Nef with modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. This open reading frame is herein described as opt nef (G2A,LLAA) and is disclosed as SEQ ID NO: 9, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jrf1 nef gene with the above mentioned modifications is disclosed herein as SEQ ID NO: 9; Figure 8. The open reading frame of SEQ ID NO: 9 encodes Nef (G2A,LLAA), disclosed herein as SEQ ID NO: 10; Figure 9.

Another recombinant adenoviral construct of use in accordance with the methods and compositions disclosed herein can comprise sequence encoding optimized HIV-1 Nef with modifications at the amino terminal myristylation site (Gly-2 to Ala-2). This open reading frame is herein described as

WO 2006/020480

PCT/US2005/027658

opt nef (G2A) and is disclosed as SEQ ID NO: 13, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jrf1 nef gene with the above mentioned modification is disclosed herein as SEQ ID NO: 12; Figure 10. The open reading frame of SEQ ID NO: 12 encodes Nef (G2A),
 5 disclosed herein as SEQ ID NO: 13; Figure 11.

Figure 12 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

Adenoviral vectors of use in the methods and compositions of the present invention may
 10 comprise one or more HIV genes/encoding nucleic acid. The administration of at least one (preferably, at least two) recombinant adenoviral vector(s) comprising two or more HIV genes, their derivatives, or modifications are anticipated as well as exemplified herein. Two or more HIV genes can be expressed on at least one of the recombinant adenoviral vector constructs and/or two or more HIV genes can be expressed across two or more constructs. One of skill in the art can readily appreciate that the present
 15 invention, therefore, encompasses those situations where, while only one antigen is in common amongst at least two of the vectors of different serotype, the vectors may have additional HIV genes that (1) differ, (2) are the same, (3) while not in common with that vector, are in common with another vector utilized in the disclosed methods or compositions, or (4) are derived from the same common antigen. Therefore, the present invention offers the possibility of using the methods and compositions of the
 20 present invention to evade/bypass host immunity and effectuate a multi-valent HIV gene administration, specific examples, but not limitations of which, include the administration of adenoviral vectors comprising nucleic acid sequence encoding (1) Gag and Nef polypeptides, (2) Gag and Pol polypeptides, (3) Pol and Nef polypeptides, and (4) Gag, Pol and Nef polypeptides.

Multiple genes/encoding nucleic acid may be ligated into a proper shuttle plasmid for
 25 generation of a pre-adenoviral plasmid comprising multiple open reading frames. Open reading frames for the multiple genes/encoding nucleic acid can be operatively linked to distinct promoters and transcription termination sequences. In other embodiments, the open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES; as disclosed in WO 95/24485), or suitable alternative allowing for transcription of
 30 the multiple open reading frames to run off of a single promoter. In certain embodiments, the open reading frames may be fused together by stepwise PCR or suitable alternative methodology for fusing together two open reading frames. Various combined modality administration regimens suitable for use in the present invention are disclosed in PCT/US01/28861, published March 21, 2002.

Several multi-valent vectors of this description are also disclosed herein (*see, e.g.*,
 35 Example 2 and the corresponding Figures) and form an important aspect of the present invention. Methods of using same in eliciting cellular-mediated immune responses specific for the HIV antigens contained therein are also encompassed herein. Said vectors comprise nucleic acid encoding at least two

WO 2006/020480

PCT/US2005/027658

antigens selected from the group consisting of gag, nef and/or pol antigens. The nucleic acid can be as disclosed herein or can be any modification, derivative or functional equivalent of same. Preferably, the nucleic acid sequences are codon-optimized or partially codon-optimized. Specific embodiments of the present invention are such constructs which are di/tri-cistronic (*i.e.*, the individual antigens are under the control of distinct promoters). Specific constructs in accordance with the above disclosure are described further as adenoviral vectors comprising nucleic acid encoding (1) gag and nef; (2) gag and pol; and (3) gag, pol and nef. In one embodiment, the adenoviral serotypes are of adenoviral serotype 5 or 6. In further embodiments the adenoviral vectors are deleted in E1 and E3 to accommodate the heterologous nucleic acid. In additional embodiments, the adenoviral vectors disclosed herein have the heterologous nucleic acid present in an E1 deletion of a region which corresponds to that of nucleotides 451-3510 of adenovirus serotype 5 or nucleotides 451-3507 of adenovirus serotype 6. In specific embodiments, the adenoviral vectors comprise the nucleic acid encoding the at least two antigens under the control of at least two promoters, one driving expression of nucleic acid encoding at least one of the antigens and at least one other driving the expression of nucleic acid encoding at least one other antigen. Specific constructs disclosed herein are adenoviral vectors comprising nucleic acid encoding: (1) nef and gag under the control of two distinct promoters; (2) nef and gag under the control of the hCMV and mCMV promoters (*see, e.g.*, Examples 2H and 2I and Figures 17 and 20); (3) gagpol (a fusion of coding sequences of gag and pol); (4) nef and gagpol; (5) nef and gagpol under the control of hCMV and mCMV promoters (*see, e.g.*, Examples 2K and 2M and Figures 27 and 35); and (6) gagpolnef (a fusion of coding sequence of gag, pol and nef). Other specific embodiments relate to adenoviral vectors comprising two or more of the gag, nef and/or pol antigens wherein nucleic acid encoding an Env antigen(s) is not present. HIV-1 Env protein (*e.g.*, gp120) elicits an immune response typified by neutralizing antibodies which tend to be extremely virus-isolate specific principally due to the high variability of gp120. While nucleic acid encoding Env may be added to the constructs described herein, the constructs absent such nucleic acid have proven sufficient to elicit a significant immune response in treated subjects. It is well within the purview of one of skill in the art to arrive at and effectively utilize various fusion/multi-valent constructs.

Further embodiments of the present invention relate to the contemporaneous administration of more than one vector administered by the at least two serotypes. For instance, two or more serotypes both comprising nucleic acid A can be co-administered with two or more serotypes both comprising nucleic acid B. In this manner, the properties of the instant administration strategies can be exploited to administer nucleic acid that one may want, for one reason or another, across more than one vector. One example solely for purposes of exemplification and not limitation would be a scenario wherein the following vectors were administered contemporaneously: (1) Ad5 comprising nucleic acid encoding antigen A; (2) Ad5 comprising nucleic acid encoding antigen A; (3) Ad6 comprising nucleic acid encoding antigens B and C; and (4) Ad5 comprising nucleic acid encoding antigens B and C.

WO 2006/020480

PCT/US2005/027658

Regardless of the antigen/method chosen, contemporaneous administration of recombinant adenoviruses in accordance with the methods of the present invention may be the subject of a single administration or form part of a broader prime/boost-type administration regimen. Prime-boost regimens can employ different viruses (including but not limited to different viral serotypes and viruses of different origin), viral vector/protein combinations, and combinations of viral and polynucleotide administrations. In this type of scenario, an individual is first administered a priming dose of a protein/antigen/derivative/modification utilizing a certain vehicle (be that a viral vehicle, purified and/or recombinant protein, or encoding nucleic acid). Multiple primings, typically 1-4, are usually employed, although more may be used. The priming dose(s) effectively primes the immune response so that, upon subsequent identification of the protein/antigen(s) in the circulating immune system, the immune response is capable of immediately recognizing and responding to the protein/antigen(s) within the host. Following some period of time, the individual is administered a boosting dose of at least one of the previously delivered protein(s)/antigen(s), derivatives or modifications thereof (administered by viral vehicle/protein/nucleic acid). The length of time between priming and boost may typically vary from about four months to a year, albeit other time frames may be used as one of ordinary skill in the art will appreciate. The follow-up or boosting administration may also be repeated at selected time intervals. In certain embodiments, contemporaneous administration in accordance herewith can be employed for both the prime and boost administrations. A mixed modality prime and boost inoculation scheme should result in an enhanced immune response, specifically where there is pre-existing anti-vector immunity.

Selection of the alternate administration vehicle (be it viral/nucleic acid/protein) to be employed in conjunction with the methods and compositions disclosed herein in a prime-boost administration regimen is not critical to the successful practice hereof. Any vehicle capable of delivering the antigen (or effectuating expression of the antigen) to sufficient levels such that a cellular and/or humoral-mediated response is elicited should be sufficient to prime or boost the presently disclosed administration. Suitable viral vehicles include but are not limited to distinct serotypes of adenovirus, including but not limited to adenovirus serotypes 6, 24, 34 and 35 (*see, e.g.*, PCT/US02/32512, published April 17, 2003 (Ad6); PCT/US2003/026145, published March 4, 2004 (Ad24, Ad34); PCT/NL00/00325, published November 23, 2000 (Ad35)). Alternatively, the adenoviral administration can be followed or preceded by a viral vehicle of diverse origin. Examples of different viral vehicles include but are not limited to adeno-associated virus ("AAV"; *see, e.g.*, Samulski *et al.*, 1987 *J. Virol.* 61:3096-3101; Samulski *et al.*, 1989 *J. Virol.* 63:3822-3828); retrovirus (*see, e.g.*, Miller, 1990 *Human Gene Ther.* 1:5-14; Ausubel *et al.*, *Current Protocols in Molecular Biology*); pox virus (including but not limited to replication-impaired NYVAC, ALVAC, TROVAC and MVA vectors, *see, e.g.*, Panicali & Paoletti, 1982 *Proc. Natl. Acad. Sci. USA* 79:4927-31; Nakano *et al.* 1982 *Proc. Natl. Acad. Sci. USA* 79: 1593-1596; Piccini *et al.*, In *Methods in Enzymology* 153:545-63 (Wu & Grossman, eds., Academic Press, San Diego); Sutter *et al.*, 1994 *Vaccine* 12:1032-40; Wyatt *et al.*, 1996 *Vaccine* 15:1451-8; and U.S. Patent Nos. 4,603,112; 4,769,330; 4,722,848; 4,603,112; 5,110,587; 5,174,993; and 5,185,146); and alpha virus

WO 2006/020480

PCT/US2005/027658

(*see, e.g.*, WO 92/10578; WO 94/21792; WO 95/07994; and U.S. Patent Nos. 5,091,309 and 5,217,879). Prime-boost protocols exploiting adenoviral and pox viral vectors for delivery of HIV antigens are discussed in International Application No. PCT/US03/07511, published September 18, 2003. An alternative to the above immunization schemes would be to employ polynucleotide administrations (including but not limited to "naked DNA" or facilitated polynucleotide delivery) in conjunction with an adenoviral prime and/or boost; *see, e.g.*, Wolff *et al.*, 1990 *Science* 247:1465, and the following patent publications: U.S. Patent Nos. 5,580,859; 5,589,466; 5,739,118; 5,736,524; 5,679,647; WO 90/11092 and WO 98/04720. Another alternative would be to employ purified/recombinant protein administration in a prime-boost scheme along with adenovirus.

Potential hosts/vaccinees/individuals that can be administered the recombinant adenoviral vectors of the present invention include but are not limited to primates and especially humans and non-human primates, and include any non-human mammal of commercial or domestic veterinary importance.

Compositions of adenoviral vectors whether of single or multiple serotype, including but not limited to vaccine compositions, administered in accordance with the methods and compositions of the present invention may be administered alone or in combination with other viral- or non-viral-based DNA/protein vaccines. They also may be administered as part of a broader treatment regimen. The present invention, thus, encompasses those situations where the disclosed adenoviral cocktails are administered in conjunction with other therapies; including but not limited to other antimicrobial (*e.g.*, antiviral, antibacterial) agent treatment therapies. A specific antimicrobial agent(s) selected is not critical to successful practice of the methods disclosed herein. The antimicrobial agent can, for example, be based on/derived from an antibody, a polynucleotide, a polypeptide, a peptide, or a small molecule. Any antimicrobial agent that effectively reduces microbial replication/spread/load within an individual is sufficient for the uses described herein.

Antiviral agents antagonize the functioning/life cycle of a virus, and target a protein/function essential to the proper life cycle of the virus; an effect that can be readily determined by an *in vivo* or *in vitro* assay. Some representative antiviral agents which target specific viral proteins are protease inhibitors, reverse transcriptase inhibitors (including nucleoside analogs; non-nucleoside reverse transcriptase inhibitors; and nucleotide analogs), and integrase inhibitors. Protease inhibitors include, for example, indinavir/CRIXIVAN®; ritonavir/NORVIR®; saquinavir/FORTOVASE®; nelfinavir/VIRACEPT®; amprenavir/AGENERASE®; lopinavir and ritonavir/KALETRA®. Reverse transcriptase inhibitors include, for example, (1) nucleoside analogs, *e.g.*, zidovudine/RETROVIR® (AZT); didanosine/VIDEX® (ddI); zalcitabine/HIVID® (ddC); stavudine/ZERIT® (d4T); lamivudine/EPIVIR® (3TC); abacavir/ZIAGEN® (ABC); (2) non-nucleoside reverse transcriptase inhibitors, *e.g.*, nevirapine/VIRAMUNE® (NVP); delavirdine/RESCRIPTOR® (DLV); efavirenz/SUSTIVA® (EFV); and (3) nucleotide analogs, *e.g.*, tenofovir DF/VIREAD® (TDF). Integrase inhibitors include, for example, the molecules disclosed in U.S. Application Publication No.

WO 2006/020480

PCT/US2005/027658

US2003/0055071, published March 20, 2003; and International Application WO 03/035077. The antiviral agents, as indicated, can target as well a function of the virus/viral proteins, such as, for instance the interaction of regulatory proteins tat or rev with the trans-activation response region ("TAR") or the rev-responsive element ("RRE"), respectively. An antiviral agent is, preferably, selected from the class
 5 of compounds consisting of: a protease inhibitor, an inhibitor of reverse transcriptase, and an integrase inhibitor. Preferably, the antiviral agent administered to an individual is some combination of effective antiviral therapeutics such as that present in highly active anti-retroviral therapy ("HAART"), a term generally used in the art to refer to a cocktail of inhibitors of viral protease and reverse transcriptase.

One of skill in the art can appreciate that the present invention can be employed in
 10 conjunction with any pharmaceutical composition useful for the treatment of microbial infections. Antimicrobial agents are typically administered in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000.

Compositions comprising the recombinant viral vectors may contain physiologically
 15 acceptable components, such as buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. In specific embodiments the viral particles are formulated in A195 formulation buffer. In certain embodiments, the formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01-2 mM MgCl₂; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about
 20 7.0-9.0, preferably about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used in the formulation. In specific embodiments, the formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM MgCl₂, 0.005% polysorbate 80 at pH 8.0. This has a pH and divalent cation composition which is near the optimum for virus stability and minimizes the potential for adsorption of virus to glass surface. It does not cause tissue irritation upon intramuscular injection. It is
 25 preferably frozen until use.

The amount of viral particles in the vaccine composition(s) to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene product(s). In general, an immunologically or prophylactically effective dose of 1×10^7 to 1×10^{12} particles and preferably about 1×10^{10} to 1×10^{11}
 30 particles per adenoviral vector is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation delivery are also contemplated. One of ordinary skill in the art can also appreciate that different modes of administration can be employed to administer the different viruses of the methods and compositions taught herein. For instance, one of ordinary skill in the art can
 35 appreciate that one serotype can feasibly be administered via one injection route and another serotype via another route and still maintain contemporaneous delivery. Preferably, the total dose of adenoviral particles administered (different serotypes combined) does not exceed 1×10^{12} .

WO 2006/020480

PCT/US2005/027658

Administration of additional agents able to potentiate or broaden the immune response (*e.g.*, the various cytokines, interleukins), concurrently with or subsequent to parenteral introduction of the viral vectors of this invention is appreciated herein as well and can be advantageous.

5 The benefits of administration as described herein should be (1) a comparable or broader population of individuals successfully immunized/treated with recombinant adenoviral vectors, and (2) in situations of immunization, a lower transmission rate to (or occurrence rate in) previously uninfected individuals (*i.e.*, prophylactic applications) and/or a reduction in/control of the levels of virus/bacteria/foreign agent within an infected individual (*i.e.*, therapeutic applications).

10 The following non-limiting examples are presented to better illustrate the workings of the invention.

EXAMPLE 1

ASSESSMENT OF NEUTRALIZATION TITERS

15 A. Human Samples

Serum samples were collected from HIV-infected patients from six countries – North America, Brazil, Thailand, Malawi, South Africa, and Cameroon. The samples were complement-inactivated at 56 °C for 90 mins before use.

B. Neutralization Assay

20 *In vitro* measurements of adenovirus neutralization titers were conducted following procedures previously reported; *see, e.g.*, Aste-Amézaga, 2004 *Hum. Gene Ther.* 15:293-304. Neutralization titers against human adenovirus serotypes 5 and 6 (Ad5 and Ad6, respectively) were determined using vectors expressing secreted alkaline phosphatase.

C. Results

25 The titers were distributed among four ranges: (a) <18 or undetectable, (b) 18-200, (c) 201-1000, and (d) >1000. The results are shown in Figure 13. The titers were generally highest against Ad5 and lowest against Ad5 and Ad6.

30 It was observed that when an individual has a high Ad5 titer, the Ad6 were much lower and vice versa. Applicants decided to test the ability of a cocktail of Ad5- and Ad6-based vaccine vectors in the circumvention of any limitation due to high neutralizing activity to either one. The “effective titer” against such a cocktail of viruses was determined to be the lower of the adenovirus titers (in this case, Ad5 or Ad6 titers) since the vaccine component corresponding to that vector would be more potent. Figure 13 contains the distribution of this “effective” Ad5/Ad6 titer. Applicants determined that Ad5/Ad6 had a titer distribution towards lower values than either Ad5 or Ad6.

WO 2006/020480

PCT/US2005/027658

EXAMPLE 2

VECTOR CONSTRUCTION

A. HIV-1 gag Gene

A synthetic gene for HIV Gag from HIV-1 strain CAM-1 was constructed using codons frequently used in humans; *see* Korber *et al.*, 1998 *Human Retroviruses and AIDS*, Los Alamos Nat'l Lab., Los Alamos, New Mexico; and Lathe, R., 1985 *J. Mol. Biol.* 183:1-12. Figure 1 illustrates the nucleotide sequence of the exemplified optimized codon version of full-length p55 gag; SEQ ID NO: 2. The gag gene of HIV-1 strain CAM-1 was selected as it closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence (Los Alamos HIV database). Advantage of this "codon-optimized" HIV gag gene as a vaccine component has been demonstrated in immunogenicity studies in mice. The "codon-optimized" HIV gag gene was shown to be over 50-fold more potent to induce cellular immunity than the wild type HIV gag gene when delivered as a DNA vaccine.

A KOZAK sequence (GCCACC) was introduced proceeding the initiating ATG of the gag gene for optimal expression. The HIV gag fragment with KOZAK sequence was amplified through PCR from a V1Jns-HIV gag vector. PV1JnsHIVgag is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; *see* Montgomery *et al.*, 1993 *DNA Cell Biol.* 12:777-783, for a description of the plasmid backbone.

20

B. MRKAd5gag Construction and Virus Rescue

1. Removal of the Intron A Portion of the hCMV Promoter

GMP grade pV1JnsHIVgag was used as the starting material to amplify the hCMV promoter. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of the hCMV promoter and a 3' primer (designed to contain the *BglII* recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *BglII*. This fragment was then cloned back into the original GMP grade pV1JnsHIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *BglII* digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pV1JnsHIVgag vector backbone. This vector is designated pV1JnsCMV(no intron).

The FLgag gene was excised from pV1JnsHIVgag using *BglII* digestion and the 1,526 bp gene was gel purified and cloned into pV1JnsCMV(no intron) at the *BglII* site. Colonies were screened using *SmaI* restriction enzymes to identify clones that carried the FLgag gene in the correct orientation.

35

WO 2006/020480

PCT/US2005/027658

This plasmid, designated pV1JnsCMV(no intron)-FLgag-bGHpA, was fully sequenced to confirm sequence integrity.

2. Construction of the Modified Shuttle Vector - "MRKpdelE1 Shuttle"

The modifications to the original Ad5 shuttle vector (pdelE1sp1A; a vector comprising Ad5 sequences from base pairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:

(1) The left ITR region was extended to include the *Pac*1 site at the junction between the vector backbone and the adenovirus left ITR sequences. This allowed for easier manipulations using the bacterial homologous recombination system.

(2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.

(3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).

These modifications effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6[®] cell line. All manipulations were performed by modifying the Ad shuttle vector pdelE1sp1A.

Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbone pAdHVE3 by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

3. Construction of Modified Adenovector Backbone

An original adenovector pADHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region) was reconstructed so that it would contain the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdelE1 shuttle) with *Pac*1 and *Bst*Z1101 and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from *Cla*1 linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from the transformation were selected and grown in Terrific[™] broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from the transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovector was designated MRKpAdHVE3 (E3+ plasmid). Virus from the new adenovector (MRKHVE3) as well as the old version were generated in the PER.C6[®] cell lines. In addition, the multiple cloning site of the original shuttle vector contained *Cla*I, *Bam*HI, *Xho*I, *Eco*RV, *Hind*III, *Sal*I, and *Bgl*II sites. This MCS was replaced with a new MCS containing *Not*I, *Cla*I, *Eco*RV and *Asc*I sites. This new MCS has been transferred to the MRKpAdHVE3 pre-plasmid along with the modification made to the packaging region and pIX gene.

4. Construction of the new shuttle vector containing modified gag transgene – “MRKpdelE1-CMV(no intron)-FLgag-bGHpA”

The modified plasmid pV1JnsCMV(no intron)-FLgag-bGHpA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 minutes at 30°C. The DNA mixture was desalted using the Qiaex II kit and then Klenow treated for 30 minutes at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdelE1 shuttle) was linearized by digestion with *EcoRV*, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel orientation.

5. Construction of the MRK FG Adenovector

The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdelE1-CMV(no intron)-FLgag-bGHpA, was digested with *PacI*. The reaction mixture was digested with *BsfZ171*. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *ClaI* overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml Terrific™ broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH₂O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from the transformation was selected and grown overnight in 3 ml LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone was identified by digestion with the restriction enzyme *BstEII* which cleaves within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size. A nucleotide sequence for pMRKAd5HIV-1gag adenoviral vector and details of its construction are disclosed in PCT/US01/28861, published March 21, 2002.

6. Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1gag”

MRK Ad5 HIV-1 gag contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *PacI* to release the vector backbone and 3.3 µg was transfected by the calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing PER.C6® cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6® cells at 80-90% confluence. Once CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell

WO 2006/020480

PCT/US2005/027658

lysate was then used to infect a 15 cm dish containing PER.C6[®] cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient). Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was
 5 extracted using pronase treatment followed by phenol chloroform. The viral DNA was then digested with *Hind*III and radioactively labeled with [³³P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *Pac*I/*Hind*III prior to labeling). The expected sizes were observed, indicating that the virus
 10 had been successfully rescued.

C. HIV-1 pol Gene

A synthetic gene for HIV Pol from HIV-1 was constructed using codons frequently used in humans; see Korber *et al.*, 1998 *Human Retroviruses and AIDS*, Los Alamos Nat'l Lab., Los Alamos, New Mexico; and Lathe, R., 1985 *J. Mol. Biol.* 183:1-12. The protein sequence is based on that of
 15 Hxb2r, a clonal isolate of IIIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber *et al.*, 1998 *Human Retroviruses and AIDS*, Los Alamos National Laboratory, Los Alamos, New Mexico). The protease gene is excluded from the DNA vaccine constructs herein to insure safety from any residual protease activity in spite of mutational inactivation.

20 Figures 4A-1 to 4A-3 illustrate the nucleotide sequence of an exemplified codon optimized version of HIV-1 pol. The pol gene encodes optimized HIV-1 Pol wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for nine codon substitution mutations which result in an inactivated Pol protein (IA Pol: SEQ ID NO: 6; Figures 4A-1 to 4A-3) which has no protease, reverse transcriptase, RNase or integrase activity, with three point mutations residing within each of the
 25 RT, RNase and In catalytic domains.

D. MRKAd5Pol Construction and Virus Rescue

1. Construction of vector: shuttle plasmid and pre-adenovirus plasmid

Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5pol, is depicted in Figure 14. Briefly, the adenoviral shuttle vector for the full-
 30 length inactivated HIV-1 pol gene is as follows. The vector MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is a derivative of the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. The vector contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a
 35 unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)ClaI (or MRKpAdHVE3) pre-plasmid. The vector, similar to the original shuttle vector contains the *Pac*I site, extension to the packaging signal region, and extension to

WO 2006/020480

PCT/US2005/027658

the pIX gene. The synthetic full-length codon-optimized HIV-1 pol gene was isolated directly from the plasmid pV1Jns-HIV-pol-inact(opt). Digestion of this plasmid with *Bgl* II releases the pol gene intact (comprising a codon optimized IA pol sequence as disclosed in SEQ ID NO: 5). The pol fragment was gel purified and ligated into the MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*II site. The clones were checked for the correct orientation of the gene by using restriction enzymes *Dra*III/*Not*I. A positive clone was isolated and named MRKpdel+hCMVmin+FL-pol+bGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows: Shuttle plasmid MRKpdel+hCMVmin+FL-pol+bGHpA(S) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I digested) adenoviral backbone plasmid, MRKpAd(E1-/E3+)Cla1. The resulting pre-plasmid originally named MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+ is now referred to as "pMRKAd5pol". The genetic structure of the resulting pMRKAd5pol was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the pol transgene in transient transfection cell culture. A nucleotide sequence for pMRKAd5HIV-1pol adenoviral vector and details of its construction are disclosed in PCT/US01/28861, published March 21, 2002.

2. Generation of research-grade recombinant adenovirus

The pre-adenovirus plasmid, pMRKAd5pol, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAd5pol was digested with restriction enzyme *Pac*I (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*I digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This pol containing recombinant adenovirus is referred to herein as "MRKAd5pol". This recombinant adenovirus expresses an inactivated HIV-1 Pol protein as shown in SEQ ID NO: 6.

E. HIV-1 nef Gene

A synthetic gene for HIV Nef from HIV-1 was constructed using codons frequently used in humans; see Korber *et al.*, 1998 *Human Retroviruses and AIDS*, Los Alamos Nat'l Lab., Los Alamos, New Mexico; and Lathe, R., 1985 *J. Mol. Biol.* 183:1-12.

Figure 8 illustrates the nucleotide sequence of an exemplified codon optimized version of HIV-1 jrf1 nef gene. The nef gene encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. The open

WO 2006/020480

PCT/US2005/027658

reading frame is herein described as opt nef (G2A,LLAA), and is disclosed as SEQ ID NO: 10, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662.

Figure 10 illustrated the nucleotide sequence of an exemplified codon optimized version of HIV-1 jrf1 nef gene. The nef gene encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2). The open reading frame is herein described as opt nef (G2A) and is disclosed as SEQ ID NO: 12, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662.

10 F. MRKAd5Nef Construction and Virus Rescue

1. Construction of vector: shuttle plasmid and pre-adenovirus plasmid

Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5nef, is depicted in Figure 15. Briefly, the vector MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. It has been modified to contain the *Pac*I site, extension to the packaging signal region, and extension to the pIX gene. It contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)ClaI pre-plasmid. The synthetic full-length codon-optimized HIV-1 nef gene was isolated directly from the plasmid pV1Jns/nef (G2A,LLAA). Digestion of this plasmid with *Bgl*II releases the pol gene intact, which comprises the nucleotide sequence as disclosed in SEQ ID NO: 9. The nef fragment was gel purified and ligated into the MRKpdeIE1+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*II site. The clones were checked for correct orientation of the gene by using restriction enzyme *Sca*I. A positive clone was isolated and named MRKpdeIE1hCMVminFL-nefBGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdeIE1hCMVminFL-nefBGHpA(s) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I digested) adenoviral backbone plasmid, MRKpAd(E1/E3+)ClaI. The resulting pre-plasmid originally named MRKpdeIE1hCMVminFL-nefBGHpA(s) is now referred to as "pMRKAd5nef". The genetic structure of the resulting pMRKAd5nef was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture. A nucleotide sequence for pMRKAd5HIV-1nef adenoviral vector and details of its construction are disclosed in PCT/US01/28861, published March 21, 2002.

WO 2006/020480

PCT/US2005/027658

2. Generation of research-grade recombinant adenovirus

The pre-adenovirus plasmid, pMRKAd5nef, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAdnef was digested with restriction enzyme *Pac*1 (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*1 digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This nef containing recombinant adenovirus is now referred to as "MRKAd5nef".

G. Generation of Adenoviral Serotype 6 Vector Constructs

1. Construction of Ad6 Pre-Adenovirus Plasmid

The general strategy used to recover a pMRKAd6E1- bacterial plasmid is illustrated in Figure 16. In general terms, cotransformation of BJ 5183 bacteria with purified wt Ad6 viral DNA and a second DNA fragment termed the Ad6 ITR cassette effectuates circularization of the viral genome by homologous recombination. The ITR cassette contains sequences from the right (bp 35460 to 35759) and left (bp 1 to 450 and bp 3508 to 3807) end of the Ad6 genome separated by plasmid sequences containing a bacterial origin of replication and an ampicillin resistance gene. These three segments were generated by PCR and cloned sequentially into pNEB193 (a commonly used commercially available cloning plasmid (New England Biolabs cat# N3051S) containing a bacterial origin of replication, an ampicillin resistance gene, and a multiple cloning site into which the PCR products are introduced), generating pNEBAd6-3 (the ITR cassette). The ITR cassette contains a deletion of E1 sequences from Ad6 sequence from 451 to 3507. The Ad6 sequences in the ITR cassette provide regions of homology with the purified Ad6 viral DNA in which recombination can occur.

pMRKAd6E1- can then be used to generate first generation Ad6 vectors containing transgenes in E1.

2. Construction of an Ad6 Pre-Adenovirus Plasmid containing the HIV-1 gag gene

(A) Construction of Adenoviral Shuttle Vector

A synthetic full-length codon-optimized HIV-1 *gag* gene was inserted into a universal shuttle vector comprising adenovirus serotype 6 ("Ad6") sequences from bp1 to bp450 and bp bp3508 to bp3807 (basepairs 451 to 3507 are deleted), a CMV promoter (minus Intron A) and bGHpA. Direction of transcription was E1 parallel. The synthetic full-length codon-optimized HIV-1 *gag* gene was obtained from plasmid pV1Jns-HIV-FLgag-opt by *Bgl*II digestion, gel purified and ligated into the *Bgl*II restriction endonuclease site in the shuttle vector. The genetic structure of the resultant shuttle vector comprising full length *gag* was verified by PCR, restriction enzyme and DNA sequence analyses.

WO 2006/020480

PCT/US2005/027658

(B) Construction of pre-adenovirus plasmid

The shuttle vector was digested with restriction enzymes *PacI* and *BstI* 107I and then co-transformed into *E. coli* strain BJ5183 with linearized (*Clal*-digested) adenoviral backbone plasmid, pAd6E1-E3+. The genetic structure of the resulting pMRKAd6gag was verified by restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for large-scale production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the gag transgene in transient transfection cell culture.

pMRKAd6gag contains Ad6 bps 1 to 450 and bps 3508 to 35759 (bp numbers refer correspond to that of an Ad6 sequence; *see, e.g.*, PCT/US02/32512, published April 17, 2003). In the plasmid the viral ITRs are joined by plasmid sequences that contain the bacterial origin of replication and an ampicillin resistance gene.

(C) Generation of research-grade recombinant MRKAd6gag

To prepare virus for pre-clinical immunogenicity studies, the pre-adenovirus plasmid pMRKAd6gag was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd6gag was digested with restriction enzyme *PacI* (New England Biolabs) and transfected into a 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *PacI* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by multiple passages in PER.C6[®] cells. At the final passage virus was purified from the cell pellet by CsCl ultracentrifugation. The identity and purity of the purified virus was confirmed by restriction endonuclease analysis of purified viral DNA and by Gag ELISA of culture supernatants from virus infected mammalian cells grown in vitro. For restriction analysis, digested viral DNA was end-labeled with P³³-dATP, size-fractionated by agarose gel electrophoresis, and visualized by autoradiography.

All viral constructs were confirmed for Gag expression by Western blot analysis.

3. Construction of an Ad6 Pre-Adenovirus Plasmid containing the HIV-1 nef gene(A) Construction of Adenoviral Shuttle Vector

A synthetic full-length codon-optimized HIV-1 *nef* gene (opt nef G2A, LLAA) was inserted into a universal shuttle vector comprising adenovirus serotype 6 ("Ad6") sequences from bp1 to bp450 and bp bp3508 to bp3807 (basepairs 451 to 3507 are deleted), a CMV promoter (minus Intron A) and bGHpA. Direction of transcription was E1 parallel. The synthetic full-length codon-optimized HIV-1 *nef* gene was obtained from plasmid pV1Jns-HIV-FLnef-opt by *BglII* digestion, gel purified and ligated into the *BglII* restriction endonuclease site in the shuttle vector. The genetic structure of the resultant shuttle vector comprising full length *nef* was verified by PCR, restriction enzyme and DNA sequence analyses.

WO 2006/020480

PCT/US2005/027658

(B) Construction of pre-adenovirus plasmid

The shuttle vector was digested with restriction enzymes *PacI* and *BstI* 107I and then co-transformed into *E. coli* strain BJ5183 with linearized (*ClaI*-digested) adenoviral backbone plasmid, pAd6E1-E3+. The genetic structure of the resulting pMRKAd6nef was verified by restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for large-scale production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture.

pMRKAd6nef contains Ad6 bps 1 to 450 and bps 3508 to 35759 (bp numbers refer correspond to that of an Ad6 sequence; *see, e.g.*, PCT/US02/32512, published April 17, 2003). In the plasmid the viral ITRs are joined by plasmid sequences that contain the bacterial origin of replication and an ampicillin resistance gene.

(C) Generation of research-grade recombinant MRKAd6nef

To prepare virus for pre-clinical immunogenicity studies, the pre-adenovirus plasmid pMRKAd6nef was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd6nef was digested with restriction enzyme *PacI* (New England Biolabs) and transfected into a 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *PacI* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by multiple passages in PER.C6[®] cells. At the final passage virus was purified from the cell pellet by CsCl ultracentrifugation. The identity and purity of the purified virus was confirmed by restriction endonuclease analysis of purified viral DNA and by nef ELISA of culture supernatants from virus infected mammalian cells grown in vitro. For restriction analysis, digested viral DNA was end-labeled with P³³-dATP, size-fractionated by agarose gel electrophoresis, and visualized by autoradiography.

All viral constructs were confirmed for nef expression by Western blot analysis.

H. Construction of an Ad5 vector containing HIV gag and nef transgenes

MRKAd5gagnef is depicted in Figure 17, with a sequence of such character being illustrated in Figure 18 (SEQ ID NO: 16). The vector is a modification of a prototype Group C Adenovirus serotype 5 whose genetic sequence has been described previously; Chroboczek *et al.*, 1992 *J. Virol.* 186:280-285. The E1 region of the wild-type Ad5 (nt 451-3510) was deleted and replaced by nef and gag expression cassettes. The nef expression cassette consists of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3) the bovine growth hormone polyadenylation signal sequence (Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334). The nef expression cassette is directly followed by the gag expression cassette which consists of: 1) the immediate early gene promoter from the mouse cytomegalovirus (Keil *et al.*, 1987 *J.*

Virol. 61:1901-1908), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene, and 3) the simian virus 40 polyadenylation signal sequence. The amino acid sequence of the Nef and Gag proteins closely resembles the Clade B consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The nef open reading frame was altered by mutating the myristylation site located at Gly-2 to an alanine and by mutating the di-leucine sequence (Leu-174 and Leu-175) to di-alanine. These mutations prevent attachment of Nef to the cytoplasmic membrane and retrotrafficking into endosomes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins. An otherwise identical version of this construct was also generated that contains the nef open reading frame with only the mutated myristylation site.

Key steps involved in the construction of MRKAd5gagnef are depicted in Figure 19 and described in the text that follows.

15 1. Construction of Adenoviral Shuttle Vector

The shuttle plasmid pMRKAd5-HCMV-nef-BGHpA-MCMV36gagSV40-S was constructed by inserting the gag expression cassette into the *AscI* site in pMRKAd5-hCMV-nef-BGHpA. The gag expression cassette was obtained by PCR using S-MRKAd5MCMV36gagSV40pA as template. The PCR primers were designed to introduce *AscI* sites at each end of the transgene. The *AscI* digested PCR fragment was ligated with pMRKAd5-hCMV-nef-BGHpA, also digested with *AscI*, generating pMRKAd5-hCMV-nef-BGHpA-mCMV36gagSV40-S. The genetic structure of pMRKAd5-hCMV-nef-BGHpA-mCMV36gagSV40-S was verified by restriction enzyme analyses and sequencing.

20 2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pMRKAd5gagnef, the transgene containing fragment was liberated from shuttle plasmid pMRKAd5-hCMV-nef-BGHpA-mCMV36gagSV40-S by digestion with restriction enzymes *BstZ17I* + *SgrAI* and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*Clal*-digested) adenoviral backbone plasmid, pHVE3. Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* Sab12TM for screening by restriction analysis. The desired plasmid pMRKAd5gagnef (also referred to as pMRKAd5-hCMV-nef-BGH-mCMV36gagSV40-S) was verified by restriction enzyme digestion and DNA sequence analysis.

30 3. Generation of recombinant MRKAd5gagnef

To prepare virus, the pre-adenovirus plasmid pMRKAd5gagnef was rescued as infectious virions in PER.C6TM adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd5gagnef was digested with restriction enzyme *PacI* (New England Biolabs) and then transfected into one T25 flask of PER.C6TM cells using the calcium phosphate co-precipitation technique. *PacI* digestion releases the viral genome from plasmid sequences, allowing viral replication to occur after

WO 2006/020480

PCT/US2005/027658

entry into PER.C6™ cells. Infected cells and media were harvested 7 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by restriction enzyme
 5 (*Hind*III) analysis. The expression of Gag and Nef was also verified by ELISA and Western blot. The rescued virus was referred to as MRKAd5gagnef (also referred to as MRK-Ad5-hCMVnefbGH-MCMV36gagSV40-S).

I. Construction of an Ad6 vector containing HIV gag and nef transgenes

MRKAd6gagnef is depicted in Figure 20, with a sequence of such character being
 10 illustrated in Figure 21 (SEQ ID NO: 17). The vector is a modification of a prototype Group C Adenovirus serotype 6; VR-6; PCT/US02/32512, published April 17, 2003. The E1 region of the wild type Ad6 (nt 451-3507) was deleted and replaced by nef and gag expression cassettes. The nef expression cassette consists of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human
 15 immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3) the bovine growth hormone polyadenylation signal sequence; Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334. The nef expression cassette is directly followed by the gag expression cassette which consists of: 1) the immediate early gene promoter from the mouse cytomegalovirus (Keil *et al.*, 1987 *J. Virol.* 61:1901-1908), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1)
 20 gene, and 3) the simian virus 40 polyadenylation signal sequence. The amino acid sequence of the Nef and Gag proteins closely resembles the Clade B consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The nef open reading frame was altered by mutating the myristylation site located at Gly-2 to an alanine (opt nef G2A). This mutation
 25 prevents attachment of Nef to cytoplasmic membranes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins.

Key steps involved in the construction of MRKAd6gagnef are depicted in Figure 22 and described in the text that follows.

30 1. Construction of adenoviral shuttle vector

The shuttle plasmid pMRKAd6-hCMV-nefG2A-BGHpA-mCMV36gagSV40-S was constructed by inserting the gag expression cassette into the *Asc*I site in pMRKAd6-hCMV-nefG2A-BGHpA. The gag expression cassette was obtained by PCR using S-MRKAd5-mCMV36gagSV40 as
 35 template. The PCR primers were designed to introduce *Asc*I sites at each end of the transgene. The *Asc*I digested PCR fragment was ligated with pMRKAd6-hCMV-nefG2A-BGHpA, also digested with *Asc*I, generating pMRKAd6-hCMV-nefG2A-BGHpA-mCMV36gagSV40-S. The genetic structure of

WO 2006/020480

PCT/US2005/027658

pMRKAd6-hCMV-nefG2A-BGHpA-mCMV36gagSV40-S was verified by restriction enzyme analyses and sequencing.

2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pMRKAd6gagnef, the transgene containing fragment was
 5 liberated from shuttle plasmid pMRKAd6-hCMV-nefG2A-BGHpA-mCMV36gagSV40-S by digestion
 with restriction enzymes *PacI* and *PmeI* and gel purified. The purified transgene fragment was then co-
 transformed into *E. coli* strain BJ5183 with linearized (*ClaI*-digested) adenoviral backbone plasmid,
 pMRKAd6E1-. Plasmid DNA isolated from BJ5183 transformants was then transformed into competent
E. coli XL-1 Blue for screening by restriction analysis. The desired plasmid pMRKAd6gagnef (also
 10 referred to as pMRKAd6-hCMV-nefG2A-BGH-mCMV36gagSV40-S) was verified by restriction
 enzyme digestion and DNA sequence analysis.

3. Generation of recombinant MRKAd6gagnef

To prepare virus the pre-adenovirus plasmid pMRKAd6gagnef was rescued as infectious
 virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of
 15 pMRKAd6gagnef was partially digested with restriction enzyme *PacI* (New England Biolabs) and then
 transfected into one T25 flask of PER.C6™ cells using the calcium phosphate co-precipitation technique.
 pMRKAd6gagnef contains three *PacI* restriction sites. One at each ITR and one located in early region
 3. Digestion conditions were used which favored the linearization of pMRKAd6gagnef (digestion at
 only one of the three *PacI* sites) since the release of only one ITR is required to allow the initiation of
 20 viral DNA replication after entry into PER.C6® cells. Infected cells and media were harvested 7 days
 post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was
 amplified by 2 passages in PER.C6™ cells. At passage 2 virus was purified on CsCl density gradients.
 To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by
 restriction enzyme (*HindIII*) analysis. The expression of Gag and Nef was also verified by ELISA. The
 25 rescued virus was referred to as MRKAd6gagnef (also referred to as Ad6-hCMVnefG2AbGH-
 MCMV36gagSV40-S).

J. Construction of an Ad5 Vector containing an HIV-1 gagpol fusion transgene

MRKAd5gagpol is depicted in Figure 23, with a sequence of such character being
 illustrated in Figure 24 (SEQ ID NO: 18). The vector is a modification of a prototype Group C Ad5
 30 whose genetic sequence has been reported previously; Chroboczek *et al.*, 1992 *J. Virol.* 186:280-285.
 The E1 region of the wild-type Ad5 (nt 451-3510) is deleted and replaced with the transgene. The
 transgene contains the gagpol expression cassette consisting of: 1) the immediate early gene promoter
 from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding
 sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene fused to the
 35 coding sequence of the human immunodeficiency virus type 1 (HIV-1) pol (strain IIB) gene, and 3) the
 bovine growth hormone polyadenylation signal sequence (Goodwin & Rottman, 1992 *J. Biol. Chem.*
 267:16330-16334). The amino acid sequence of the GagPol protein closely resembles the Clade B

WO 2006/020480

PCT/US2005/027658

consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins. The pol open reading frame encodes the reverse transcriptase, RNase H, and integrase proteins, each of which was completely inactivated by substitution of alanine residues for each amino acid residue that was part of the enzymatic active sites (reverse transcriptase Asp-112, Asp-187 and Asp-188; RNase H Asp-445, Glu-480, and Asp-500; integrase Asp-626, Asp-678, and Glu-714) for a total of nine site mutations; Larder *et al.*, 1987 *Nature* 327:716-717; Larder *et al.*, 1989 *Proc. Natl. Acad. Sci.* 86:4803-4807; Davies *et al.*, 1991 *Science* 252:88-95; Schatz *et al.*, 1989 *FEBS Lett.* 257:311-314; Mizrahi *et al.*, 1990 *Nucl. Acids Res.* 18:5359-5363; Leavitt *et al.*, 1993 *J. Biol. Chem.* 268:2113-2119; Wiskercehn & Muesing, 1995 *J. Virol.* 69:376-386. In addition to the deletion of the E1 region, the vector has an E3 deletion (nt 28138 to 30818) in order to accommodate the transgene.

Key steps involved in the construction of MRKAd5gagpol are depicted in Figures 25 and 26 and described in the text that follows.

1. Construction of Adenoviral Shuttle Vector

The shuttle plasmid pMRKAd5gagpol was constructed by inserting a synthetic full-length codon-optimized HIV-1 *gagpol fusion* gene into MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.). The synthetic full-length codon-optimized HIV-1 *gagpol* gene was obtained by overlap PCR as depicted in Figure 26. The final PCR product was gel purified and ligated into the *Bgl*III restriction endonuclease site in MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.), generating plasmid pMRKAd5gagpol. The genetic structure of pMRKAd5gagpol was verified by restriction enzyme and DNA sequence analyses.

2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pMRKAd5DE1HCMVgagpolBGHpADE3, the transgene containing fragment was liberated from shuttle plasmid pMRKAd5gagpol by digestion with restriction enzymes *Pac*I and *Bst*Z17I and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*Cl*aI-digested) adenoviral backbone plasmid, pAd5HVO (also referred to as pAd5 E1-E3-). Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* XL-1 Blue for screening by restriction analysis. The desired plasmid pMRKAd5DE1HCMVgagpolBGHpADE3 (also referred to as pAd5HVOMRKgagpol) was verified by restriction enzyme digestion and DNA sequence analysis.

3. Generation of recombinant MRKAd5gagpol

To prepare virus the pre-adenovirus plasmid pMRKAd5DE1HCMVgagpolBGHpADE3 was rescued as infectious virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd5DE1HCMVgagpolBGHpADE3 was digested with restriction enzyme *Pac*I (New England Biolabs) and then transfected into one T25 flask of PER.C6® cells using the calcium phosphate co-precipitation technique. *Pac*I digestion releases the viral genome from plasmid sequences,

allowing viral replication to occur after entry into PER.C6™ cells. Infected cells and media were harvested 10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by restriction enzyme (*HindIII*) analysis. The expression of the GagPol fusion was also verified by Western blot. The rescued virus was referred to as MRKAd5gagpol.

The strategy followed to fuse the gag and pol open reading frames is outlined in Figure 26. Three PCR reactions were carried out. In the first reaction the gag open reading frame was amplified using PCR primers GP-1 and GP-2 (GP-

1=5'AGTGAGATCTACCATGGGTGCTAGG (SEQ ID NO: 14), GP-2=5'GCACAGTCTCAATGGGGGAGATGGGCTGGGAGGAGGGGTCGTTGCCAAAC (SEQ ID NO: 15)). PCR primer GP-1 was designed to contain a *Bgl*III site (underlined) for cloning. PCR primer GP-2 was designed to define the desired junction region between gag and pol, one half of the primer consists of 3' end of gag (bold) and the other the 5' end of pol (italics). In the second PCR reaction the pol open reading frame was amplified using PCR primers GP-3 and GP-4 (GP-3=5'GTTTGGCAACGACCCCTCCTCCCAGCCCATCTCCCCATTGAGACTGTGC (SEQ ID NO: 23), GP-4=5' CAGCAGATCTGCCCGGGCTTTAGTC (SEQ ID NO: 24)). PCR primer GP-3 was designed to be complementary to primer GP-2 thus defining the desired junction region between gag and pol. Primer GP-4 was designed to contain a *Bgl* II site (underlined) for cloning. In PCR reaction three the products of PCR reactions one and two were mixed with PCR primers GP-1 and GP-4. The homologous sequences in PCR product 1 and product 2 allow them to prime the amplification of the full gagpol fusion product.

K. Construction of an Ad5 vector containing HIV gagpol and nef transgenes

MRKAd5nef-gagpol is depicted in Figure 27, with a sequence of such character being illustrated in Figure 28 (SEQ ID NO: 19). The vector is a modification of a prototype Group C Ad5 whose genetic sequence has been reported previously; Chroboczek *et al.*, 1992 *J. Virol.* 186:280-285. The E1 region of the wild-type Ad5 (nt 451-3510) is deleted and replaced with the transgene. The tri-antigen transgene contains the nef expression cassette consisting of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3) the bovine growth hormone polyadenylation signal sequence (Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334). The nef cassette is directly followed by the gagpol expression cassette consisting of: 1) the immediate early gene promoter from the mouse cytomegalovirus (Keil *et al.*, 1987 *J. Virol.* 61:1901-1908), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) pol (strain IIB) gene, and 3) the simian virus 40 polyadenylation signal sequence. The amino acid sequence of the Nef, Gag and Pol proteins closely resembles the Clade B consensus amino acid sequence (G.

WO 2006/020480

PCT/US2005/027658

Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The nef open reading frame was altered by mutating the myristylation site located at Gly-2 to an alanine. This mutation prevents attachment of Nef to the cytoplasmic membrane and retrotrafficking into endosomes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins. The pol open reading frame encodes the reverse transcriptase, RNase H, and integrase proteins, each of which was completely inactivated by substitution of alanine residues for each amino acid residue that was part of the enzymatic active sites (reverse transcriptase Asp-112, Asp-187 and Asp-188; RNase H Asp-445, Glu-480, and Asp-500; integrase Asp-626, Asp-678, and Glu-714) for a total of nine site mutations; Larder *et al.*, 1987 *Nature* 327:716-717; Larder *et al.*, 1989 *Proc. Natl. Acad. Sci.* 86:4803-4807; Davies *et al.*, 1991 *Science* 252:88-95; Schatz *et al.*, 1989 *FEBS Lett.* 257:311-314; Mizrahi *et al.*, 1990 *Nucl. Acids Res.* 18:5359-5363; Leavitt *et al.*, 1993 *J. Biol. Chem.* 268:2113-2119; Wiskercehn & Muesing, 1995 *J. Virol.* 69:376-386. In addition to the deletion of the E1 region, the vector has an E3 deletion (nt 28138 to 30818) in order to accommodate the transgene.

Key steps involved in the construction of MRKAd5nef-gagpol are depicted in Figure 29 and described in the text that follows.

1. Construction of Ad shuttle vector

Shuttle plasmid pMRKAd5HCMVnefMCMVgagpol was constructed in two steps. First the gagpol fusion open reading frame was obtained from pMRKAd5gagpol (described in Example 2J) by *Bgl*III digestion and inserted into the *Bgl*III site in S-MRKAd5-mCMV36-SV40, generating MRKAd5MCMVgagpolSV40. MRKAd5MCMVgagpolSV40 was then digested with *Mfe*I and *Xho*I to generate a gagpol transgene containing fragment that was cloned into the *Mfe*I and *Xho*I sites in MRKAd5-hCMVnefG2ABGH-mCMV36gagSv40-S, generating pMRKAd5HCMVnefMCMVgagpol. The genetic structure of pMRKAd5HCMVnefMCMVgagpol was verified by restriction enzyme analysis and sequencing.

2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus

pAd5MRKDE1HCMVnefG2ABGHMCMV36gagpolSV40DE3, the transgene containing fragment was liberated from shuttle plasmid pMRKAd5HCMVnefMCMVgagpol by digestion with restriction enzymes *Pac*I and *Bst*Z17I and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I-digested) adenoviral backbone plasmid pAd5HVO, (also referred to as pAd5E1-E3-). Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* XL-1 Blue for screening by restriction analysis. The desired plasmid pAd5MRKDE1HCMVnefG2ABGHMCMV36gagpolSV40DE3 was verified by restriction enzyme digestion and DNA sequence analysis.

3. Generation of recombinant MRKAd5nef-gagpol

To prepare virus the pre-adenovirus plasmid

pAd5MRKDE1HCMVnefG2ABGHMCMV36gagpolSV40DE3 was rescued as infectious virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of
 5 pAd5MRKDE1HCMVnefG2ABGHMCMV36gagpolSV40DE3 was digested with restriction enzyme *PacI* (New England Biolabs) and then transfected into one T25 flask of PER.C6™ cells using the calcium phosphate co-precipitation technique. *PacI* digestion releases the viral genome from plasmid sequences, allowing viral replication to occur after entry into PER.C6™ cells. Infected cells and media were harvested 10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The
 10 virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by restriction enzyme (*HindIII*) analysis. The expression of Nef and the GagPol fusion proteins were also verified by Western blot. The rescued virus was referred to as MRKAd5nef-gagpol.

15 L. Construction of an Ad5 vector containing an HIV gagpolnef fusion transgene

MRKAd5gagpolnef is depicted in Figure 30, with a sequence of such character being illustrated in Figure 31 (SEQ ID NO: 20). The vector is a modification of a prototype Group C Ad5 whose genetic sequence has been reported previously; Chroboczek *et al.*, 1992 *J. Virol.* 186:280-285. The E1 region of the wild-type Ad5 (nt 451-3510) is deleted and replaced with the transgene. The
 20 transgene contains the gagpolnef expression cassette consisting of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) pol (strain IIB) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3)
 25 the bovine growth hormone polyadenylation signal sequence (Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334). The amino acid sequence of the Gag, Pol and Nef proteins closely resembles the Clade B consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The gag open reading frame encodes the matrix, capsid, and nucleocapsid
 30 proteins. The pol open reading frame encodes the reverse transcriptase, RNase H, and integrase proteins, each of which was completely inactivated by substitution of alanine residues for each amino acid residue that was part of the enzymatic active sites (reverse transcriptase Asp-112, Asp-187 and Asp-188; RNase H Asp-445, Glu-480, and Asp-500; integrase Asp-626, Asp-678, and Glu-714) for a total of nine site mutations; Larder *et al.*, 1987 *Nature* 327:716-717; Larder *et al.*, 1989 *Proc. Natl. Acad. Sci.* 86:4803-4807; Davies *et al.*, 1991 *Science* 252:88-95; Schatz *et al.*, 1989 *FEBS Lett.* 257:311-314;
 35 Mizrahi *et al.*, 1990 *Nucl. Acids Res.* 18:5359-5363; Leavitt *et al.*, 1993 *J. Biol. Chem.* 268:2113-2119; Wiskercehn & Muesing, 1995 *J. Virol.* 69:376-386. The nef open reading frame was altered by mutating

WO 2006/020480

PCT/US2005/027658

the myristylation site located at Gly-2 to an alanine. This mutation prevents attachment of Nef to the cytoplasmic membrane and retrotrafficking into endosomes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. In addition to the deletion of the E1 region, the vector has an E3 deletion (nt 28138 to 30818) in order to accommodate the transgene.

Key steps involved in the construction of MRKAd5gagpolnef are depicted in Figures 32 to 34 and described in the text that follows.

1. Construction of Adenoviral Shuttle Vector

The shuttle plasmid pMRKAd5gagpolnef was constructed in three steps (Figure 32).

First shuttle plasmid pMRKAd5gagpol (described in Example 2J) was digested with *Bam*HI to remove part of the gagpol transgene, generating pMRKAd5gagpolBamHIIcollapse. The BamHI fragment containing the partial gagpol transgene was gel purified and used in step three. In the next step the *polnef* fusion gene, obtained by overlap PCR as depicted in Figure 33, was ligated into the *Bam*HI and *Bgl*II sites in pMRKAd5gagpolBamHIIcollapse, generating pMRKAd5gagpolBamHIIcollapsenef. In the final step the *Bam*HI fragment containing the partial gagpol transgene obtained in step one was inserted into the *Bam*HI site in pMRKAd5gagpolBamHIIcollapsenef, generating pMRKAd5gagpolnef. The genetic structure of pMRKAd5gagpolnef was verified by restriction enzyme and DNA sequence analyses.

2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pMRKAd5DE1HCMVgagpolnefBGHPADE3 (Figure 34), the transgene containing fragment was liberated from shuttle plasmid pMRKAd5gagpolnef by digestion with restriction enzymes *Pac*I and *Bst*Z17I and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I-digested) adenoviral backbone plasmid, pAd5HVO (also referred to as pAd5E1-E3-). Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* XL-1 Blue for screening by restriction analysis. The desired plasmid pMRKAd5DE1HCMVgagpolBGHPADE3 (also referred to as pAd5HVOMRKgagpol) was verified by restriction enzyme digestion and DNA sequence analysis.

3. Generation of recombinant MRKAd5gagpol

To prepare virus the pre-adenovirus plasmid pMRKAd5DE1HCMVgagpolnefBGHPADE3 was rescued as infectious virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd5DE1HCMVgagpolnefBGHPADE3 was digested with restriction enzyme *Pac*I (New England Biolabs) and then transfected into one T25 flask of PER.C6™ cells using the calcium phosphate co-precipitation technique. *Pac*I digestion releases the viral genome from plasmid sequences, allowing viral replication to occur after entry into PER.C6™ cells. Infected cells and media were harvested 10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by

WO 2006/020480

PCT/US2005/027658

restriction enzyme (*Hind*III) analysis. The expression of the GagPolNef fusion was also verified by Western blot. The rescued virus was referred to as MRKAd5gagpolnef.

The strategy followed to fuse the pol and nef open reading frames is outlined in Figure 33. Three PCR reactions were carried out. In the first reaction a portion of the pol open reading frame was amplified using PCR primers PN-1 and PN-2 (PN-1=5' CACCTGGATCCCTGAGTGGGAGTTTG (SEQ ID NO: 25), PN-2=5' CGGACCTCTTGGACCACTTGCCGGCGTCCTCATCCTGCCTGGAGGCCACA (SEQ ID NO: 26)). PCR primer PN-1 was chosen to overlap an existing *Bam*HI site (underlined) in the pol sequence that was used for cloning. PCR primer PN-2 was designed to define the desired junction region between pol and nef, one half of the primer consists of 3' end of pol (bold) and the other the 5' end of nef (italics). In the second PCR reaction the nef open reading frame was amplified using PCR primers PN-3 and PN-4 (PN-3=5' TGTGGCCTCCAGGCAGGATGAGGACGCCGGCAAGTGGTCCAAGAGGTCCG (SEQ ID NO: 27), PN-4=5' CAGCAGATCTGCCCGGGCTTTAGCAG (SEQ ID NO: 28)). PCR primer PN-3 was designed to be complementary to primer PN-2 thus defining the desired junction region between pol and nef. Primer PN-4 was designed to contain a *Bgl*II site for cloning. In PCR reaction three the products of PCR reactions one and two were mixed with PCR primers PN-1 and PN-4. The homologous sequences in PCR product 1 and product 2 allow them to prime the amplification of the full gagpol fusion product.

20 M. Construction of an Ad6 vector containing HIV gagpol and nef transgenes

MRKAd6nef-gagpol is depicted in Figure 35, with a sequence of such character being illustrated in Figure 36 (SEQ ID NO: 21). The vector is a modification of a prototype Group C Adenovirus serotype 6; VR-6; PCT/US02/32512, published April 17, 2003. The E1 region of the wild type Ad6 (nt 451-3507) was deleted and replaced by the transgene. The transgene contains the nef expression cassette consisting of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3) the bovine growth hormone polyadenylation signal sequence; Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334. The nef cassette is directly followed by the gagpol expression cassette consisting of: 1) the immediate early gene promoter from the mouse cytomegalovirus (Keil *et al.*, 1987 *J. Virol.* 61:1901-1908), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) pol (strain IIB) gene, and 3) the simian virus 40 polyadenylation signal sequence. The amino acid sequence of the Nef, Gag and Pol proteins closely resembles the Clade B consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The nef open reading frame was altered by mutating the myristylation site located at Gly-2 to an alanine. This mutation prevents attachment of Nef

WO 2006/020480

PCT/US2005/027658

to the cytoplasmic membrane and retrotrafficking into endosomes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins. The pol open reading frame encodes the reverse transcriptase, RNase H, and integrase proteins, each of which was completely inactivated by substitution of alanine residues for each amino acid residue that was part of the enzymatic active sites (reverse transcriptase Asp-112, Asp-187 and Asp-188; RNase H Asp-445, Glu-480, and Asp-500; integrase Asp-626, Asp-678, and Glu-714) for a total of nine site mutations; Larder *et al.*, 1987 *Nature* 327:716-717; Larder *et al.*, 1989 *Proc. Natl. Acad. Sci.* 86:4803-4807; Davies *et al.*, 1991 *Science* 252:88-95; Schatz *et al.*, 1989 *FEBS Lett.* 257:311-314; Mizrahi *et al.*, 1990 *Nucl. Acids Res.* 18:5359-5363; Leavitt *et al.*, 1993 *J. Biol. Chem.* 268:2113-2119; Wiskercehn & Muesing, 1995 *J. Virol.* 69:376-386. In addition to the deletion of the E1 region, the vector has an E3 deletion (nt 28138 to 30818) in order to accommodate the transgene.

Key steps involved in the construction of MRKAd6nef-gagpol are depicted in Figure 37 and described in the text that follows.

15 1. Construction of Ad shuttle vector

Shuttle plasmid pNEBAd6-2HCMVnefMCMVgagpol was constructed by inserting the nef-gagpol transgene from pMRKHCMVnefMCMVgagpol (described in Example 2K) into the *AscI* and *NotI* sites in pNEBAd6-2. To obtain the nef-gagpol transgene fragment, pMRKHCMVnefMCMVgagpol was digested to completion with *NotI* and *PvuI* and then partially digested with *AscI*. *PvuI* was used to digest and thus reduce in size the unwanted plasmid fragment so that the desired *NotI/AscI* transgene fragment could be more easily gel purified. Once purified the *NotI/AscI* transgene fragment was ligated with pNEBAd6-2 also digested with *NotI* and *AscI*, generating pNEBAd6-2HCMVnefMCMVgagpol. The genetic structure of pNEBAd6-2HCMVnefMCMVgagpol was verified by restriction enzyme analysis and sequencing.

25 2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pAd6MRKDE1HCMVnefBGHMCMVgagpolSV40DE3, the transgene containing fragment was liberated from shuttle plasmid pNEBAd6-2HCMVnefMCMVgagpol by digestion with restriction enzymes *PacI* and *PmeI* and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*ClaI*-digested) adenoviral backbone plasmid, pAd6MRKDE1DE3. Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* XL-1 Blue for screening by restriction analysis. The desired plasmid pAd6MRKDE1HCMVnefBGHMCMVgagpolSV40DE3 was verified by restriction enzyme digestion and DNA sequence analysis.

35 3. Generation of recombinant MRKAd6nef-gagpol

To prepare virus the pre-adenovirus plasmid pAd6MRKDE1HCMVnefBGHMCMVgagpolSV40DE3 was rescued as infectious virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of

WO 2006/020480

PCT/US2005/027658

pAd6MRKDE1HCMVnefBGHMCMVgagpolSV40DE3 was digested with restriction enzyme *PacI* (New England Biolabs) and then transfected into one T25 flask of PER.C6™ cells using the calcium phosphate co-precipitation technique. *PacI* digestion releases the viral genome from plasmid sequences, allowing viral replication to occur after entry into PER.C6™ cells. Infected cells and media were harvested 10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by restriction enzyme (*HindIII*) analysis. The expression of Nef and the GagPol fusion proteins were also verified by Western blot. The rescued virus was referred to as MRKAd6nef-gagpol.

10 N. Construction of an Ad6 vector containing an HIV gagpolnef fusion transgene

MRKAd6gagpolnef is depicted in Figure 38, with a sequence of such character being illustrated in Figure 39 (SEQ ID NO: 22). The vector is a modification of a prototype Group C Adenovirus serotype 6; VR-6; PCT/US02/32512, published April 17, 2003. The E1 region of the wild type Ad6 (nt 451-3507) was deleted and replaced by the transgene. The transgene contains the gagpolnef expression cassette consisting of: 1) the immediate early gene promoter from the human cytomegalovirus (Chapman *et al.*, 1991 *Nucl. Acids Res.* 19:3979-3986), 2) the coding sequence of the human immunodeficiency virus type 1 (HIV-1) gag (strain CAM-1) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) pol (strain IIB) gene fused to the coding sequence of the human immunodeficiency virus type 1 (HIV-1) nef (strain JR-FL) gene, and 3) the bovine growth hormone polyadenylation signal sequence; Goodwin & Rottman, 1992 *J. Biol. Chem.* 267:16330-16334. The amino acid sequence of the Gag, Pol and Nef proteins closely resembles the Clade B consensus amino acid sequence (G. Myers *et al.*, eds., Human Retroviruses and AIDS, 1995: II-A-1 to II-A-22) and the codon usage was optimized for expression in human cells; R. Lathe, 1985 *J. Molec. Biol.* 183:1-12. The gag open reading frame encodes the matrix, capsid, and nucleocapsid proteins. The pol open reading frame encodes the reverse transcriptase, RNase H, and integrase proteins, each of which was completely inactivated by substitution of alanine residues for each amino acid residue that was part of the enzymatic active sites (reverse transcriptase Asp-112, Asp-187 and Asp-188; RNase H Asp-445, Glu-480, and Asp-500; integrase Asp-626, Asp-678, and Glu-714) for a total of nine site mutations; Larder *et al.*, 1987 *Nature* 327:716-717; Larder *et al.*, 1989 *Proc. Natl. Acad. Sci.* 86:4803-4807; Davies *et al.*, 1991 *Science* 252:88-95; Schatz *et al.*, 1989 *FEBS Lett.* 257:311-314; Mizrahi *et al.*, 1990 *Nucl. Acids Res.* 18:5359-5363; Leavitt *et al.*, 1993 *J. Biol. Chem.* 268:2113-2119; Wiskercehn & Muesing, 1995 *J. Virol.* 69:376-386. The nef open reading frame was altered by mutating the myristylation site located at Gly-2 to an alanine. This mutation prevents attachment of Nef to the cytoplasmic membrane and retrotrafficking into endosomes, thereby functionally inactivating Nef; Pandori *et al.*, 1996 *J. Virol.* 70:4283-4290; Bresnahan *et al.*, 1998 *Curr. Biol.* 8:1235-1238. In addition to the deletion of the E1 region, the vector has an E3 deletion (nt 28138 to 30818) in order to accommodate the transgene.

Key steps involved in the construction of MRKAd6gagpolnef are depicted in Figure 40 and described in the text that follows.

1. Construction of Ad shuttle vector

Shuttle plasmid pNEBAd6-2gagpolnef was constructed by inserting the gagpolnef transgene from pMRKAd5gagpolnef (described in Example 2K) into the *AscI* and *NotI* sites in pNEBAd6-2. To obtain the gagpolnef transgene fragment, pMRKAd5gagpolnef was digested with *NotI* and *AscI* and transgene fragment gel purified. The *NotI/AscI* transgene fragment was then ligated with pNEBAd6-2 also digested with *NotI* and *AscI*, generating pNEBAd6-2HCMVgagpolnef. The genetic structure of pNEBAd6-2gagpolnef was verified by restriction enzyme analysis and sequencing.

2. Construction of pre-adenovirus plasmid

To construct pre-adenovirus pAd6MRKDE1HCMVgagpolnefBGHPADE3, the transgene containing fragment was liberated from shuttle plasmid pNEBAd6-2gagpolnef by digestion with restriction enzymes *PacI* and *PmeI* and gel purified. The purified transgene fragment was then co-transformed into *E. coli* strain BJ5183 with linearized (*Clai*-digested) adenoviral backbone plasmid, pAd6MRKDE1DE3. Plasmid DNA isolated from BJ5183 transformants was then transformed into competent *E. coli* XL-1 Blue for screening by restriction analysis. The desired plasmid pAd6MRKDE1HCMVgagpolnefBGHPADE3 was verified by restriction enzyme digestion.

3. Generation of recombinant MRKAd6gagpolnef

To prepare virus the pre-adenovirus plasmid pAd6MRKDE1HCMVgagpolnefBGHPADE3 was rescued as infectious virions in PER.C6™ adherent monolayer cell culture. To rescue infectious virus, 10 µg of pAd6MRKDE1HCMVgagpolnefBGHPADE3 was digested with restriction enzyme *PacI* (New England Biolabs) and then transfected into one T25 flask of PER.C6™ cells using the calcium phosphate co-precipitation technique. *PacI* digestion releases the viral genome from plasmid sequences, allowing viral replication to occur after entry into PER.C6™ cells. Infected cells and media were harvested 10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by 2 passages in PER.C6™ cells. At passage 2, virus was purified on CsCl density gradients. To verify that the rescued virus had the correct genetic structure, viral DNA was isolated and analyzed by restriction enzyme (*HindIII*) analysis. The expression of the GagPolNef fusion protein was also verified by Western blot. The rescued virus was referred to as MRKAd6gagpolnef.

EXAMPLE 3

IMMUNIZATION WITH MRKAD5 AND MRKAD6 HIV NEF

A. Immunization

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 ml of buffered solution. The macaques were anesthetized (ketamine-xylazine), and the vaccines were delivered intramuscularly ("i.m.") in 0.5-mL aliquots into both deltoid

WO 2006/020480

PCT/US2005/027658

muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Plasma and peripheral blood mononuclear cells (PBMC) sampled were following standard protocols.

B. ELISPOT and ICS Assays

Ninety-six-well flat-bottomed plates (Millipore, Immobilon-P membrane) were coated with 1 µg/well of anti-gamma interferon (IFN-γ) mAb MD-1 (U-Cytech-BV) overnight at 4°C. The plates were then washed three times with PBS and blocked with R10 medium (RPMI, 0.05 mM 2-mercaptoethanol, 1 mM sodium pyruvate, 2mM L-glutamate, 10 mM HEPES, 10% fetal bovine serum) for 2 h at 37°C. The medium was discarded from the plates, and freshly isolated peripheral blood mononuclear cells (PBMC) were added at 1-4 x 10⁵ cells/well. The cells were stimulated in the absence (mock) or presence of a nef peptide pool (4 µg/mL per peptide). The pool, consisting of 15 amino acid ("aa") (15-aa) peptides shifting by 4 aa (Synpep, CA), was constructed from the HIV-1 JRFL nef sequence. Cells were then incubated for 20-24 h at 37°C in 5% CO₂. Plates were washed six times with PBST (PBS, 0.05% Tween 20) and 100 µL/well of 1:400 dilution of anti-IFN-γ polyclonal biotinylated detector antibody solution (U-Cytech-BV) was added. The plates were incubated overnight at 37°C. The plates were washed six times with PBST. Color was developed by incubating in NBT/BCP (Pierce) for 10 mins. Spots, which represent IFN-γ secreting cells, were counted under a dissecting microscope and normalized to 1 x 10⁶ PBMC.

C. Results

Nine macaques, prior to this protocol, had received multiple doses of a non-Nef-encoding Ad5 vector. The Ad5-specific neutralizing titers in these animals ranged from 2800 to >4600. The animals were distributed equally to three cohorts of three macaques. One cohort received 10¹⁰ vp MRKAd6 HIV nef at weeks 0, 4, and 30; the second cohort received 10¹⁰ vp MRKAd5 HIV nef at weeks 0, 4, and 30; and the third cohort received a mixture of 5 x 10⁹vp MRKAd5 HIV nef and 5 x 10⁹vp MRKAd6 HIV nef at weeks 0, 4 and 30. As controls, three cohorts of three naïve macaques received each of the three vaccines listed above. Figure 41 lists, in tabular format, the mock-corrected levels of Nef-specific T cells as measured by the IFN-γ ELISpot assay.

When comparing the immune responses in animals that received the MRKAd5 HIV nef vector in the presence or absence of pre-existing Ad5 immunity, it is apparent that the responses were attenuated in the pre-exposed animals after the first Ad5 immunization. Pre-existing Ad5 immunity did not have any apparent detrimental effect on the induced Nef-specific immunity if either MRKAd6 HIV nef or the Ad5/Ad6 cocktail is used. This suggests that a vector-specific immunity to one Ad serotype can be circumvented by using another serotype. This study, therefore, supports the utility of cocktails of different Ad serotype vectors to improve the breadth of patient coverage and/or the magnitude of the induced immunity.

WO 2006/020480

PCT/US2005/027658

EXAMPLE 4**IMMUNIZATION WITH MRKAD5 AND MRKAD6 HIV-1 GAG****A. Immunization**

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 mL of buffer. The macaques were anesthetized (ketamine/xylazine) and the vaccines were delivered i.m. in 0.5-mL aliquots into both deltoid muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were prepared from blood samples collected at several time points during the immunization regimen. All animal care and treatment were in accordance with standards approved by the Institutional Animal Care and Use Committee according to the principles set forth in the Guide for Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council.

B. ELISPOT Assay

The IFN- γ ELISPOT assays for rhesus macaques were conducted following a previously described protocol (Allen *et al.*, 2001 *J. Virol.* 75(2):738-749), with some modifications. For antigen-specific stimulation, a peptide pool was prepared from 15-aa peptides that encompass the entire HIV-1 gag sequence with 11-aa overlaps (Synpep Corp., Dublin, CA). To each well, 50 μ L of $2-4 \times 10^5$ peripheral blood mononuclear cells (PBMCs) were added; the cells were counted using Beckman Coulter Z2 particle analyzer with a lower size cut-off set at 80 fL. Either 50 μ L of media or the gag peptide pool at 8 μ g/mL concentration per peptide was added to the PBMC. The samples were incubated at 37°C, 5% CO₂ for 20-24 hrs. Spots were developed accordingly and the plates were processed using custom-built imager and automatic counting subroutine based on the ImagePro platform (Silver Spring, MD); the counts were normalized to 10^6 cell input.

C. Results

Two cohorts of 4 rhesus macaques with pre-existing Ad5-specific neutralization were immunized with either (1) 10^{10} vp MRKAd5 gag or (2) a mixture of 10^{10} vp MRKAd5 gag and 10^{10} vp MRKAd6 gag. A control cohort consisting of animals with no pre-existing Ad5 neutralizing activity was given 10^{10} vp MRKAd5 gag. Vaccine-induced T cell responses against HIV-1 Gag were quantified using IFN-gamma ELISPOT assay against a pool of 15-aa peptides that encompassed the entire protein sequence. The results are illustrated in Figure 42. They are expressed as the number of spot-forming cells (SFC) per million peripheral blood mononuclear cells (PBMCs) that responded to the peptide pool and to the mock or no peptide control.

The Gag-specific responses induced by MRKAd5 gag vaccine were attenuated (10-fold at wk 4 and 5-fold at wk 8) in the animals with significant Ad5-specific neutralizing titers prior to immunization relative to the control cohort. Immunization of animals having similar levels of pre-existing Ad5 titer with a mixture of MRKAd5 and MRKAd6 vaccines resulted in improved Gag-specific T cell responses. This is presumably due to the supply of the MRKAd6 component which is not effected by the pre-existing anti-Ad5 titers.

EXAMPLE 5**IMMUNIZATION WITH MRKAD5 HIV-1 GAG, POL AND NEF CONSTRUCTS****A. Immunization**

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 mL of buffer. The macaques were anesthetized (ketamine/xylazine) and the vaccines were delivered i.m. in 0.5-mL aliquots into both deltoid muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were prepared from blood samples collected at several time points during the immunization regimen. All animal care and treatment were in accordance with standards approved by the Institutional Animal Care and Use Committee according to the principles set forth in the Guide for Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council.

B. ELISPOT Assay

The IFN- γ ELISPOT assays for rhesus macaques were conducted following a previously described protocol (Allen *et al.*, 2001 *J. Virol.* 75(2):738-749), with some modifications. For antigen-specific stimulation, peptide pools were prepared from 15-aa peptides that encompass the entire HIV-1 nef, gag, and pol sequences with 11-aa overlaps (Synpep Corp., Dublin, CA). To each well, 50 μ L of $2-4 \times 10^5$ peripheral blood mononuclear cells (PBMCs) were added; the cells were counted using Beckman Coulter Z2 particle analyzer with a lower size cut-off set at 80 fL. Either 50 μ L of media or the respective peptide pool at 8 μ g/mL concentration per peptide was added to the PBMC. The samples were incubated at 37°C, 5% CO₂ for 20-24 hrs. Spots were developed accordingly and the plates were processed using custom-built imager and automatic counting subroutine based on the ImagePro platform (Silver Spring, MD); the counts were normalized to 10^6 cell input.

C. Results

Cohorts of 3-4 animals were immunized at wk 0, 4 with either 10^{10} vp/vector or 10^8 vp/vector dose of one of the following vaccines: (1) MRKAd5 gag + MRKAd5 pol + MRKAd5 nef; (2) MRKAd5hCMVnefmCMVgag + MRKAd5 pol; (3) MRKAd5hCMVnef mCMVgagpol; and (4) MRKAd5hCMVgagpolnef. The HIV-specific T cell responses induced by these vaccines at the 10^{10} vp/vector dose are listed in Figure 43.

All four vectors were able to induce specific T cell response to all 3 antigens at 10^{10} vp/vector dose. While the responses induced by the two-virus or one-virus vaccines appeared to trend lower relative to the three-virus cocktail, the differences were not statistically significant. The immunogenicity of the vaccines at 10^8 vp/vector dose is described in Figure 44.

Even at a lower 10^8 vp/vector dose, all four vectors were able to elicit detectable specific T cell response to all three antigens.

WO 2006/020480

PCT/US2005/027658

EXAMPLE 6**IMMUNIZATION FOR MRKAD5 AND MRKAD6 HIV-1 GAG, POL AND NEF CONSTRUCTS****A. Immunization**

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 mL of buffer. The macaques were anesthetized (ketamine/xylazine) and the vaccines delivered i.m. in 0.5-mL aliquots into both deltoid muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were prepared from blood samples collected at several time points during the immunization regimen. All animal care and treatment were in accordance with standards approved by the Institutional Animal Care and Use Committee according to the principles set forth in the Guide for Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council.

B. ELISPOT Assay

The IFN- γ ELISPOT assays for rhesus macaques were conducted following a previously described protocol (Allen *et al.*, 2001 *J. Virol.* 75(2):738-749), with some modifications. For antigen-specific stimulation, peptide pools were prepared from 15-aa peptides that encompass the entire HIV-1 nef, gag and pol sequences with 11-aa overlaps (Synpep Corp., Dublin, CA). To each well, 50 μ L of $2-4 \times 10^5$ peripheral blood mononuclear cells (PBMCs) were added; the cells were counted using Beckman Coulter Z2 particle analyzer with a lower size cut-off set at 80 fL. Either 50 μ L of media or the respective peptide pool at 8 μ g/mL concentration per peptide was added to the PBMC. The samples were incubated at 37°C, 5% CO₂ for 20-24 hrs. Spots were developed accordingly and the plates were processed using custom-built imager and automatic counting subroutine based on the ImagePro platform (Silver Spring, MD); with the counts normalized to 10^6 cell input.

C. Protocol

Cohorts of 3 macaques were immunized at weeks 0 and 4 with either 10^{10} vp/vector or 10^8 vp/vector dose of one of the following vaccines: (1) MRKAd5nefgagpol; (2) MRKAd6nefgagpol; and (3) MRKAd5nefgagpol + MRKAd6nefgagpol. The HIV-specific T cell responses induced by these vaccines at the 10^{10} vp/vector dose are listed in Figure 45.

In all three vaccination groups, the vectors were able to induce specific T cell response to all 3 antigens at 10^{10} vp/vector dose. The immunogenicity of the Ad5 and Ad6 vectors is comparable when delivered alone or in combination. The immunogenicity of the vaccines at 10^8 vp/vector dose is described in Figure 46. Even at a lower 10^8 vp/vector dose, specific T cell response to all three antigens were detected.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

WO 2006/020480

PCT/US2005/027658

WHAT IS CLAIMED IS:

1. A method for delivery and expression of heterologous nucleic acid encoding a polypeptide(s) of interest, which comprises:
 - 5 contemporaneously administering purified replication-defective adenovirus particles of at least two different serotypes;
wherein said replication-defective adenovirus particles comprise heterologous nucleic acid encoding at least one common polypeptide.
- 10 2. A method in accordance with claim 1 wherein the purified replication-defective adenovirus particles comprise adenovirus serotype 5.
3. A method in accordance with claim 1 wherein the purified replication-defective adenovirus particles comprise adenovirus serotype 6.
- 15 4. A method in accordance with claim 1 wherein the purified replication-defective adenovirus particles comprise adenovirus serotypes 5 and 6.
5. A method in accordance with claim 1 wherein the heterologous nucleic acid
20 encodes an Human Immunodeficiency Virus ("HIV") antigen.
6. A method in accordance with claim 1 wherein the purified replication-defective adenovirus particles are administered simultaneously.
- 25 7. A method for eliciting a cellular-mediated immune response against HIV in an individual which comprises:
 - contemporaneously administering purified replication-defective adenovirus particles of at least two different serotypes;
wherein said replication-defective adenovirus particles comprise heterologous nucleic
30 acid encoding at least one common HIV antigen.
8. A method in accordance with claim 7 wherein the heterologous nucleic acid comprises sequence encoding HIV-1 Gag or an immunogenic modification or fragment thereof.
- 35 9. A method in accordance with claim 7 wherein the heterologous nucleic acid comprises sequence encoding HIV-1 Nef or an immunogenic modification or fragment thereof.

WO 2006/020480

PCT/US2005/027658

10. A method in accordance with claim 7 wherein the heterologous nucleic acid comprises sequence encoding HIV-1 Pol or an immunogenic modification or fragment thereof.

5 11. A method in accordance with claim 7 wherein the purified replication-defective adenovirus particles are administered simultaneously.

12. A composition comprising purified replication-defective adenovirus particles of at least two different serotypes, wherein said replication-defective adenovirus particles comprise heterologous nucleic acid encoding at least one common polypeptide.

10

13. A composition in accordance with claim 12 wherein the heterologous nucleic acid comprises a gene expression cassette comprising:

- (a) nucleic acid encoding a polypeptide;
- (b) a heterologous promoter operatively linked to the nucleic acid encoding the
- 15 polypeptide; and
- (c) a transcription termination sequence.

14. A composition in accordance with claim 12 wherein the polypeptide is an antigen.

20

15. A composition in accordance with claim 14 wherein the antigen is derived from HIV.

16. A composition in accordance with claim 12 which comprises a physiologically

25 acceptable carrier.

17. A composition in accordance with claim 12 wherein the replication-defective adenovirus particles comprise adenovirus serotype 5.

30 18. A composition in accordance with claim 12 wherein the replication-defective adenovirus particles comprise adenovirus serotype 6.

19. A composition in accordance with claim 12 wherein the replication-defective adenovirus particles comprise adenovirus serotypes 5 and 6.

35

WO 2006/020480

PCT/US2005/027658

20. An adenoviral vector comprising nucleic acid encoding HIV antigens Nef and Gag, wherein nucleic acid sequences encoding Nef and Gag are operatively linked to two distinct promoters.

5 21. An adenoviral vector in accordance with claim 20 wherein the two distinct promoters are immediate early promoters of human and murine cytomegalovirus promoters.

22. An adenoviral vector in accordance with claim 20 wherein the nucleic acid encoding Nef comprises open reading frame nucleic acid sequence of a sequence selected from the group
10 consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12.

23. An adenoviral vector in accordance with claim 20 wherein the nucleic acid encoding Gag comprises open reading frame nucleic acid sequence of SEQ ID NO: 2.

15 24. An adenoviral vector in accordance with claim 20 wherein the nucleic acid comprises:

(a) open reading frame nucleic acid sequence of a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12; and

(b) open reading frame nucleic acid sequence of SEQ ID NO: 2.

20

25. A method for eliciting a cellular-mediated immune response against HIV in an individual which comprises administering to said individual an adenoviral vector in accordance with claim 20.

25 26. An adenoviral vector of serotype 6 comprising a fusion of nucleic acid sequences encoding HIV Gag and Pol.

27. An adenoviral vector in accordance with claim 26 wherein the nucleic acid sequences encoding HIV Gag and Pol are open reading frame nucleic acid sequences of SEQ ID NO: 2
30 and SEQ ID NO: 5, respectively.

28. A method for eliciting a cellular-mediated immune response against HIV in an individual which comprises administering to said individual an adenoviral vector in accordance with claim 26.

35

WO 2006/020480

PCT/US2005/027658

29. An adenoviral vector comprising nucleic acid encoding HIV antigens Nef, Gag and Pol, wherein nucleic acid sequences encoding Nef, Gag and Pol are operatively linked to at least two distinct promoters.

5 30. An adenoviral vector in accordance with claim 29 comprising:
 (a) nucleic acid sequence encoding Nef operatively linked to a first promoter; and
 (b) a fusion of nucleic acid sequences encoding Gag and Pol operatively linked to a second promoter.

10 31. An adenoviral vector in accordance with claim 29 wherein the nucleic acid encoding Nef comprises open reading frame nucleic acid sequence of a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12.

15 32. An adenoviral vector in accordance with claim 29 wherein the nucleic acid encoding Gag comprises open reading frame nucleic acid sequence of SEQ ID NO: 2.

 33. An adenoviral vector in accordance with claim 29 wherein the nucleic acid encoding Pol comprises open reading frame nucleic acid sequence of SEQ ID NO: 5.

20 34. An adenoviral vector in accordance with claim 29 wherein the nucleic acid comprises:
 (a) open reading frame nucleic acid sequence of a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12; and
 (b) a fusion of open reading frame nucleic acid sequences of SEQ ID NO: 2 and SEQ ID
 25 NO: 5.

 35. A method for eliciting a cellular-mediated immune response against HIV in an individual which comprises administering to said individual an adenoviral vector in accordance with claim 29.

30 36. An adenoviral vector comprising a fusion of nucleic acid sequences encoding HIV Gag, Pol and Nef.

35 37. An adenoviral vector in accordance with claim 36 wherein the nucleic acid encoding Gag comprises open reading frame nucleic acid sequence of SEQ ID NO: 2.

WO 2006/020480

PCT/US2005/027658

38. An adenoviral vector in accordance with claim 36 wherein the nucleic acid encoding Pol comprises open reading frame nucleic acid sequence of SEQ ID NO: 5.

5 39. An adenoviral vector in accordance with claim 36 wherein the nucleic acid encoding Nef comprises open reading frame nucleic acid sequence of a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12.

40. An adenoviral vector in accordance with claim 36 wherein the nucleic acid sequences encoding HIV Gag, Pol and Nef comprise:
10 (a) open reading frame nucleic acid sequence of SEQ ID NO: 2;
(b) open reading frame nucleic acid sequence of SEQ ID NO: 5; and
(c) open reading frame nucleic acid sequence of a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 9 and SEQ ID NO: 12.

15 41. A method for eliciting a cellular-mediated immune response against HIV in an individual which comprises administering to said individual an adenoviral vector in accordance with claim 36.

1/126

Sequence of the open reading frame for FL-gag (human codon optimized)

atgggtgctagggcttctgtgctgtctggtggtgagctggacaagtgggagaagatcaggctgaggcctggtggc
aagaagaagtacaagctaaagcacattgtgtggccctccaggagctggagagggttgctgtgaaccctggcc
tgctggagacctctgaggggtgcaggcagatcctgggccagctccagccctccctgcaaacaggctctgagga
gctgaggtccctgtacaacacagtggctaccctgtactgtgtgcaccagaagattgatgtgaaggacaccaagg
aggccctggagaagattgaggaggagcagaacaagtccaagaagaaggcccagcaggctgctgctggcac
aggcaactccagccagggtgtccagaactacccattgtgcagaacctccagggccagatggtgcaccaggc
catctccccccggaccctgaatgcctgggtgaagggtggtggaggagaaggccttctccctgaggtgatcccca
tgttctctgccctgtctgaggggtgccacccccaggacctgaacaccatgctgaacacagtggggggccatcag
gctgccatgcagatgctgaaggagaccatcaatgaggaggctgctgagtgggacaggctgcatcctgtgcacg
ctggccccattgcccccgccagatgaggggagcccaggggctctgacattgctggcaccacctccacctcca
ggagcagattggctggatgaccaacaacccccccatccctgtgggggaaatctacaagaggtggatcatcctg
ggcctgaacaagattgtgaggatgtactccccacctccatcctggacatcaggcaggggccccaaggagccct
tcagggactatgtggacaggttctacaagacctgagggctgagcaggcctcccaggaggtgaagaactggat
gacagagacctgtgtgtgcagaatgccaaacctgactgcaagaccatcctgaaggccctgggcccctgctgcc
acctggaggagatgatgacagcctgccagggggtggggggccctggtcacaaggccagggtgctggctga
ggccatgtcccagggtgaccaactccgccaccatcatgatgcagaggggcaacttcaggaaccagaggaaga
cagtgaagtgttcaactgtggcaagggtgggccacattgccaagaactgtaggggccccaggaagaagggt
gctggaagtgtggcaaggaggggccaccagatgaaggactgcaatgagaggcaggccaacttccctgggcaa
aatctggccctcccacaagggcaggcctggcaacttctccagtccaggcctgagcccacagcccctcccag
gagtccttcagggttggggaggagaagaccacccccagccagaagcaggagcccattgacaaggagctgta
ccccctggcctccctgagggtccctgtttggcaacgacccctcctcccagtaaaataaagcccgggcagat
(SEQ ID NO: 2)

FIG. 1

2/126

AGATCTACCA TGGCCCCCAT CTCCCCCAT T GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG
GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGATGTGGG GGATGCCTAC
TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
AACAAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
CCTGACATTG TGATCTACCA GTACATGGAT GACCTGTATG TGGGCTCTGA CCTGGAGATT
GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCCTGAGA AGGACTCCTG GACTGTGAAT
GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGAAGTGGT GATCCCCCTG
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTTGTG
GGGGCTGAGA CCTTCTATGT GGATGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGAAGTACAC CACCAACCAG
AAGACTGAGC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
GTGACTGACT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC
ATCAGGAAGG TGCTGTTTCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
CACTCCAACT GGAGGGCTAT GGCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG
ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC
TGCTCCCCTG GCATCTGGCA GCTGGACTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG
GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT

FIG. 2A-1

WO 2006/020480

PCT/US2005/027658

3/126

GACAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGA GTCCATGAAC
AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
GTGCAGATGG CTGTGTTTAT CCACAACTTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC
GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
CAGATCACCA AGATCCAGAA CTTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
GACATCAAGG TGGTGCCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT
(SEQ ID NO:3)

FIG. 2A-2

4/126

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg
Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Asp
Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly
Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala
Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu
Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys

FIG. 3A-1

5/126

Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
Leu Asp Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly
Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
Lys Thr Ile His Thr Asp Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
Tyr Asn Pro Gln Ser Gln Gly Val Val Glu Ser Met Asn Lys Glu Leu
Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
Glu Asp (SEQ ID NO:4)

FIG. 3A-2

WO 2006/020480

PCT/US2005/027658

6/126

AGATCTACCATGGCCCCCATCTCCCCATTGAGACTGTGCCTGTGAAGCTGAAGCCTGGCATGGATGGCCCCAAGGTGAA
BgIII MetAlaProIleSerProIleGluThrValProValLysLeuLysProGlyMetAspGlyProLysVally
1 10 20

GCAGTGGCCCCCTGACTGAGGAGAAGATCAAGGCCCTGGTGGAAATCTGCACTGAGATGGAGAAGGAGGGCAAAATCTCCA
sGlnTrpProLeuThrGluGluLysIleLysAlaLeuValGluIleCysThrGluMetGluLysGluGlyLysIleSerL
30 40 50

AGATTGGCCCCGAGAACCCCTACAACACCCCTGTGTTTGCCATCAAGAAGAAGGACTCCACCAAGTGGAGGAAGCTGGTG
ysIleGlyProGluAsnProTyrAsnThrProValPheAlaIleLysLysLysAspSerThrLysTrpArgLysLeuVal
60 70

GACTTCAGGGAGCTGAACAAGAGGACCCAGGACTTCTGGGAGGTGCAGCTGGGCATCCCCACCCCGCTGGCCTGAAGAA
AspPheArgGluLeuAsnLysArgThrGlnAspPheTrpGluValGlnLeuGlyIleProHisProAlaGlyLeuLysLy
80 90 100

GAAGAAGTCTGTGACTGTGCTGGCTGTGGGGATGCCTACTTCTCTGTGCCCTGGATGAGGACTTCAGGAAGTACACTG
sLysLysSerValThrValLeuAlaValGlyAspAlaTyrPheSerValProLeuAspGluAspPheArgLysTyrThrA
110 120 130

CCTTCACCATCCCTCCATCAACAATGAGACCCCTGGCATCAGGTACCAGTACAATGTGCTGCCCCAGGGCTGGAAGGGC
laPheThrIleProSerIleAsnAsnGluThrProGlyIleArgTyrGlnTyrAsnValLeuProGlnGlyTrpLysGly
140 150

TCCCCTGCCATCTTCCAGTCCTCCATGACCAAGATCCTGGAGCCCTTCAGGAAGCAGAACCCTGACATTGTGATCTACCA
SerProAlaIlePheGlnSerSerMetThrLysIleLeuGluProPheArgLysGlnAsnProAspIleValIleTyrGl
160 170 180

GTACATGGCTGCCCTGTATGTGGGCTCTGACCTGGAGATTGGGCAGCACAGGACCAAGATTGAGGAGCTGAGGCAGCACC
nTyrMetAlaAlaLeuTyrValGlySerAspLeuGluIleGlyGlnHisArgThrLysIleGluGluLeuArgGlnHisL
190 200 210

TGCTGAGGTGGGGCCTGACCACCCCTGACAAGAAGCACCAGAAGGAGCCCCCTTCCTGTGGATGGGCTATGAGCTGCAC
euLeuArgTrpGlyLeuThrThrProAspLysLysHisGlnLysGluProProPheLeuTrpMetGlyTyrGluLeuHis
220 230

CCCGACAAGTGGACTGTGCAGCCCATTGTGCTGCCTGAGAAGGACTCCTGGACTGTGAATGACATCCAGAAGCTGGTGGG
ProAspLysTrpThrValGlnProIleValLeuProGluLysAspSerTrpThrValAsnAspIleGlnLysLeuValGl
240 250 260

CAAGCTGAACTGGGCCTCCCAAATCTACCCCTGGCATCAAGGTGAGGCAGCTGTGCAAGCTGCTGAGGGGCACCAAGGCCC
yLysLeuAsnTrpAlaSerGlnIleTyrProGlyIleLysValArgGlnLeuCysLysLeuLeuArgGlyThrLysAlaL
270 280 290

TGACTGAGGTGATCCCCCTGACTGAGGAGGCTGAGCTGGAGCTGGCTGAGAACAGGGAGATCCTGAAGGAGCCTGTGCAT
EuThrGluValIleProLeuThrGluGluAlaGluLeuGluLeuAlaGluAsnArgGluIleLeuLysGluProValHis
300 310

GGGGTGTACTATGACCCCTCCAAGGACCTGATTGCTGAGATCCAGAAGCAGGGCCAGGGCCAGTGGACCTACCAAATCTA
GlyValTyrTyrAspProSerLysAspLeuIleAlaGluIleGlnLysGlnGlyGlnGlyGlnTrpThrTyrGlnIleTy
320 330 340

CCAGGAGCCCTTCAAGAACCTGAAGACTGGCAAGTATGCCAGGATGAGGGGGGCCACACCAATGATGTGAAGCAGCTGA
rGlnGluProPheLysAsnLeuLysThrGlyLysTyrAlaArgMetArgGlyAlaHisThrAsnAspValLysGlnLeuT
350 360 370

CTGAGGCTGTGCAGAAGATCACCCTGAGTCCATTGTGATCTGGGGCAAGACCCCAAGTTCAAGCTGCCCATCCAGAAG
hrGluAlaValGlnLysIleThrThrGluSerIleValIleTrpGlyLysThrProLysPheLysLeuProIleGlnLys
380 390

FIG. 4A-1

WO 2006/020480

PCT/US2005/027658

7/126

GAGACCTGGGAGACCTGGTGGACTGAGTACTGGCAGGCCACCTGGATCCCTGAGTGGGAGTTTGTGAACACCCCCCCCCT
GluThrTrpGluThrTrpTrpThrGluTyrTrpGlnAlaThrTrpIleProGluTrpGluPheValAsnThrProProLe
400 410 420

GGTGAAGCTGTGGTACCAGCTGGAGAAGGAGCCCATTGTGGGGGCTGAGACCTTCTATGTGGCTGGGGCTGCCAACAGGG
uValLysLeuTrpTyrGlnLeuGluLysGluProIleValGlyAlaGluThrPheTyrValAlaGlyAlaAlaAsnArgG
430 440 450

AGACCAAGCTGGGCAAGGCTGGCTATGTGACCAACAGGGGCAGGCAGAAGGTGGTGACCCTGACTGACACCACCAACCAG
luThrLysLeuGlyLysAlaGlyTyrValThrAsnArgGlyArgGlnLysValValThrLeuThrAspThrThrAsnGln
460 470

AAGACTGCCCTCCAGGCCATCTACCTGGCCCTCCAGGACTCTGGCCTGGAGGTGAACATTGTGACTGCCTCCCAGTATGC
LysThrAlaLeuGlnAlaIleTyrLeuAlaLeuGlnAspSerGlyLeuGluValAsnIleValThrAlaSerGlnTyrAl
480 490 500

CCTGGGCATCATCCAGGCCCAGCCTGATCAGTCTGAGTCTGAGCTGGTGAACCAGATCATTGAGCAGCTGATCAAGAAGG
aLeuGlyIleIleGlnAlaGlnProAspGlnSerGluSerGluLeuValAsnGlnIleIleGluGlnLeuIleLysLysG
510 520 530

AGAAGGTGTACCTGGCCTGGGTGCCCTGCCACAAGGGCATTGGGGGCAATGAGCAGGTGGACAAGCTGGTGTCTGCTGGC
luLysValTyrLeuAlaTrpValProAlaHisLysGlyIleGlyGlyAsnGluGlnValAspLysLeuValSerAlaGly
540 550

ATCAGGAAGGTGCTGTTCCTGGATGGCATTGACAAGGCCCAGGATGAGCATGAGAAGTACCACTCCAACCTGGAGGGCTAT
IleArgLysValLeuPheLeuAspGlyIleAspLysAlaGlnAspGluHisGluLysTyrHisSerAsnTrpArgAlaMe
560 570 580

GGCCTCTGACTTCAACCTGCCCCCTGTGGTGGCTAAGGAGATTGTGGCCTCCTGTGACAAGTGCCAGCTGAAGGGGGAGG
tAlaSerAspPheAsnLeuProProValValAlaLysGluIleValAlaSerCysAspLysCysGlnLeuLysGlyGluA
590 600 610

CCATGCATGGGCAGGTGGACTGCTCCCCTGGCATCTGGCAGCTGGCCTGCACCCACCTGGAGGGCAAGGTGATCCTGGTG
laMetHisGlyGlnValAspCysSerProGlyIleTrpGlnLeuAlaCysThrHisLeuGluGlyLysValIleLeuVal
620 630

GCTGTGCATGTGGCCTCCGGCTACATTGAGGCTGAGGTGATCCCTGCTGAGACAGGCCAGGAGACTGCCTACTTCCTGCT
AlaValHisValAlaSerGlyTyrIleGluAlaGluValIleProAlaGluThrGlyGlnGluThrAlaTyrPheLeuLe
640 650 660

GAAGCTGGCTGGCAGGTGGCCTGTGAAGACCATCCACACTGCCAATGGCTCCAACCTTCACTGGGGCCACAGTGAGGGCTG
uLysLeuAlaGlyArgTrpProValLysThrIleHisThrAlaAsnGlySerAsnPheThrGlyAlaThrValArgAlaA
670 680 690

CCTGCTGGTGGGCTGGCATCAAGCAGGAGTTTGGCATCCCCCTACAACCCCCAGTCCCAGGGGGTGGTGGCCTCCATGAAC
laCysTrpTrpAlaGlyIleLysGlnGluPheGlyIleProTyrAsnProGlnSerGlnGlyValValAlaSerMetAsn
700 710

AAGGAGCTGAAGAAGATCATTGGGCAGGTGAGGGACCAGGCTGAGCACCTGAAGACAGCTGTGCAGATGGCTGTGTTCAT
LysGluLeuLysLysIleIleGlyGlnValArgAspGlnAlaGluHisLeuLysThrAlaValGlnMetAlaValPheIl
720 730 740

CCACAACCTCAAGAGGAAGGGGGGCATCGGGGGCTACTCCGCTGGGGAGAGGATTGTGGACATCATTGCCACAGACATCC
eHisAsnPheLysArgLysGlyGlyIleGlyGlyTyrSerAlaGlyGluArgIleValAspIleIleAlaThrAspIleG
750 760 770

AGACCAAGGAGCTCCAGAAGCAGATCACCAAGATCCAGAACTTCAGGGTGTACTACAGGGACTCCAGGAACCCCCTGTGG
lnThrLysGluLeuGlnLysGlnIleThrLysIleGlnAsnPheArgValTyrArgAspSerArgAsnProLeuTrp
780 790

FIG. 4A-2

WO 2006/020480

PCT/US2005/027658

8/126

AAGGGCCCTGCCAAGCTGCTGTGGAAGGGGGAGGGGGCTGTGGTGATCCAGGACAACTCTGACATCAAGGTGGTGCCCAG
LysGlyProAlaLysLeuLeuTrpLysGlyGluGlyAlaValValIleGlnAspAsnSerAspIleLysValValProAr
800 810 820

GAGGAAGGCCAAGATCATCAGGGACTATGGCAAGCAGATGGCTGGGGATGACTGTGTGGCCTCCAGGCAGGATGAGGACT
gArgLysAlaLysIleIleArgAspTyrGlyLysGlnMetAlaGlyAspAspCysValAlaSerArgGlnAspGluAsp
830 840 850

AAAGCCCGGGCAGATCT (SEQ ID NO: 5)
*Bgl*III (SEQ ID NO: 6)

FIG. 4A-3

WO 2006/020480

PCT/US2005/027658

9/126

GATCTGCCAC CATGGGCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
GCTTCCCCGT GAGGCCCCAG GTGCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
TGTCCCCTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
ACACCCCCGG CCCCAGCATC AGGTTCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC CTGCTGCACC
CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGACT
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
AAAGCCCGG C (SEQ ID NO: 7)

FIG. 5

WO 2006/020480

PCT/US2005/027658

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val

10/126

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val
Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Leu Leu His
Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO: 8)

FIG. 6

WO 2006/020480

PCT/US2005/027658

Run 1' Run 2' Run 3' Run 4'

11/126

WT	-	ATG	GGT	GGC	AAG	TGG	TCA	AAA	CGT	AGT	GTG	CCT	GGA	TGG	TCT	-42
OPT	-	ATG	GGC	GGC	AAG	TGG	TCC	AAG	AGG	TCC	GTG	CCC	GGC	TGG	TCC	
		M	G	G	K	W	S	K	R	S	V	P	G	W	S	-14
WT	-	ACT	GTA	AGG	GAA	AGA	ATG	AGA	CGA	GCT	GAG	CCA	GCA	GCA	GAT	-84
OPT	-	ACC	GTG	AGG	GAG	AGG	ATG	AGG	AGG	GCC	GAG	CCC	GCC	GCC	GAC	
		T	V	R	E	R	M	R	R	A	E	P	A	A	D	-28
WT	-	AGG	GTG	AGA	CGA	ACT	GAG	CCA	GCA	GCA	GTA	GGG	GTG	GGA	GCA	-126
OPT	-	AGG	GTG	AGG	AGG	ACC	GAG	CCC	GCC	GCC	GTG	GGC	GTG	GGC	GCC	
		R	V	R	R	T	E	P	A	A	V	G	V	G	A	-42
WT	-	GTA	TCT	CGA	GAC	CTG	GAA	AAA	CAT	GGA	GCA	ATC	ACA	AGT	AGC	-168
OPT	-	GTG	TCC	AGG	GAC	CTG	GAG	AAG	CAC	GGC	GCC	ATC	ACC	TCC	TCC	
		V	S	R	D	L	E	K	H	G	A	I	T	S	S	-56
WT	-	AAT	ACA	GCA	GCT	ACC	AAT	GCT	GAT	TGT	GCC	TGG	CTA	GAA	GCA	-210
OPT	-	AAC	ACC	GCC	GCC	ACC	AAC	GCC	GAC	TGC	GCC	TGG	CTG	GAG	GCC	
		N	T	A	A	T	N	A	D	C	A	W	L	E	A	-70
WT	-	CAA	GAG	GAT	GAG	GAA	GTG	GGT	TTT	CCA	GTC	AGA	CCT	CAG	GTA	-252
OPT	-	CAG	GAG	GAC	GAG	GAG	GTG	GGC	TTC	CCC	GTG	AGG	CCC	CAG	GTG	
		Q	E	D	E	E	V	G	F	P	V	R	P	Q	V	-84
WT	-	CCT	TTA	AGA	CCA	ATG	ACT	TAC	AAG	GGA	GCT	GTA	GAT	CTT	AGC	-294
OPT	-	CCC	CTG	AGG	CCC	ATG	ACC	TAC	AAG	GGC	GCC	GTG	GAC	CTG	TCC	
		P	L	R	P	M	T	Y	K	G	A	V	D	L	S	-98
WT	-	CAC	TTT	TTA	AAA	GAA	AAG	GGG	GGA	CTG	GAA	GGG	CTA	ATT	CAC	-336
OPT	-	CAC	TTC	CTG	AAG	GAG	AAG	GGC	GGC	CTG	GAG	GGC	CTG	ATC	CAC	
		H	F	L	K	E	K	G	G	L	E	G	L	I	H	-112
WT	-	TCA	CAG	AAA	AGA	CAA	GAT	ATC	CTT	GAT	CTG	TGG	GTC	TAC	CAC	-378
OPT	-	TCC	CAG	AAG	AGG	CAG	GAC	ATC	CTG	GAC	CTG	TGG	GTG	TAC	CAC	
		S	Q	K	R	Q	D	I	L	D	L	W	V	Y	H	-126
WT	-	ACA	CAA	GGC	TAC	TTC	CCT	GAT	TGG	CAG	AAC	TAC	ACA	CCA	GGG	-420
OPT	-	ACC	CAG	GGC	TAC	TTC	CCC	GAC	TGG	CAG	AAC	TAC	ACC	CCC	GGC	
		T	Q	G	Y	F	P	D	W	Q	N	Y	T	P	G	-140
WT	-	CCA	GGA	ATC	AGA	TTT	CCA	TTG	ACC	TTT	GGA	TGG	TGC	TTC	AAG	-462
OPT	-	CCC	GGC	ATC	AGG	TTC	CCC	CTG	ACC	TTC	GGC	TGG	TGC	TTC	AAG	
		P	G	I	R	F	P	L	T	F	G	W	C	F	K	-154

FIG. 7A-1

WO 2006/020480

PCT/US2005/027658

Seq. ID No. 11

12/126

WT	-	CTA	GTA	CCA	GTT	GAG	CCA	GAA	AAG	GTA	GAA	GAG	GCC	AAT	GAA	-504
OPT	-	CTG	GTG	CCC	GTG	GAG	CCC	GAG	AAG	GTG	GAG	GAG	GCC	AAC	GAG	-168
		L	V	P	V	E	P	E	K	V	E	E	A	N	E	
WT	-	GGA	GAG	AAC	AAC	TGC	TTG	TTA	CAC	CCT	ATG	AGC	CAG	CAT	GGG	-546
OPT	-	GGC	GAG	AAC	AAC	TGC	CTG	CTG	CAC	CCC	ATG	TCC	CAG	CAC	GGC	-182
		G	E	N	N	C	L	L	H	P	M	S	Q	H	G	
WT	-	ATA	GAG	GAC	CCG	GAG	AAG	GAA	GTG	TTA	GAG	TGG	AGG	TTT	GAC	-588
OPT	-	ATC	GAG	GAC	CCC	GAG	AAG	GAG	GTG	CTG	GAG	TGG	AGG	TTC	GAC	-196
		I	E	D	P	E	K	E	V	L	E	W	R	F	D	
WT	-	AGC	AAG	CTA	GCA	TTT	CAT	CAC	GTG	GCC	CGA	GAG	CTG	CAT	CCG	-630
OPT	-	TCC	AAG	CTG	GCC	TTC	CAC	CAC	GTG	GCC	AGG	GAG	CTG	CAC	CCC	-210
		S	K	L	A	F	H	H	V	A	R	E	L	H	P	
WT	-	GAG	TAC	TAC	AAG	GAC	TGC	TGA	(SEQ ID NO: 11)							-651
OPT	-	GAG	TAC	TAC	AAG	GAC	TGC	TAA	(contained within SEQ ID NO: 7)							-216
		E	Y	Y	K	D	C		(SEQ ID NO: 8)							

FIG. 7A-2

WO 2006/020480

PCT/US2005/027658

Seq. ID No. 9

13/126

GATCTGCCAC CATGGCCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
GCTTCCCCGT GAGGCCCCAG GTGCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
TGTCCCCTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
ACACCCCCGG CCCCGGCATC AGGTTCCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC GCCGCCACC
CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGCGACT
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
AAAGCCCGGG C (SEQ ID NO: 9)

FIG. 8

14/126

Met Ala Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val
Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Ala Ala His
Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO: 10)

FIG. 9

WO 2006/020480

PCT/US2005/027658

15/126

```
1 gatctgccac catggccggc aagtgggtcca agagggtccgt gcccgggtgg tccaccgtga
61 gggagaggat gaggagggcc gagcccgccg ccgacagggt gaggaggacc gagcccgccg
121 cagtgggcgt gggcgccgtg tccagggacc tggagaagca cggcgccatc acctcctcca
181 acaccgccgc caccaacgcc gactgcgcct ggctggagge ccaggaggac gaggaggtgg
241 gcttccccgt gaggccccag gtgcccctga ggcccatgac ctacaagggc gccgtggacc
301 tgtcccactt cctgaaggag aagggcgggc tggagggcct gatccactcc cagaagaggc
361 aggacatcct ggacctgtgg gtgtaccaca cccagggtta cttccccgac tggcagaact
421 acacccccgg ccccggcata aggttcccc tgaccttcgg ctggtgcttc aagctggtgc
481 ccgtggagcc cgagaagggt gaggaggcca acgagggcga gaacaactgc ctgctgcacc
541 ccatgtccca gcacggcata gaggaccccg agaaggaggt gctggagtgg aggttcgact
601 ccaagctggc cttccaccac gtggccaggg agctgcaccc cgagtactac aaggactgct
661 aaagcccggg c (SEQ ID NO: 12)
```

FIG. 10

WO 2006/020480

PCT/US2005/027658

16/126

1 MAGKWSKRSV PGWSTVRERM RRAEPAADRV RTEPAAVGV GAVSRDLEKH GAITSSNTAA
61 TNADCAWLEA QEDEEVGFPV RPQVPLRPMT YKGAVDLSHF LKEKGGLEGL IHSQKRQDIL
121 DLWVYHTQGY FPDWQNYTPG PGIRFPLTFG WCFKLVPVEP EKVEEANEGE NNCLLHPMSQ
181 HGIEDPEKEV LEWRFD SKLA FHHVARELHP EYYKDC (SEQ ID NO: 13)

FIG. 11

17/126

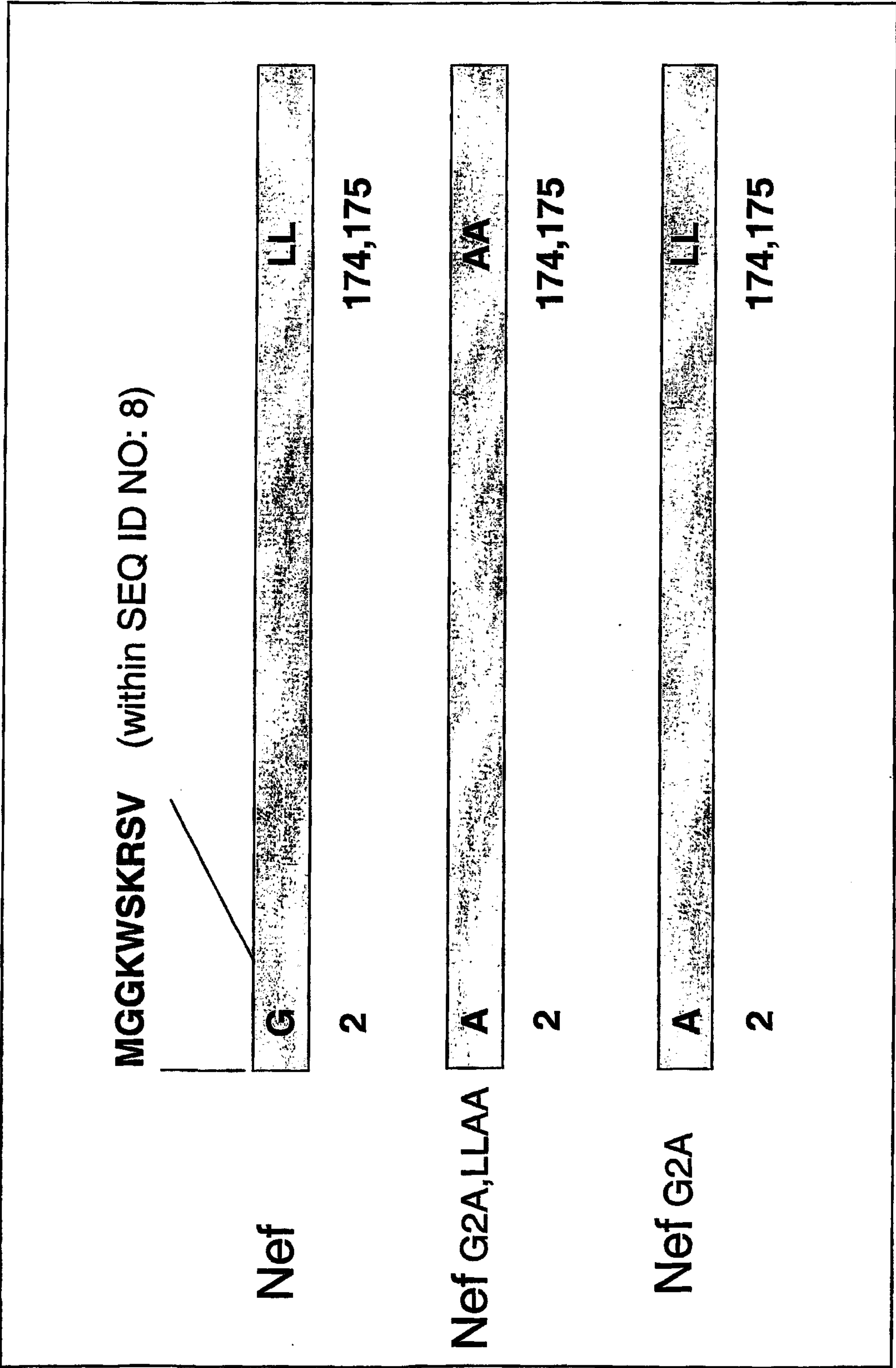


FIG. 12

18/126

Seroprevalence of Adenovirus subtypes 5 and 6
 Brazilian & Thai Subjects were selected for high risk behavior for HIV infection

	Titers ≥ 18 (%)	Titers ≥ 200 (%)	Titers ≥ 1000 (%)
Ad5	53	N. America (n = 100) 30	11
Ad6	40	21	4
Ad5 and Ad6	23	7	0
Ad5	90	Brazil (n = 58) 55	9
Ad6	50	17	2
Ad5 and Ad6	47	12	0
Ad5	98	Thailand (n = 65) 88	37
Ad6	80	51	14
Ad5 and Ad6	80	49	6
Ad5	88	Malawi (n = 49) 59	14
Ad6	72	31	6
Ad5 and Ad6	63	12	2
Ad5	80	South Africa (n = 50) 60	12
Ad6	70	14	0
Ad5 and Ad6	58	14	0
Ad5	89	Cameroon (n = 72) 50	10
Ad6	72	27	6
Ad5 and Ad6	63	10	0

FIG. 13

WO 2006/020480

PCT/US2005/027658

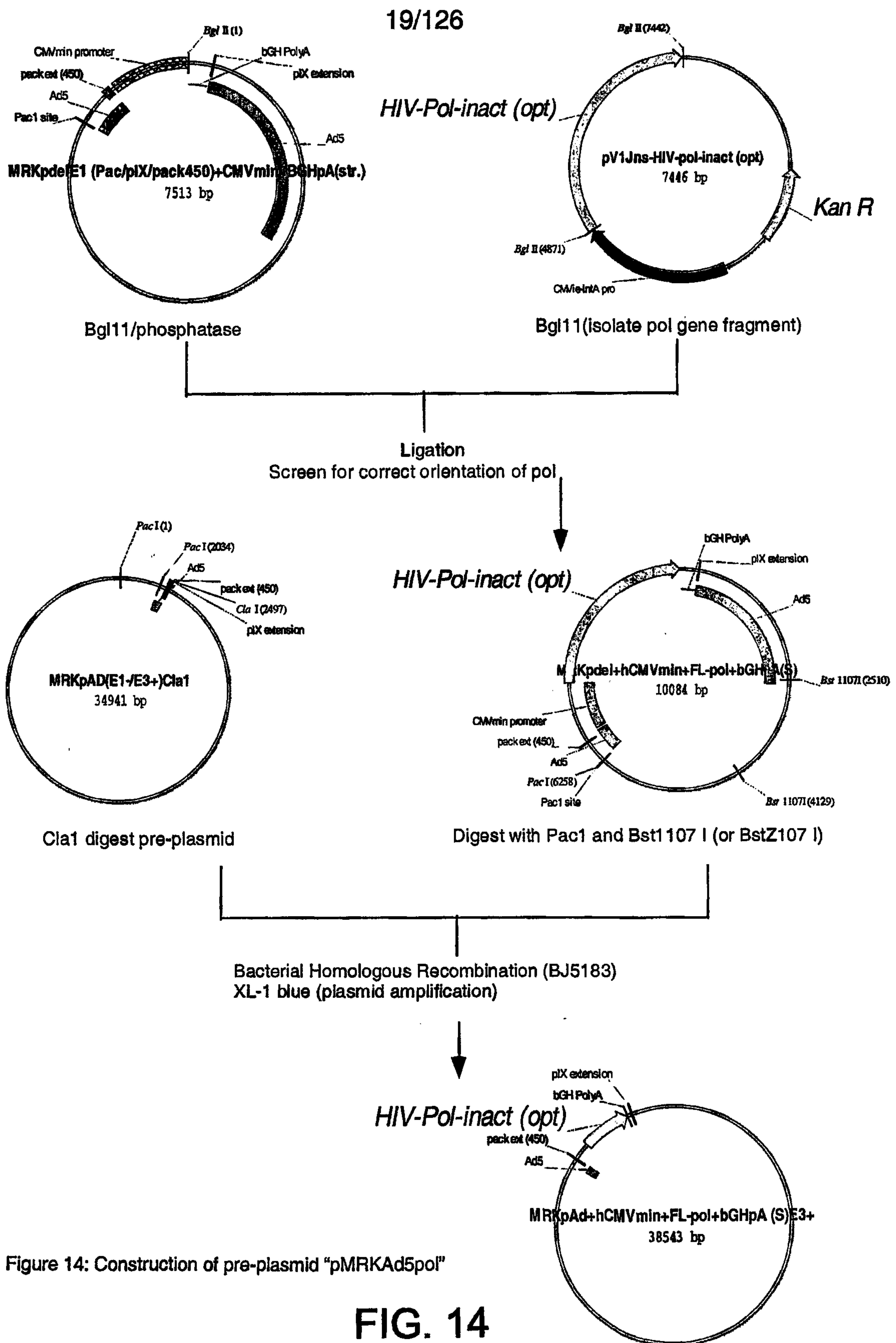


Figure 14: Construction of pre-plasmid "pMRKAd5pol"

FIG. 14

WO 2006/020480

PCT/US2005/027658

20/126

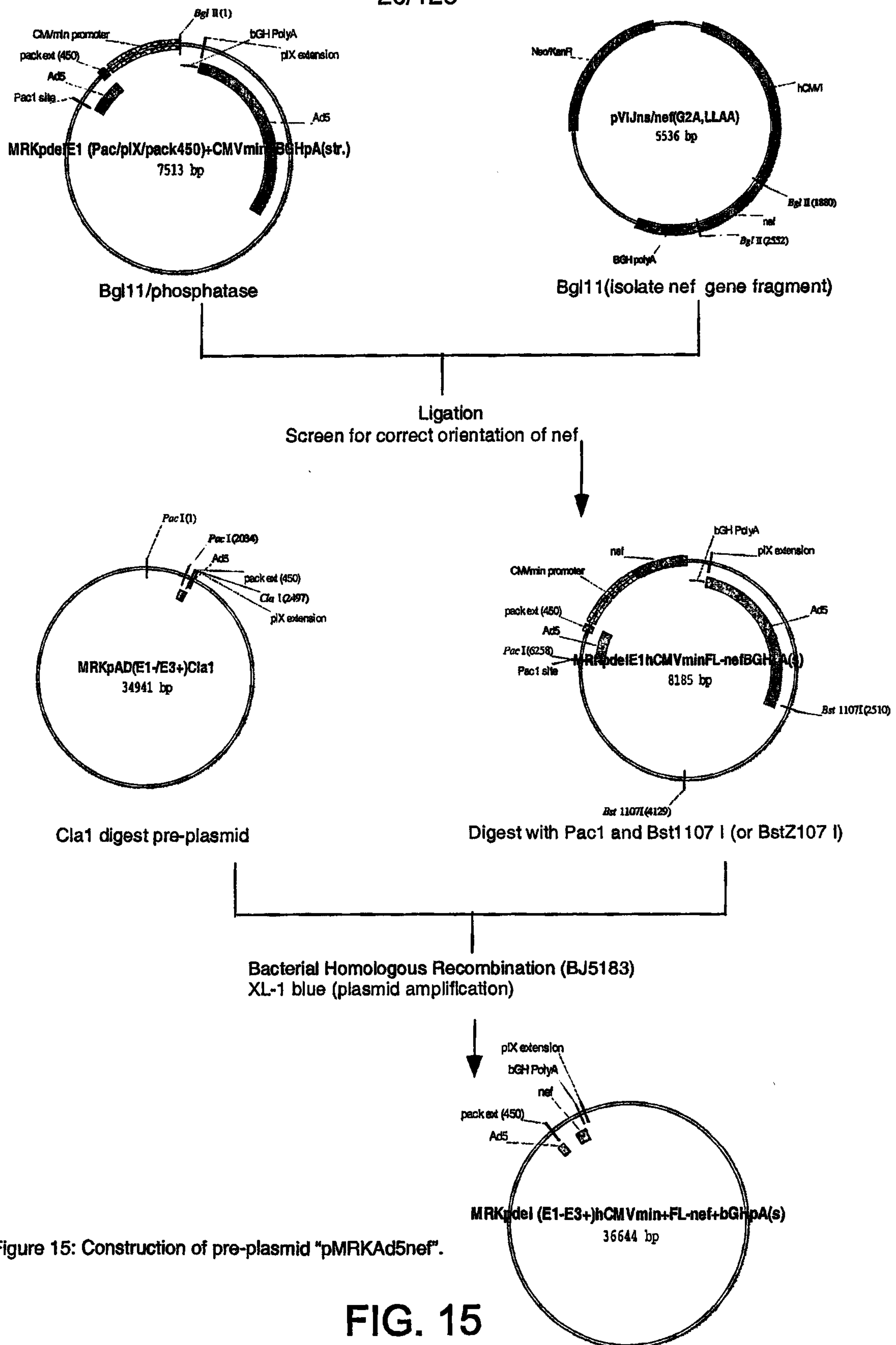


Figure 15: Construction of pre-plasmid "pMRKAd5nef".

FIG. 15

21/126

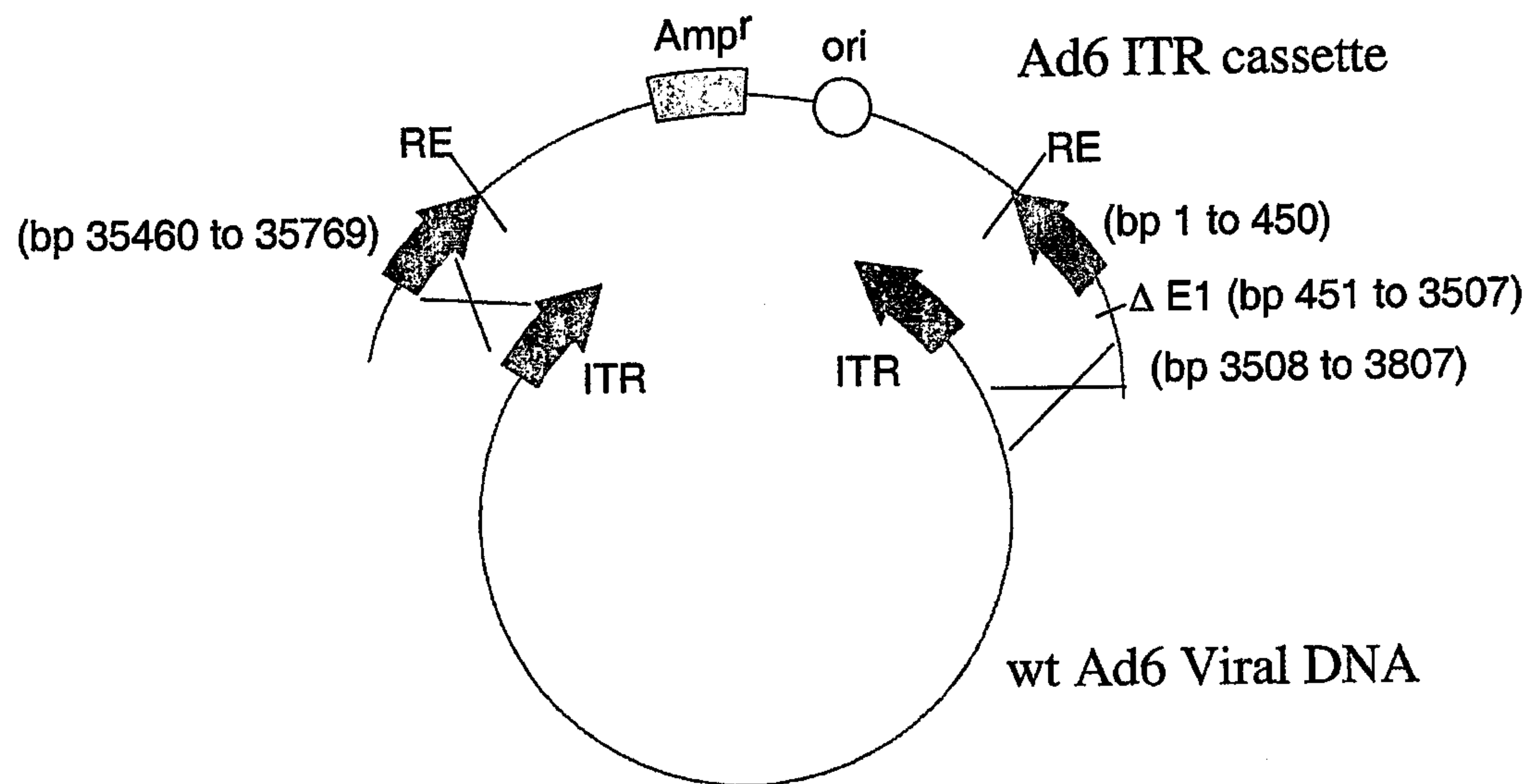


FIG. 16

WO 2006/020480

PCT/US2005/027658

22/126

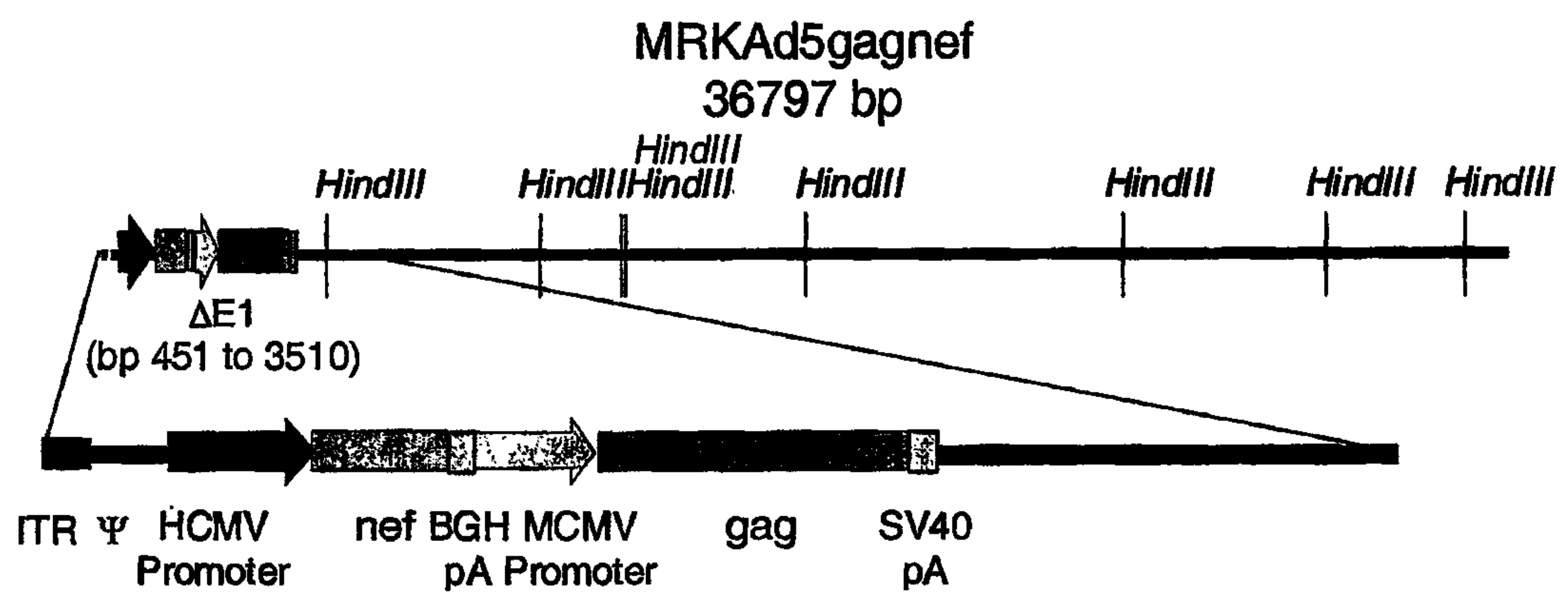


FIG. 17

23/126

MRKAd5gagnef

KEY:	___ HCMV promoter	___ Nef	___ BGH pA	 MCMV promoter	 Gag	 SV40 pA
------	-------------------	---------	------------	---------------------	-----------	---------------

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgcaa gtgtggcggg acacatgtaa gcgacggatg tggcaaaagt gacgtttttg
181 gtgtgcgcgc gtgtacacag gaagtgcaca ttttcgcgcg gttttaggcg gatgtttag
241 taaatttggg cgtaaccgag taagatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataatttt gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcgtttt attattatag gcggccgcga tccattgcat acgttgatc
481 catatcataa tatgtacatt tatattggct catgtccaac attaccgcca tgttgacatt
541 gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata
601 tggagttccg cgttacataa cttacggtaa atggcccgcg tggctgaccg cccaacgacc
661 cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc
721 attgacgtca atgggtggag tatttacggt aaactgccc cttggcagta catcaagtgt
781 atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt
841 atgccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca
901 tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg
961 actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc
1021 aaaatcaacg ggactttcca aaatgtcgta acaactccgc ccattgacg caaatgggcg
1081 gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgtcagatcg
1141 cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac cgatccagcc
1201 tccgcggcgc ggaacggtgc attggaacgc ggattcccc tgccaagagt gagatctgcc
1261 accatggccg gcaagtgtgc caagaggtcc gtgcccgcgt ggtccaccgt gaggagagag
1321 atgaggaggg ccgagccgcg cgcgcacagg gtgaggagga ccgagccgcg cgcagtgggc
1381 gtgggcgcgc tgtccaggga cctggagaag cacggcgcca tcacctctc caacaccgc
1441 gccaccaacg ccgactgcgc ctggttgagg gccagggagg acgaggaggt gggcttcccc
1501 gtgaggcccc aggtgcccct gaggcccatg acctacaagg gcgccgtgga cctgtccac
1561 ttctgaagg agaagggcg cctggagggc ctgatccact ccagaagag gcaggacatc
1621 ctggacctgt ggtgtacca caccagggc tacttcccc actggcagaa ctacaccccc
1681 ggcgccgcca tcaggttccc cctgaccttc ggtgtgtgt tcaagctggt gcccgtggag
1741 cccgagaagg tggaggaggc caacgagggc gagaacaact gcctgtgca cccatgtcc
1801 cagcacgga tggaggacc cagaaggag gtgctggagt gagggttcca ctccaagctg
1861 gccttccacc acgtggccag gtagctgcac cccgagtact acaaggactg ctaaagcccc
1921 ggcagatctg ctgtgccttc tagttgccag ccattctgtt tttgcccctc cccgtgctt
1981 tccttgacce tgaagggtgc cactccact gtcctttcct aataaaatga ggaattgca
2041 tcgcattgtc tgaataggtg tcattctatt ctggggggtg ggtggggca ggcagcaag
2101 gggaggatt ggaagacaa tagcagcat cctggggatg cgtgggctc tatggccgat
2161 cggcgcgcca tatactgagt cattagggac ttccaatgg gttttgcca gtacataagg
2221 tcaatagggg tgaatcaaca ggaagtccc attggagcca agtacactga gtcaataggg
2281 actttccatt ggtttttgcc cagtacaaa ggtcaatagg ggtgagtca atgggtttt
2341 cccattattg gcacgtacat aaggtcaata ggggtgagtc attgggtttt tccagccaat
2401 ttataaaacg ccattgtact tcccaccatt gacgtcaatg ggtattgaa actaatgcaa
2461 cgtgaccttt aaacggtact ttcccatagc tgattaatgg gaaagtaccg ttctcgagcc
2521 aatacacgtc aatgggaagt gaaagggcag ccaaaacgta acaccgccc ggttttcccc
2581 tggaaattcc atattggcac gcattctatt gctgagctg ctttctacgt ggtataaga
2641 ggcgcgacca gcgtcggtac cgtcgagtc ttgggtctga ccaccgtaga acgcagatcg
2701 agatctacca tgggtgctag ggcttctgtg ctgtctggtg gtgagctgga caagtggag
2761 aagatcaggc tgaggcctgg tggcaagaag aagtacaagc taaagcacat tgtgtgggc
2821 tccagggagc tggagaggtt tctgtgaac cctggcctgc tggagacctc tgaagggtgc

```

FIG. 18A-1

24/126

2881 aggcagatcc tgggccagct ccagccctcc ctgcaaacag gctctgagga gctgaggtcc
2941 ctgtacaaca cagtggctac cctgtactgt gtgcaccaga agattgatgt gaaggacacc
3001 aaggaggccc tggagaagat tgaggaggag cagaacaagt ccaagaagaa gcccagcag
3061 gctgctgctg gcacaggcaa ctccagccag gtgtcccaga actaccccat tgtgcagaac
3121 ctccagggcc agatggtgca ccaggccatc tccccccgga ccctgaatgc ctgggtgaag
3181 gtggtggagg agaaggcctt ctcccctgag gtgatcccca tgttctctgc cctgtctgag
3241 ggtgccacc ccaggacct gaacaccatg ctgaacacag tggggggcca tcaggctgcc
3301 atgcagatgc tgaaggagac catcaatgag gaggctgctg agtgggacag gctgcatcct
3361 gtgcacgctg gcccattgc cccgggccag atgaggagc ccaggggctc tgacattgct
3421 ggcaccacct ccaccctcca ggagcagatt ggctggatga ccaacaaccc ccccatccct
3481 gtgggggaaa tctacaagag gtggatcatc ctgggcctga acaagattgt gaggatgtac
3541 tccccacctt ccctcctgga catcaggcag gcccacaagg agcccttcag ggactatgtg
3601 gacaggttct acaagaccct gagggctgag caggcctccc aggaggtgaa gaactggatg
3661 acagagacc tctgtgtgca gaatgccaac cctgactgca agaccatcct gaaggccctg
3721 ggcctgctg ccaccctgga ggagatgatg acagcctgcc agggggtggg gggccctggt
3781 cacaaggcca ggtgctggc tgaggccatg tcccagggtg ccaactccgc caccatcatg
3841 atgcagagg gcaacttcag gaaccagagg aagacagtga agtgcttcaa ctgtggcaag
3901 gtgggccaca ttgccaagaa ctgtagggcc ccaggaaga agggctgctg gaagtgtggc
3961 aaggagggcc accagatgaa ggactgcaat gagaggcagg ccaacttcct gggcaaatc
4021 tggccctccc acaagggcag gcctggcaac ttctccagt ccaggcctga gcccacagcc
4081 cctcccaggg agtccttcag gtttggggag gagaagacca ccccagcca gaagcaggag
4141 ccattgaca aggagctgta cccctggcc tccctgaggt ccctgtttgg caacgacccc
4201 tctcccagt aataaaagc ccgggcagat ctaacttgtt tattgcaagt tataatggtt
4261 acaataaag caatagcatc acaatttca caataaagc atttttttca ctgcattcta
4321 gttgtggttt gtccaaactc atcaatgtat cttatcatgt ctggatcggc ggcgcgtact
4381 gaaatgtgtg ggcgtggctt aagggtggga aagaatatat aagggtgggg tcttatgtag
4441 ttttgtatct gttttgcagc agccgccgcc gccatgagca ccaactcgtt tgatggaagc
4501 attgtgagct catatttgac aacgcgcagt ccccatggg ccggggtgcg tcagaatgtg
4561 atgggctcca gcattgatgg tcgccccgtc ctgcccgcaa actctactac cttgacctac
4621 gagaccgtgt ctggaacgcc gttggagact gcagcctccg ccgccgcttc agccgctgca
4681 gccaccgccc gcgggattgt gactgacttt gctttcctga gcccgcttgc aagcagtgca
4741 gcttcccggt catccgcccg cgatgacaag ttgacggctc ttttggcaca attggattct
4801 ttgaccgggg aacttaatgt cgtttctcag cagctgttgg atctgcgcca gcaggtttct
4861 gccctgaagg cttcctcccc tcccaatgcg gtttaaaaca taaataaaaa accagactct
4921 gtttggattt ggatcaagca agtgtcttgc tgtctttatt taggggtttt gcgcgcgcgg
4981 tagggccggg accagcggtc tcggctggtt agggctcgtt gtattttttc caggacgtgg
5041 taaaggtagc tctggatgtt cagatacatg ggcataagcc cgtctctggg gtggaggtag
5101 caccactgca gagcttcatg ctgcgggggtg gtgttgtaga tgatccagtc gtagcaggag
5161 cgctgggctt ggtgcctaaa aatgtctttc agtagcaagc tgattgccag gggcaggccc
5221 ttggtgtaag tgtttacaaa gcggttaagc tgggatgggt gcatacgtgg ggatatgaga
5281 tgcactttgg actgtatttt taggttggct atgttcccag ccatatccct ccggggattc
5341 atgttgtgca gaaccaccag cacagtgtat ccggtgcact tgggaaattt gtcattgtagc
5401 ttagaaggaa atgcgtggaa gaacttgag acgcccctgt gacctccaag attttccatg
5461 cattcgtcca taatgatggc aatgggcca cgggcggcgg cctgggcgaa gatatttctg
5521 ggatcactaa cgtcatagtt gtgttcagg atgagatcgt cataggccat ttttacaag
5581 cgcgggcgga ggggtgccaga ctgcgggtata atggttccat ccggcccagg ggcgtagtta
5641 ccctcacaga tttgcatttc ccacgctttg agttcagatg gggggatcat gtctacctgc
5701 ggggcgatga agaaaacggt ttccggggta ggggagatca gctgggaaga aagcaggttc
5761 ctgagcagct gcgacttacc gcagccggtg ggcccgtaaa tcacacctat taccggctgc
5821 aactggtagt taagagagct gcagctgccg tcatccctga gcaggggggc cacttcgtta
5881 agcatgtccc tgactcgcat gttttccctg accaaatccg ccagaaggcg ctgcgccccc
5941 agcgatagca gttcttgcaa ggaagcaaag tttttcaacg gtttgagacc gtccgcgcta
6001 ggcattgctt tgagcgtttg accaagcagt tccaggcggt cccacagctc ggtcacctgc
6061 tctacggcat ctgatccag catatctcct cgtttcgcgg gttggggcgg ctttcgctgt
6121 acggcagtag tcggtgctcg tccagacggg ccagggtcat gtctttccac ggggcaggg

FIG. 18A-2

25/126

6181 tcctcgtcag cgtagtctgg gtcacgggtga aggggtgctgc tccgggctgc gcgctggcca
6241 ggggtgcgctt gaggtcggtc ctgctgggtgc tgaagcgtcg ccggtcttcg ccctgcgcgt
6301 cggccaggta gcatttgacc atggtgtcat agtccagccc ctccgcggcg tggcccttgg
6361 cgcgcagctt gcccttggag gaggcgcgcg acgaggggca gtgcagactt ttgagggcgt
6421 agagcttggg cgcgagaaat accgattccg gggagtaggc atccgcgcgc caggccccgc
6481 agacggtctc gcattccacg agccagggtga gctctggccg ttcgggggtca aaaaccagggt
6541 ttcccccatg ctttttgatg cgtttcttac ctctggtttc catgagccgg tgtccacgct
6601 cgggtgacgaa aaggctgtcc gtgtccccgt atacagactt gagaggcctg tcctcgagcg
6661 gtgttccgcg gtcctcctcg tatagaaact cggaccactc tgagacaaag gctcgcgtcc
6721 aggccagcac gaaggaggct aagtgaggag ggtagcggtc gttgtccact aggggggtcca
6781 ctgcctccag ggtgtgaaga cacatgtcgc cctcttcggc atcaaggaaag gtgattgggt
6841 tgtaggtgta ggccacgtga ccgggtgttc ctgaaggggg gctataaaaag ggggtggggg
6901 cgcgttcgtc ctactctctt tccgcctcgc tgtctgcgag ggccagctgt tgggggtgagt
6961 actccctctg aaaagcgggc atgacttctg cgctaagatt gtcagtttcc aaaaacgagg
7021 aggatttgat attcacctgg ccgcgggtga tgcctttgag ggtggccgca tccatctggt
7081 cagaaaagac aatctttttg ttgtcaagct tgggtggcaaa cgaccctag agggcggttg
7141 acagcaactt ggcgatggag cgcagggttt ggtttttgtc gcgacggcg cgctccttgg
7201 ccgcgatgtt tagctgcacg tattcgcgcg caacgcaccg ccattcggga aagacggtgg
7261 tgcgctcgtc gggcaccagg tgcacgcgcg aaccgcgggt gtgcagggtg acaagggtcaa
7321 cgctgggtggc tacctctccg cgtaggcgct cgttgggtcca gcagaggcgg ccgcccttgc
7381 gcgagcagaa tggcggtagg ggggtctagct gcgtctcgtc cgggggggtct gcgtccacgg
7441 taaagacccc gggcagcagg cgcgcgtcga agtagtctat cttgcatcct tgcaagtcta
7501 gcgcctgctg ccatgcgcgg gcggcaagcg cgcgctcgta tgggttgagt gggggacccc
7561 atggcatggg gtgggtgagc gcggaggcgt acatgccgca aatgtcgtaa acgtagaggg
7621 gctctctgag tattccaaga tatgtagggt agcatcttcc accgcggatg ctggcgcgca
7681 cgtaatcgta tagttcgtgc gagggagcga ggaggtcggg accgaggttg ctacgggcgg
7741 gctgctctgc tcggaagact atctgcctga agatggcatg tgagttggat gatattggtg
7801 gacgctggaa gacgttgaag ctggcgtctg tgagacctac cgcgtcacgc acgaaggagg
7861 cgtaggagtc gcgcagcttg ttgaccagct cggcgggtgac ctgcacgtct agggcgagct
7921 agtccagggt ttccttgatg atgtcatact tatcctgtcc cttttttttc cacagctcgc
7981 ggttgaggac aaactcttcg cggctcttcc agtactcttg gatcggaac ccgtcggcct
8041 ccgaacggta agagcctagc atgtagaact ggttgacggc ctggtaggcg cagcatccct
8101 tttctacggg tagcgcgtat gcctgcgcgg ccttccggag cgagggtgtg gtgagcgcaa
8161 aggtgtccct gaccatgact ttgaggtaact ggtatttgaa gtcagtgtcg tcgcatccgc
8221 cctgctccca gagcaaaaag tccgtgcgct ttttggaacg cggatttggc agggcgaggg
8281 tgacatcggt gaagagtatc tttccgcgcg gaggcataaa gttgcgtgtg atgcggaagg
8341 gtcccggcac ctcggaacgg ttgttaatta cctgggaggc gagcacgac tcgtcaaagc
8401 cgttgatgtt gtggcccaca atgtaaagtt ccaagaagcg cgggatgccc ttgatggaag
8461 gcaatttttt aagttcctcg taggtgagct cttcaggggg gctgagcccg tgctctgaaa
8521 gggcccagtc tgcaagatga ggggttggaag cgacgaatga gctccacagg tcacgggcca
8581 ttagcatttg cagggtggtcg cgaaagggtc taaactggcg acctatggcc attttttctg
8641 ggggtgatgca gtagaaggta agcgggtctt gttcccagcg gtcccatcca aggttcgcgg
8701 ctaggtctcg cgcggcagtc actagaggct catctccgcc gaacttcatg accagcatga
8761 agggcacgag ctgcttccca aaggccccc tccaagtata ggtctctaca tcgtagggtga
8821 caaagagacg ctcggtgcga ggatgcgagc cgatcgggaa gaactggatc tcccgcacc
8881 aattggagga gtggctattg atgtggtgaa agtagaagtc cctgcgacgg gccgaacact
8941 cgtgctggct tttgtaaaaa cgtgcgcagt actggcagcg gtgcacgggc tgtacatcct
9001 gcacgaggtt gacctgacga ccgcgcacaa ggaagcagag tgggaatttg agcccctcgc
9061 ctggcgggtt tggctggtgg tcttctactt cggctgcttg tccttgaccg tctggctgct
9121 cgaggggagt tacggtggat cggaccacca cgccgcgcga gcccaaagtc cagatgtccg
9181 cgcgcggcgg tcggagcttg atgacaacat cgcgcagatg ggagctgtcc atggtctgga
9241 gctcccgcgg cgtcagggtca ggcgggagct cctgcagggt tacctcgcac agacgggtca
9301 gggcgcgggc tagatccagg tgatacctaa tttccagggg ctggttggtg gcggcgtcga
9361 tggcttgcaa gaggccgcat cccgcggcgg cgactacggg accgcgcggc gggcggtggg
9421 ccgcgggggt gtccttggat gatgcactca aaagcgggtga cgcgggagag ccccgagg

FIG. 18A-3

26/126

9481 tagggggggc tccggacccg ccgggagagg gggcaggggc acgtcggcgc cgcgcgcggg
9541 caggagctgg tgctgcgcgc gtaggttgct ggcgaacgcg acgacgcggc ggttgatctc
9601 ctgaatctgg cgcctctgcg tgaagacgac gggcccgggtg agcttgaacc tgaaagagag
9661 ttcgacagaa tcaatttcgg tgctggtgac ggcggcctgg cgcaaaatct cctgcacgtc
9721 tcctgagttg tcttgatagg cgatctcggc catgaactgc tcgatctctt cctcctggag
9781 atctccgcgt ccggctcgct ccacggtggc ggcgaggtcg ttggaaatgc gggccatgag
9841 ctgcgagaag gcgttgaggc ctccctcggt ccagacgcgg ctgtagacca cgcccccttc
9901 ggcacgcggg gcgcgcgatga ccacctgcgc gagattgagc tccacgtgcc gggcgaagac
9961 ggcgtagttt cgcaggcgct gaaagaggta gttgaggggtg gtggcgggtg gttctgccac
10021 gaagaagtac ataaccacgc gtcgcaacgt ggattcggtg atatcccca aggcctcaag
10081 gcgctccatg gcctcgtaga agtccacggc gaagttgaaa aactgggagt tgcgcgccga
10141 cacggttaac tcctcctcca gaagacggat gagctcggcg acagtgtcgc gcacctcgcg
10201 ctcaaaggct acaggggcct cttcttcttc ttcaatctcc tcttccataa gggcctcccc
10261 ttcttcttct tctggcggcg gtgggggagg ggggacacgg cggcgacgac ggcgcaccgg
10321 gaggcggtcg acaaagcgct cgatcatctc cccgcggcga cggcgcatgg tctcggtgac
10381 ggcgcggccg ttctcgcggg ggcgcagttg gaagacgcgg cccgtcatgt cccggttatg
10441 ggttggcggg gggctgccat gcggcaggga tacggcgcta acgatgcac tcaacaattg
10501 ttgtgtaggt actccgcgcg cgagggacct gagcgagtcg gcacgcaccg gatcgaaaaa
10561 cctctcgaga aaggcgtcta accagtcaca gtcgcaaggt aggctgagca ccgtggcggg
10621 cggcagcggg cggcggtcgg ggttgtttct ggcggaggtg ctgctgatga tgtaattaaa
10681 gtaggcggtc ttgagacggc ggatggtcga cagaagcacc atgtccttgg gtccggcctg
10741 ctgaatgcgc aggcggtcgg ccatgcccc a ggccttcgtt tgacatcggc gcaggtcttt
10801 gtagtagtct tgcatgagcc tttctaccgg cacttcttct tctccttctt cttgtcctgc
10861 atctcttgca tctatcgctg cggcggcggc ggagtttggc cgtaggtggc gccctcttcc
10921 tcccatgcgt gtgaccccca agccccctcat cggctgaagc agggctaggt cggcgacaac
10981 gcgctcggct aatatggcct gctgcacctg cgtgagggtg gactggaagt catccatgtc
11041 cacaagcggg tggatgcgc ccgtgttgat ggtgtaagtg cagttggcca taacggacca
11101 gttaacggtc tggtagcccg gctgcgagag ctcggtgtac ctgagacgcg agtaagccct
11161 cgagtcaaat acgtagtcgt tgcaagtccg caccaggtac tggatcccca ccaaaaagtg
11221 cggcggcggc tggcggtaga ggggccagcg tagggtggcc ggggctccgg gggcgagatc
11281 ttccaacata aggcgatgat atccgtagat gtacctggac atccaggtga tgccggcggc
11341 ggtggtggag gcgcgcggaa agtcgcggac gcggttccag atgttgcgca gcggcaaaaa
11401 gtgctccatg gtcgggacgc tctggccggg caggcgcgcg caatcgttga cgctctagac
11461 cgtgcaaaaag gagagcctgt aagcgggcac tcttccgtgg tctggtggat aaattcgcaa
11521 gggatatcatg gcggacgacc ggggttcgag ccccgatatc ggccgtccgc cgtgatccat
11581 gcggttaccg cccgcgtgtc gaaccaggt gtgcgacgtc agacaacggg ggagtgtctc
11641 ttttggcttc cttccaggcg cggcggctgc tgcgctagct tttttggcca ctggccgcgc
11701 gcagcgtaag cggttaggct ggaaagcgaa agcattaagt ggctcgctcc ctgtagccgg
11761 agggttatth tccaagggtt gagtcgcggg acccccgggt cgagtctcgg accggccgga
11821 ctgcggcgaa cgggggtttg cctccccgtc atgcaagacc ccgcttgcaa attcctccgg
11881 aaacagggac gagccccctt tttgcttttc ccagatgcat ccggtgtctg ggcagatgcg
11941 cccccctcct cagcagcggc aagagcaaga gcagcggcag acatgcaggg caccctcccc
12001 tectctacc gcgtcaggag gggcgacatc cgcggttgac gcggcagcag atggtgatta
12061 cgaacccccg cggcgccggg cccggcacta cctggacttg gaggagggcg agggcctggc
12121 gcggctagga gcgccctctc ctgagcggca cccaagggtg cagctgaagc gtgatacgcg
12181 tgaggcgtag gtgccggggc agaacctgtt tcgcgaccgc gaggagagg agcccgagga
12241 gatgcgggat cgaaagtccc acgcagggcg cgagctgcgg catggcctga atcgcgagcg
12301 gttgctgcgc gaggaggact ttgagcccga cgcgcgaacc gggattagtc ccgcgcgcgc
12361 acacgtggcg gccgcccacc tggtaaccgc atacgagcag acggtgaacc aggagattaa
12421 ctttcaaaaa agctttaaca accacgtgcg tacgcttggt gcgcgcgagg aggtggctat
12481 aggactgatg catctgtggg actttgtgaa cgcgctggag caaaacccaa atagcaagcc
12541 gctcatggcg cagctgttcc ttatagtgcg gcacagcagg gacaacgagg cattcagggg
12601 tgcgctgcta aacatagtag agcccagggg ccgctggctg ctcgatttga taaacatcct
12661 gcagagcata gtggtgcagg agcgcagctt gagcctggct gacaaggtgg ccgccatcaa
12721 ctattccatg cttagcctgg gcaagtttta cgcccgaag atataccata ccccttacgt

FIG. 18A-4

27/126

12781 tcccatagac aaggaggttaa agatcgaggg gttctacatg cgcattggcgc tgaagggtgct
12841 taccttgagc gacgacctgg gcgtttatcg caacgagcgc atccacaagg ccgtgagcgt
12901 gagccggcgg cgcgagctca gcgaccgcga gctgatgcac agcctgcaaa gggccctggc
12961 tggcacgggc agcggcgata gagaggccga gtcctacttt gacgcgggcg ctgacctggc
13021 ctggggccca agccgacgcg ccctggaggg agctggggcc ggacctgggc tggcggtggc
13081 acccgcgcg cctggcaacg tcggcggcgt ggaggaatat gacgaggacg atgagtacga
13141 gccagaggac ggcgagtact aagcgggtgat gtttctgac agatgatgca agacgcaacg
13201 gaccggcgcg tgcggggcgg gctgcagagc cagccgtccg gccttaactc cacggacgac
13261 tggcgccagg tcatggaccg catcatgtcg ctgactgcgc gcaatcctga cgcgttccgg
13321 cagcagccgc aggccaaacc gctctccgca attctggaag cgggtggccc ggcgcgcgca
13381 aaccccacgc acgagaaggt gctggcgatc gtaaacgcgc tggccgaaaa cagggccatc
13441 cggcccgcag aggccggcct ggtctacgac gcgctgcttc agcgcgtggc tcgttacaac
13501 agcggcaacg tgcagaccaa cctggaccgg ctggtggggg atgtgcgcga ggccgtggcg
13561 cagcgtgagc gcgcgcagca gcagggcaac ctgggctcca tgggtgact aaacgccttc
13621 ctgagtacac agcccgcga cgtgccgcgg ggacaggagg actacaccaa ctttgtgagc
13681 gactgcggc taatggtgac tgagacaccg caaagtgagg tgtaccagtc tgggccagac
13741 tattttttcc agaccagtag acaaggcctg cagaccgtaa acctgagcca ggctttcaaa
13801 aacttgcagg ggctgtgggg ggtgcgggct cccacaggcg accgcgcgac cgtgtctagc
13861 ttgctgagc ccaactcgc cctgttgctg ctgctaatag cgcccttcac ggacagtggc
13921 agcgtgtccc gggacacata cctaggtcac ttgctgacac tgtaccgcga ggccataggt
13981 caggcgcatg tggacgagca tactttccag gagattacaa gtgtcagccg cgcgctgggg
14041 caggaggaca cgggcagcct ggaggcaacc cttaaactacc tgctgaccaa ccggcggcag
14101 aagatcccct cgttgacacg tttaaacagc gaggaggagc gcattttgcg ctacgtgcag
14161 cagagcgtga gccttaacct gatgcgcgac ggggtaacgc ccagcgtggc gctggacatg
14221 accgcgcgca acatggaacc gggcatgtat gcctcaaacc ggccgtttat caaccgccta
14281 atggactact tgcacgcgc ggccgcccgt aaccccgagt atttcaccaa tgccatcttg
14341 aaccgcgact ggctaccgcc ccctggtttc tacaccgggg gattcgaggt gcccgagggt
14401 aacgatggat tcctctggga cgacatagac gacagcgtgt ttccccgca accgcagacc
14461 ctgctagagt tgcaacagcg cgagcaggca gaggcggcgc tgcgaaagga aagcttccgc
14521 aggccaagca gcttgtccga tctaggcgct gcggccccgc ggtcagatgc tagtagccca
14581 tttccaagct tgatagggtc tcttaccagc actcgcacca cccgcccgcg cctgctgggc
14641 gaggaggagt acctaaacaa ctgcgtgctg cagccgcagc gcgaaaaaaa cctgcctccg
14701 gcattttcca acaacgggat agagagccta gtggacaaga tgagtagatg gaagacgtac
14761 gcgcaggagc acagggacgt gccaggcccg cgcgcgcca cccgtcgtca aaggcacgac
14821 cgtcagcggg gtctggtgtg ggaggacgat gactcggcag acgacagcag cgtcctggat
14881 ttgggaggga gtggcaaccc gtttgcgac cttcgcccca ggctggggag aatgttttaa
14941 aaaaaaaaaa agcatgatgc aaaataaaaa actcaccaag gccatggcac cgagcgttgg
15001 ttttcttgta ttccccttag tatgcggcgc gcggcgatgt atgaggaagg tcctcctccc
15061 tcctacgaga gtgtggtgag cgcggcgcca gtggcgggcg cgtgggttc tccttcgat
15121 gctcccctgg acccgccgtt tgtgcctccg cggtagctgc ggctaccgg ggggagaaac
15181 agcatccgtt actctgagtt ggcaccctta ttcgacacca cccgtgtgta cctggtggac
15241 aacaagtcaa cggatgtggc atccctgaac taccagaacg accacagcaa ctttctgacc
15301 acggtcattc aaaacaatga ctacagcccg ggggaggcaa gcacacagac catcaatctt
15361 gacgaccggt cgcactgggg cggcgacctg aaaaccatcc tgcatacca catgccaat
15421 gtgaacgagt tcatgtttac caataagttt aaggcgcggg tgatggtgtc gcgcttgctt
15481 actaaggaca atcaggtgga gctgaaatac gagtgggtgg agttcacgct gcccgagggc
15541 aactactccg agaccatgac catagacctt atgaacaacg cgatcgtgga gcaactctt
15601 aaagtgggca gacagaacgg ggttctggaa agcgacatcg gggtaaagt tgcacccgc
15661 aacttcagac tgggggttga ccccgctact ggtcttgta tgcctgggg atatacaaac
15721 gaagccttcc atccagacat cattttgctg ccaggatgcg ggggtggactt caccacagc
15781 cgcctgagca acttggtggg catccgcaag cggcaaccct tccaggagg ctttaggac
15841 acctacgat atctggaggg tggtaacatt cccgcactgt tggatgtgga cgcctaccag
15901 gcgagcttga aagatgacac cgaacagggc gggggtggcg caggcggcag caacagcagt
15961 ggcagcggcg cggaagagaa ctccaacgcg gcagccgcgg caatgcagcc ggtggaggac
16021 atgaacgatc atgccattcg cggcgacacc tttgccacac gggctgagga gaagcgcgt

FIG. 18A-5

28/126

16081 gagggccgaag cagcgggccga agctgccgcc cccgctgcgc aacccgaggt cgagaagcct
16141 cagaagaaac cggatgatcaa acccctgaca gaggacagca agaaacgcag ttacaaccta
16201 ataagcaatg acagcacctt caccagtagc cgcagctggg accttgcata caactacggc
16261 gaccctcaga ccggaatccg ctcatggacc ctgctttgca ctctgacgt aacctgcggc
16321 tcggagcagg tctactggte gttgccagac atgatgcaag acccgtgac cttccgctcc
16381 acgcgccaga tcagcaactt tccgggtggg ggcgccgagc tgttgcccgt gcactccaag
16441 agcttctaca acgaccaggc cgtctactcc caactcatcc gccagtttac ctctctgacc
16501 cacgtgttca atcgctttcc cgagaaccag attttggcgc gcccgccagc cccaccatc
16561 accaccgtca gtgaaaacgt tcctgctctc acagatcacg ggacgctacc gctgcgcaac
16621 agcatcggag gagtccagcg agtgaccatt actgacgcca gacgccgcac ctgcccctac
16681 gtttacaagg ccctgggcat agtctcggcg cgcgtcctat cgagccgcac tttttgagca
16741 agcatgtcca tccttatatc gccagcaat aacacaggct ggggcctgcg cttcccaagc
16801 aagatgtttg gcggggccaa gaagcgctcc gaccaacacc cagtgcgcgt gcgcgggcac
16861 taccgcgcgc cctggggcgc gcacaaacgc ggccgcaact ggccgaccac cgtcgatgac
16921 gccatcgacg cggatggatga ggaggcgcg aactacacgc ccacgccgcc accagtgtcc
16981 acagtggacg cggccattca gaccgtggg cgcggagccc ggcgctatgc taaaatgaag
17041 agacggcgga ggcgcgtagc acgtcgccac cgcgcgcgac ccggcactgc cgcccaacgc
17101 gcggcgcgcg ccctgcttaa ccgcgcacgt cgcaccggcc gacgggcggc catgcggggc
17161 gctcgaaggc tggccgcggg tattgtcact gtgccccca ggtccaggcg acgagcgcc
17221 gccgcagcag ccgcggccat tagtgctatg actcagggtc gcaggggcaa cgtgtattgg
17281 gtgcgcgact cggttagcgg cctgcgcgtg cccgtgcgca cccgcccccc gcgcaactag
17341 attgcaagaa aaaactactt agactcgtac tgttgatagt atccagcggc ggcggcgcg
17401 aacgaagcta tgtccaagcg caaatcaaa gaagagatgc tccaggtcat cgcgccggag
17461 atctatggcc cccgaagaa ggaagagcag gattacaagc cccgaaagct aaagcgggtc
17521 aaaaagaaaa agaaagatga tgatgatgaa cttgacgacg aggtggaact gctgcacgt
17581 accgcgcccc ggcgacgggt acagtggaaa ggtcgacgcg taaaacgtgt tttgcgaccc
17641 ggcaccaccg tagtctttac gcccggtgag cgctccaccc gcacctaaa gcgcgtgtat
17701 gatgaggtgt acggcgacga ggacctgctt gagcaggcca acgagcgct cggggagtgt
17761 gcctacggaa agcggcataa ggacatgctg gcgttgccgc tggacgaggg caaccaca
17821 cctagcctaa agcccgtaac actgcagcag gtgctgcccc cgcttgacc gtccgaagaa
17881 aagcgcgccc taaagcgga gtctggtgac ttggcaccga ccgtgcagct gatggtaccc
17941 aagcgccagc gactggaaga tgtcttgga aaaatgaccg tggaaacctg gctggagccc
18001 gaggtccgcg tgcggccaat caagcaggtg gcgcggggac tgggcgtgca gaccgtggac
18061 gttcagatac ccactaccag tagcaccagt attgccaccg ccacagaggg catggagaca
18121 caaacgtccc cggttgcctc agcgggtggc gatgccgcgg tgcaggcggc cgctgcggcc
18181 gcgtccaaga cctctacgga ggtgcaaacg gaccctgga tgtttcgcgt ttcagcccc
18241 cggcgcccg cccgttcgag gaagtacggc gccgcagcg cgctactgcc cgaatatgcc
18301 ctacatcctt ccattgcgc taccgccggc tatcgtgggt acacctaccg cccagaagaa
18361 cgagcaacta cccgacgcgc aaccaccact ggaaccgcgc gccgcgctcg ccgtcgccag
18421 cccgtgctgg ccccgatttc cgtgcgcagg gtggctcgcg aaggaggcag gaccctgggt
18481 ctgccaacag cgcgctacca cccagcatc gtttaaaagc cggctcttgt ggttcttgca
18541 gatattggcc tcacctgcc cctccgtttc ccggtgcccg gattccgagg aagaatgcac
18601 cgtaggaggg gcatggccgg ccacggcctg acgggcggca tgcgtcgtgc gcaccaccgg
18661 cggcgcgcg cgtcgcaccg tcgcatgcgc ggccgtatcc tgccctcctt tattccactg
18721 atcgccgcgg cgattggcg cgtgcccga attgcatccg tggccttgca ggcgcagaga
18781 cactgattaa aaacaagtgt catgtggaaa aatcaaaata aaaagtctgg actctcacgc
18841 tcgcttggtc ctgtaactat tttgtagaat ggaagacatc aactttgcgt ctctggcccc
18901 gcgacacggc tcgcgcccgt tcatgggaaa ctggcaagat atcggcacca gcaatatgag
18961 cggatggcgcc ttcagctggg gctcgctgtg gagcgccatt aaaaatttcg gttccaccgt
19021 taagaactat ggcagcaagg cctggaacag cagcacaggc cagatgctga gggataagtt
19081 gaaagagcaa aatttccaac aaaaggtgg agatggcctg gcctctggca ttagcggggg
19141 ggtggacctg gccaaccagg cagtgcacaa taagattaac agtaagcttg atccccgcc
19201 tcccgtagag gagcctccac cggccgtgga gacagtgtct ccagaggggc gtggcgaaaa
19261 gcgtccgcgc cccgacaggg aagaaactct ggtgacgcaa atagacgagc ctccctcgta
19321 cgaggaggca ctaaagcaag gcctgccac caccgctccc atcgcgccca tggctaccgg

FIG. 18A-6

WO 2006/020480

PCT/US2005/027658

29/126

19381 agtgctgggc cagcacacac ccgtaacgct ggacctgcct ccccccgcgc acaccagca
19441 gaaacctgtg ctgccaggcc cgaccgccgt tgttgtaacc cgtcctagcc gcgcgtccct
19501 gcgcgcgcgc gccagcggtc cgcgatcggt gcggcccgtg gccagtggca actggcaaag
19561 cacactgaac agcatcgtgg gtctgggggt gcaatccctg aagcgccgac gatgcttctg
19621 atagctaacg tgcgtatgt gtgtcatgta tgcgtccatg tcgccgccag aggagctgct
19681 gagccggcgc gcgcccgtt tccaagatgg ctacccttc gatgatgccg cagtggctct
19741 acatgcacat ctccggccag gacgcctcgg agtacctgag ccccgggctg gtgcagtttg
19801 cccgcgccac cgagacgtac ttcagcctga ataacaagtt tagaaacccc acgggtggcg
19861 ctacgcacga cgtgaccaca gaccgggtccc agcgtttgac gctgcgggtc atccctgtgg
19921 accgtgagga tactgcgtac tcgtacaagg cgcggttcac cctagctgtg ggtgataacc
19981 gtgtgctgga catggcttcc acgtactttg acatccgcgg cgtgctggac aggggcccta
20041 cttttaagcc ctactctggc actgcctaca acgcccgtgg tccaaggggt gcccacaaatc
20101 cttgcgaatg ggatgaagct gctactgctc ttgaaataaa cctagaagaa gaggacgatg
20161 acaacgaaga cgaagtagac gagcaagctg agcagcaaaa aactcacgta tttgggcagg
20221 cgccttattc tggataaaat attacaaagg aggggtattca aatagggtgc gaaggtaaaa
20281 cacctaaata tgccgataaa acatttcaac ctgaacctca aataggagaa tctcagtggg
20341 acgaaacaga aattaatcat gcagctggga gagtccataa aaagactacc ccaatgaaac
20401 catgttacgg ttcatatgca aaaccacaa atgaaaatgg agggcaaggc attcttgtaa
20461 agcaacaaaa tggaaagcta gaaagtcaag tggaaatgca atttttctca actactgagg
20521 cagccgcagg caatgggtgat aacttgactc cttaaagtgg attgtacagt gaagatgtag
20581 atatagaaac cccagacact catatttctt acatgccac tattaaggaa ggtaaactcac
20641 gagaactaat gggccaacaa tctatgcccac agggcctaa ttacattgct tttagggaca
20701 attttattgg tctaattgat tacaacagca cgggtaatat ggggtgtctg gcgggccaaag
20761 catcgcagtt gaatgctgtt gtagatttgc aagacagaaa cacagagctt tcataccagc
20821 ttttgcttga ttccattggg gatagaacca ggtacttttc tatgtggaat caggctgttg
20881 acagctatga tccagatgtt agaattattg aaaatcatgg aactgaagat gaacttccaa
20941 attactgctt tccactggga ggtgtgatta atacagagac tcttaccag gtaaaaccta
21001 aaacaggtca ggaaaatgga tgggaaaaag atgctacaga attttcagat aaaaatgaaa
21061 taagagttgg aaataatttt gccatggaaa tcaatctaaa tgccaacctg tggagaaatt
21121 tcctgtactc caacatagcg ctgtatttgc ccgacaagct aaagtacagt ccttccaacg
21181 taaaaatttc tgataacca aacacctacg actacatgaa caagcgagtg gtggctcccg
21241 ggctagtgga ctgctacatt aaccttgagg cacgctgggc ccttgactat atggacaacg
21301 tcaaccatt taaccaccac cgcaatgctg gcctgcgcta ccgctcaatg ttgctgggca
21361 atggtcgcta tgtgcccttc cacatccagg tgcctcagaa gttctttgcc attaaaaacc
21421 tccttctcct gccgggctca tacacctacg agtggaactt caggaaggat gttaacatgg
21481 ttctgcagag ctccctagga aatgacctaa ggggtgacgg agccagcatt aagtttgata
21541 gcatttgcct ttacgccacc ttcttcccca tggcccacaa caccgcctcc acgcttgagg
21601 ccatgcttag aaacgacacc aacgaccagt cctttaacga ctatctctcc gccgccaaca
21661 tgctctaccc tatacccgcc aacgctacca acgtgcccac atccatcccc tcccgaact
21721 gggcggtctt ccgcggtgg gccttcacgc gccttaagac taaggaaacc ccatcactgg
21781 gctcgggcta cgacccttat tacacctact ctggctctat accctaccta gatggaacct
21841 tttacctcaa ccacacctt aagaagggtg ccattacctt tgactcttct gtcagctggc
21901 ctggcaatga ccgcctgctt acccccaacg agtttgaaat taagcgctca gttgacgggg
21961 agggttacaa cgttgcccag tgtaacatga ccaaagactg gttcctggta caaatgctag
22021 ctaactataa cattggctac cagggcttct atatcccaga gagctacaag gaccgcatgt
22081 actccttctt tagaaacttc cagcccatga gccgtcagg ggtggatgat actaaataca
22141 aggactacca acaggtgggc atcctacacc aacacaacaa ctctggattt gttggctacc
22201 ttgccccac catgcgcgaa ggacaggcct accctgctaa cttcccctat ccgcttatag
22261 gcaagaccgc agttgacagc attaccaga aaaagtctt ttcgcatcgc acccttgggc
22321 gcatcccat ctccagtaac tttatgtcca tgggcgact cacagacctg ggccaaaacc
22381 ttctctacgc caactccgcc cagcgctag acatgacttt tgaggtggat cccatggacg
22441 agcccaccct tctttatgtt ttgtttgaag tctttgacgt ggtccgtgtg caccagccgc
22501 accgcggtc catcgaaacc gtgtacctgc gcacgcctt ctccggcggc aacgccacaa
22561 cataaagaag caagcaacat caacaacagc tgccgccatg ggctccagt agcaggaact
22621 gaaagccatt gtcaaagatc ttgggtgtgg gccatatttt ttgggcacct atgacaagcg

FIG. 18A-7

WO 2006/020480

PCT/US2005/027658

30/126

```

22681 ctttccaggc tttgtttctc cacacaagct cgcctgcgcc atagtcaata cggccgggtcg
22741 cgagactggg ggcgtacact ggatggcctt tgcctggaac ccgactcaa aaacatgcta
22801 cctctttgag ccctttggct tttctgacca gcgactcaag caggtttacc agtttgagta
22861 cgagtcactc ctgcgccgta gcgccattgc ttcttcccc gaccgctgta taacgctgga
22921 aaagtccacc caaagcgtac agggggcccaa ctccggccgcc tgtggactat tctgctgcat
22981 gtttctccac gcctttgcca actggcccca aactcccatg gatcacaacc ccaccatgaa
23041 ccttattacc ggggtaccca actccatgct caacagtccc caggtacagc ccaccctgcg
23101 tcgcaaccag gaacagctct acagcttcct ggagcgccac tcgccctact tccgcagcca
23161 cagtgcgcag attaggagcg ccacttcttt ttgtcacttg aaaaacatgt aaaaataatg
23221 tactagagac actttcaata aaggcaaatg cttttatttg tacactctcg ggtgattatt
23281 tacccccacc cttgccgtct gcgccgttta aaaatcaaag gggttctgcc gcgcatcgct
23341 atgcgccact ggcagggaca cgttgcgata ctggtgttta gtgctccact taaactcagg
23401 cacaaccatc cgcggcagct cgggtgaagt ttactccac aggctgcgca ccatcaccaa
23461 cgcgttttagc aggtcggggc cgcatactct gaagtcgcag ttggggcctc cgccctgcgc
23521 gcgcgagttg cgatacacag ggttgacgca ctggaacact atcagcgccg ggtggtgcac
23581 gctggccagc acgctcttgt cggagatcag atccgcgtcc aggtcctccg cgttgctcag
23641 ggcgaacgga gtcaactttg gtagctgcct tcccaaaaag ggcgcgtgcc caggctttga
23701 gttgcactcg caccgtagtg gcatcaaaag gtgaccgtgc ccggtctggg cgttaggata
23761 cagcgcttgc ataaaagcct tgatctgctt aaaagccacc tgagcctttg cgccttcaga
23821 gaagaacatg ccgcaagact tgccggaaaa ctgattggcc ggacaggccg cgtcgtgcac
23881 gcagcacctt gcgtcgggtg tggagatctg caccacattt cggccccacc ggttcttcac
23941 gatcttggcc ttgctagact gctccttcag cgcgcgctgc ccgttttcgc tcgtcacatc
24001 catttcaatc acgtgctcct tatttatcat aatgcttccg tgtagacact taagctcgcc
24061 ttcgatctca gcgcagcggg gcagccacaa cgcgcagccc gtgggctcgt gatgcttgta
24121 ggtcacctct gcaaacgact gcaggtacgc ctgcaggaat cgccccatca tcgtcacaaa
24181 ggtcttggtg ctggtgaagg tcagctgcaa cccgcgggtg tcctcgttca gccaggtctt
24241 gcatacggcc gccagagctt ccacttggtc aggcagtagt ttgaagtctg cctttagatc
24301 gttatccacg tggtaacttg ccatcagcgc gcgcgcagcc tccatgcctt tctcccacgc
24361 agacacgatc ggcacactca gcgggttcac caccgtaatt tcactttccg cttcgttggg
24421 ctcttcctct tcctcttgcg tccgcatacc acgcgccact gggtcgtctt cattcagccg
24481 ccgactgtg cgcttacctc ctttgccatg cttgattagc accggtgggt tgctgaaacc
24541 caccatttgt agcgccacat cttctctttc ttctcgtctg tccacgatta cctctggtga
24601 tggcggggcg tcgggcttgg gagaagggcg cttctttttc ttcttggggc caatggccaa
24661 atccgcgcgc gaggtcgatg gccgcgggct ggggtgtgcg gccaccagcg cgtcttggtg
24721 tgagtcttcc tcgtcctcgg actcgatacg ccgcctcacc cgcttttttg ggggcgcccg
24781 gggaggcggc ggcgacgggg acggggacga cagtcctcc atggttgggg gacgtcgcgc
24841 cgcaccgcgt ccgcgctcgg ggggtggttt gcgctgctcc tcttcccacg tggccatttc
24901 cttctcctat aggcagaaaa agatcatgga gtcagtgcag aagaaggaca gcctaaccgc
24961 cccctctgag ttcgccacca ccgcctccac cgatgccgcc aacgcgccta ccacctccc
25021 cgtcgaggca ccccgcttg aggaggagga agtgattatc gagcaggacc caggttttgt
25081 aagcgaagac gacgaggacc gctcagtacc aacagaggat aaaaagcaag accaggacaa
25141 cgcagaggca aacgaggaa aagtcgggcg gggggacgaa aggcattggc actacctaga
25201 tgtgggagac gacgtgctgt tgaagcatct gcagcgccag tgcgccatta tctgcgacgc
25261 gttgcaagag cgcagcgatg tgcccctcgc catagcggat gtcagccttg cctacgaacg
25321 ccacctattc tcaccgcgcg tacccccaca acgccaagaa aacggcacat gcgagcccaa
25381 cccgcgcctc aacttctacc ccgtatttgc cgtgccagag gtgcttgcca cctatcacat
25441 ctttttccaa aactgcaaga taccctatc ctgccgtgcc aaccgcagcc gagcggacaa
25501 gcagctggcc ttgcggcagg gcgctgtcat acctgatata gcctcgtcga acgaagtgcc
25561 aaaaatcttt gagggctctg gacgcgacga gaagcgcgcg gcaaacgctc tgcaacagga
25621 aaacagcgaa aatgaaagtc actctggagt gttggtggaa ctcgagggtg acaacgcgcg
25681 cctagccgta ctaaaacgca gcatcgaggt caccactttt gcctaccgga cacttaacct
25741 acccccacag gtcattgagc cagtcattgag tgagctgate gtgcgccgtg cgcagccctt
25801 ggagagggat gcaaatttgc aagaacaaac agaggagggc ctaccgcagc ttggcgacga
25861 gcagctagcg cgctggcttc aaacgcgcga gcctgccgac ttggaggagc gacgcaact
25921 aatgatggcc gcagtgtctg ttaccgtgga gcttgagtgc atgcagcggg tctttgctga

```

FIG. 18A-8

WO 2006/020480

PCT/US2005/027658

31/126

```

25981 cccggagatg cagcgcaagc tagaggaaac attgcactac acctttcgac agggctacgt
26041 acgccaggcc tgcaagatct ccaacgtgga gctctgcaac ctggtctcct accttggaat
26101 tttgcacgaa aaccgccttg ggcaaaacgt gcttcattcc acgctcaagg gcgaggcgcg
26161 ccgcgactac gtccgcgact gcgtttactt atttctatgc tacacctggc agacggccat
26221 gggcgtttgg cagcagtgtc tggaggagtg caacctcaag gagctgcaga aactgctaaa
26281 gcaaaacttg aaggacctat ggacggcctt caacgagcgc tccgtggccg cgcacctggc
26341 ggacatcatt ttccccgaac gcctgcttaa aacctgcaa cagggctctgc cagacttcac
26401 cagtcaaagc atgttgacaga actttaggaa ctttatccta gagcgctcag gaatcttgcc
26461 cgccacctgc tgtgcacttc ctagecactt tgtgcccatt aagtaccgcg aatgccctcc
26521 gccgctttgg ggccactgct acctctcgca gctagccaac taccttgccct accactctga
26581 cataatggaa gacgtgagcg gtgacggctc actggagtgt cactgtcgtc gcaacctatg
26641 caccgccac cgctccctgg tttgcaattc gcagctgctt aacgaaagtc aaattatcgg
26701 tacctttgag ctgcaggggtc cctcgectga cgaaaagtcg gcggctccgg ggttgaaact
26761 cactccgggg ctgtggacgt cggcttacct tcgcaaattt gtacctgagg actaccacgc
26821 ccacgagatt aggttctacg aagaccaatc ccgccgcctt aatgcggagc ttaccgctg
26881 cgtcattacc cagggccaca ttcttgcca attgcaagcc atcaacaaag ccgcacaaga
26941 gtttctgcta cgaaagggac ggggggttta cttggacccc cagtccggcg aggagctcaa
27001 cccaatcccc ccgccgccgc agccctatca gcagcagccg cgggcccttg cttcccagga
27061 tggcacccaa aaagaagctg cagctgccgc cgccaccac ggacgaggag gaatactggg
27121 acagtcaggc agaggaggtt ttggacgagg aggaggagga catgatggaa gactgggaga
27181 gcctagacga ggaagcttcc gaggtcgaag aggtgtcaga cgaaacaccg tcacctcgg
27241 tcgcattccc ctgcgccggc cccagaaat cggcaaccgg ttccagcatg gctacaacct
27301 ccgctcctca ggccgccggc gcactgcccg ttcgccgacc caaccgtaga tgggacacca
27361 ctggaaccag ggccggtaag tccaagcagc cgccgccgtt agcccaagag caacaacagc
27421 gccaaaggcta ccgctcatgg cgcgggcaca agaacgccat agttgcttgc ttgcaagact
27481 gtgggggcaa catctccttc gcccgccgct ttcttctcta ccatcacggc gtggccttcc
27541 cccgtaacat cctgcattac taccgtcatc tctacagccc atactgcacc ggcggcagcg
27601 gcagcaacag cagcggccac acagaagcaa aggcgaccgg atagcaagac tctgacaaag
27661 cccaagaaat ccacagcggc ggcagcagca ggaggaggag cgctgcgtct ggcgcccaac
27721 gaaccctgat cgaccccgca gcttagaaac aggatthttt ccactctgta tgctatatth
27781 caacagagca ggggccaaga acaagagctg aaaataaaaa acaggtctct gcgatccctc
27841 acccgagct gcctgtatca caaaagcgaa gatcagcttc ggcgcacgct ggaagacgcg
27901 gaggtctctc tcagtaaata ctgcgcgtg actcttaagg actagtttcg cgcccttctc
27961 caaatthtaag cgcgaaaact acgtcatctc cagcggccac acccggcgcc agcacctggt
28021 gtcagcgcca ttatgagcaa ggaaattccc acgccctaca tgtggagtta ccagccacaa
28081 atgggacttg cggctggagc tgcccaagac tactcaacct gaataaacta catgagcgcg
28141 ggaccccaca tgatatcccg ggtcaacgga atacgcgcc accgaaaccg aattctcctg
28201 gaacaggcgg ctattaccac cacacctcgt aataacctta atccccgtag ttggcccgct
28261 gccctggtgt accaggaaag tcccgctccc accactgtgg tacttcccag agacgccag
28321 gccgaagttc agatgactaa ctacggggcg cagcttgccg gcggctttcg tcacagggtg
28381 cggtcgcccg ggcagggtat aactcacctg acaatcagag ggcgaggtat tcagctcaac
28441 gacgagtcgg tgagctcctc gcttggtctc cgtccggacg ggacatttca gatcggcggc
28501 gccggccgct cttcattcac gcctcgtcag gcaatcctaa ctctgcagac ctctcctct
28561 gagccgcgct ctggaggcat tggaactctg caatttattg aggagtthgt gccatcggtc
28621 tactthtaacc cttctcggg acctcccggc cactatccgg atcaatttat tcctaactth
28681 gacgcggtaa aggactcggc ggacggctac gactgaatgt taagtggaga ggcagagcaa
28741 ctgcgcctga aacacctggt ccactgtcgc cgccacaagt gctttgcccg cgactccggt
28801 gagthttgct actthgaatt gcccgaggat catatcgagg gcccggcgca cggcgctcgg
28861 cttaccgccc agggagagct tgcccgtagc ctgattcggg agthtaccba gcgccccctg
28921 ctagttgagc gggacagggg acctgtgtt ctactgtga tttgcaactg tcctaacctc
28981 ggattacatc aagatctthg ttgccatctc tgtgctgagt ataataaata cagaaatthaa
29041 aatatactgg ggctcctatc gccatcctgt aaacgccacc gtcttcaccc gcccaagcaa
29101 accaaggcga accttacctg gtactthtaa catctctccc tctgtgattt acaacagtht
29161 caaccagac ggagtgagtc tacgagagaa cctctccgag ctgagctact ccatcagaaa
29221 aaacaccacc ctcttacct gccgggaacg tacgagtgcg tcaccggccg ctgcaccaca

```

FIG. 18A-9

WO 2006/020480

PCT/US2005/027658

32/126

```

29281 cctaccgcct gaccgtaaac cagacttttt ccggacagac ctcaataact ctgtttacca
29341 gaacaggagg tgagcttaga aaacccttag ggtattaggc caaaggcgca gctactgtgg
29401 ggtttatgaa caattcaagc aactctacgg gctattctaa ttcaggtttc tctagaatcg
29461 gggttggggg tattctctgt cttgtgatcc tctttattct tatactaacg cttctctgcc
29521 taaggctcgc cgcctgctgt gtgcacattt gcattttattg tcagcttttt aaacgctggg
29581 gtcgccaccc aagatgatta ggtacataat cctaggttta ctcacccttg cgtcagocca
29641 cgggtaccacc caaaagggtg attttaagga gccagcctgt aatgttacat tcgcagctga
29701 agctaataag tgcaccactc ttataaaatg caccacagaa catgaaaagc tgcttattcg
29761 ccacaaaaac aaaattggca agtatgctgt ttatgctatt tggcagccag gtgacactac
29821 agagtataat gttacagttt tccagggtaa aagtcataaa acttttatgt atacttttcc
29881 attttatgaa atgtgcgaca ttaccatgta catgagcaaa cagtataagt tgtggccccc
29941 acaaaattgt gtggaaaaca ctggcacttt ctgctgcact gctatgctaa ttacagtgtc
30001 cgctttgggc tgtaccctac tctatattaa atacaaaagc agacgcagct ttattgagga
30061 aaagaaaatg ccttaattta ctaagttaca aagctaattg caccactaac tgctttactc
30121 gctgcttgca aaacaaattc aaaaagttag cattataatt agaataggat ttaaaccccc
30181 cggctcatttc ctgctcaata ccattcccct gaacaattga ctctatgtgg gatatgctcc
30241 agcgctacaa ccttgaagtc aggcttcctg gatgtcagca tctgactttg gccagcacct
30301 gtcccgcgga tttgttccag tccaactaca gcgaccacc ctaacagaga tgaccaacac
30361 aaccaacgcg gccgcgcgta ccggacttac atctaccaca aatacacccc aagtttctgc
30421 ctttgtcaat aactgggata acttgggcat gtggtgggttc tccatagcgc ttatgtttgt
30481 atgccttatt attatgtggc tcatctgctg cctaaagcgc aaacgcgccc gaccacccat
30541 ctatagtccc atcattgtgc tacacccaaa caatgatgga atccatagat tggacggact
30601 gaaacacatg ttcttttctc ttacagtatg attaaatgag acatgattcc tcgagttttt
30661 atattactga cccttgttgc gcttttttgt gcgtgctcca cattggctgc ggtttctcac
30721 atcgaagtag actgcattcc agccttcaca gtctatttgc tttacggatt tgtcaccctc
30781 acgctcatct gcagcctcat cactgtgggc atcgccctta tccagtgcac tgactgggtc
30841 tgtgtgcgct ttgcatatct cagacacccat cccagtagca gggacaggac tatagctgag
30901 cttcttagaa ttctttaatt atgaaattta ctgtgacttt tctgctgatt atttgcaccc
30961 tatctgcgtt ttgttccccg acctccaagc ctcaaagaca tatatcatgc agattcactc
31021 gtatatggaa tattccaagt tgctacaatg aaaaaagcga tctttccgaa gcctggttat
31081 atgcaatcat ctctgttatg gtgttctgca gtaccatctt agccctagct atatatccct
31141 accttgacat tggctggaac gcaatagatg ccatgaacca cccaactttc cccgcgcccg
31201 ctatgcttcc actgcaacaa gttgttgccg gcggctttgt cccagccaat cagcctcgcc
31261 caccttctcc cacccccact gaaatcagct actttaatct aacaggagga gatgactgac
31321 accctagatc tagaaatgga cggaattatt acagagcagc gcctgctaga aagacgcagg
31381 gcagcggccg agcaacagcg catgaatcaa gagctccaag acatggttaa cttgcaccag
31441 tgcaaaaggg gtatcttttg tctcgtaaag caggccaaag tcacctacga cagtaatacc
31501 accggacacc gccttagcta caagttgcca accaagcgtc agaaattggg ggtcatgggtg
31561 ggagaaaagc ccattaccat aactcagcac tcggtagaaa ccgaaggctg cattcactca
31621 ccttgtcaag gacctgagga tctctgcacc cttattaaga cctgtgcggt tctcaaagat
31681 cttattccct ttaactaata aaaaaaata ataaagcatc acttacttaa aatcagttag
31741 caaatttctg tccagtttat tcagcagcac ctccctgccc tcctcccagc tctgggtattg
31801 cagcttcctc ctggctgcaa actttctcca caatctaaat ggaatgtcag tttcctcctg
31861 ttcctgtcca tccgcaccca ctatcttcat gttgttgtag atgaagcgcg caagaccgtc
31921 tgaagatacc ttcaaccccc tgtatccata tgacacggaa accggtcctc caactgtgcc
31981 ttttcttact cctccctttg tatcccccaa tgggtttcaa gagagtcccc ctgggggtact
32041 ctctttgcgc ctatccgaac ctctagttac ctccaatggc atgcttgccg tcaaaatggg
32101 caacggcctc tctctggagc aggccggcaa ccttacctcc caaaatgtaa ccactgtgag
32161 cccacctctc aaaaaaacca agtcaaacat aaacctggaa atatctgcac ccctcacagt
32221 tacctcagaa gccctaactg tggctgccgc cgcacctcta atggtcgcggt gcaacacact
32281 caccatgcaa tcacaggccc cgctaaccgt gcacgactcc aaacttagca ttgccaccca
32341 aggaccctc acagtgtcag aaggaaagct agccctgcaa acatcaggcc ccctcaccac
32401 caccgatagc agtaccctta ctatcactgc ctcacccctc ctaactactg ccactggtag
32461 cttgggcatt gacttgaaag agcccattta tacacaaaat ggaaaactag gactaaagta
32521 cggggctcct ttgcatgtaa cagacgacct aaacactttg accgtagcaa ctgggtccagg

```

FIG. 18A-10

WO 2006/020480

PCT/US2005/027658

33/126

```

32581 tgtgactatt aataatactt ccttgcaaac taaagttact ggagccttgg gttttgattc
32641 acaaggcaat atgcaactta atgtagcagg aggactaagg attgattctc aaaacagacg
32701 ccttatactt gatgttagtt atccgtttga tgctcaaaac caactaaatc taagactagg
32761 acagggccct ctttttataa actcagccca caacttggat attaaactaca acaaaggcct
32821 ttacttggtt acagcttcaa acaattccaa aaagcttgag gttaacctaa gcactgccaa
32881 ggggttgatg tttgacgcta cagccatagc cattaatgca ggagatgggc ttgaatttgg
32941 ttcacctaat gcaccaaaaca caaatcccct caaaacaaaa attggccatg gcctagaatt
33001 tgattcaaac aaggctatgg ttcctaaact aggaactggc cttagttttg acagcacagg
33061 tgccattaca gtaggaaaca aaaataatga taagctaact ttgtggacca caccagctcc
33121 atctcctaac tgtagactaa atgcagagaa agatgctaaa ctcactttgg tcttaacaaa
33181 atgtggcagt caaataactg ctacagtttc agttttggct gttaaaggca gtttggctcc
33241 aatatctgga acagttcaaa gtgctcatct tattataaga tttgacgaaa atggagtgtc
33301 actaaacaat tccttcctgg acccagaata ttggaacttt agaaatggag atcttactga
33361 aggcacagcc tatacaaacg ctgttggatt tatgcctaac ctatcagctt atccaaaatc
33421 tcacggtaaa actgccaaaa gtaacattgt cagtcaagtt tacttaaacg gagacaaaaac
33481 taaacctgta acactaacca ttacactaaa cggtagacag gaaacaggag acacaactcc
33541 aagtgcatac tctatgtcat tttcatggga ctggtctggc cacaactaca ttaatgaaat
33601 atttgccaca tcctcttaca ctttttcata cattgcccaa gaataaagaa tcgtttgtgt
33661 tatgtttcaa cgtgtttatt tttcaattgc agaaaatttc aagtcatttt tcattcagta
33721 gtatagcccc accaccacat agcttatata gatcaccgta ccttaatcaa actcacagaa
33781 ccctagtatt caacctgcca cctccctccc aacacacaga gtacacagtc ctttctcccc
33841 ggctggcctt aaaaagcatc atatcatggg taacagacat attcttaggt gttatattcc
33901 acacgggttc ctgtcgagcc aaacgctcat cagtgatatt aataaactcc ccgggcagct
33961 cacttaagtt catgtcgctg tccagctgct gagccacagg ctgctgtcca acttgcggtt
34021 gcttaacggg cggcgaagga gaagtccacg cctacatggg ggtagagtca taatcgtgca
34081 tcaggatagg gcggtggtgc tgcagcagcg cgogaataaa ctgctgccgc cgccgctccg
34141 tcctgcagga atacaacatg gcagtggctc cctcagcgat gattcgcacc gcccgagca
34201 taaggcgctt tgtcctccgg gcacagcagc gcacctgat ctcactaaa tcagcacagt
34261 aactgcagca cagcaccaca atattgttca aaatcccaca gtgcaaggcg ctgtatccaa
34321 agctcatggc ggggaccaca gaaccacgt ggccatcata ccacaagcgc aggtagatta
34381 agtggcgacc cctcataaac acgctggaca taaacattac ctcttttggc atgttgtaat
34441 tcaccacctc ccggtaccat ataaacctct gattaaacat ggcgccatcc accaccatcc
34501 taaaccagct ggccaaaacc tgcccgcggc ctatacactg cagggaaccg ggactggaac
34561 aatgacagtg gagagcccag gactcgtaac catggatcat catgctcgtc atgatatcaa
34621 tgttggcaca acacaggcac acgtgcatac acttcctcag gattacaagc tcctcccgcg
34681 ttagaaccat atcccaggga acaaccatt cctgaatcag cgtaaattccc aactgcagg
34741 gaagacctcg cacgtaactc acgttgtgca ttgtcaaagt gttacattcg ggcagcagcg
34801 gatgatectc cagtatggta gcgcgggttt ctgtctcaaa aggaggtaga cgatccctac
34861 tgtacggagt gcgcccagac aaccgagatc gtgttggtcg tagtgtcatg ccaaattgaa
34921 cgccggacgt agtcatattt cctgaagcaa aaccagggtc gggcggtgaca aacagatctg
34981 cgtctccggt ctgcgcgctt agatcgctct gtgtagtagt tgtagtatat ccactctctc
35041 aaagcatcca ggcgccccct ggcttcgggt tctatgtaaa ctccttcatt cgccgctgcc
35101 ctgataacat ccaccaccgc agaataagcc acaccagcc aacctacaca ttcgttctgc
35161 gagtcacaca cgggaggagc ggggaagagc ggaagaacca tgtttttttt tttattccaa
35221 aagattatcc aaaacctcaa aatgaagatc tattaagtga acgcgctccc ctccggtggc
35281 gtggtcaaac tctacagcca aagaacagat aatggcattt gtaagatgtt gcacaatggc
35341 ttccaaaagg caaacggccc tcacgtccaa gtggacgtaa aggctaaacc cttcagggtg
35401 aatctcctct ataaacattc cagcaccttc aaccatgccc aaataattct catctcgcca
35461 ccttctcaat atatctctaa gcaaatcccg aatattaagt ccggccattg taaaaatctg
35521 ctccagagcg ccctccacct tcagcctcaa gcagcgaatc atgattgcaa aaattcaggt
35581 tcctcacaga cctgtataag attcaaaagc ggaacattaa caaaaatacc gcgatcccgt
35641 aggtcccttc gcagggccag ctgaacataa tcgtgcaggt ctgcacggac cagcgcggcc
35701 acttccccgc caggaaccat gacaaaagaa cccacactga ttatgacacg catactcgga
35761 gctatgctaa ccagcgtagc cccgatgtaa gcttggtgca tggcgggcga tataaatgc
35821 aaggtgctgc tcaaaaaatc aggcaaagcc tcgcgcaaaa aagaaagcac atcgtagtca

```

FIG. 18A-11

34/126

35881 tgctcatgca gataaaggca ggtaagctcc ggaaccacca cagaaaaaga caccattttt
35941 ctctcaaaca tgtctgctggg tttctgcata aacacaaaat aaaataacaa aaaaacattt
36001 aaacattaga agcctgtctt acaacaggaa aaacaaccct tataagcata agacggacta
36061 cggccatgcc ggcgtgaccg taaaaaaact ggtcaccgtg attaaaaagc accaccgaca
36121 gctcctcggg catgtccgga gtcataatgt aagactcggg aaacacatca ggttgattca
36181 catcgggtcag tgctaaaaag cgaccgaaat agcccggggg aatacatacc cgcaggcgta
36241 gagacaacat tacagccccc ataggaggta taacaaaatt aataggagag aaaaacacat
36301 aaacacctga aaaaccctcc tgcctaggca aaatagcacc ctcccgtctc agaacaacat
36361 acagcgcttc cacagcggca gccataacag tcagccttac cagtaaaaaa gaaaacctat
36421 taaaaaaaca ccactcgaca cggcaccagc tcaatcagtc acagtgtaaa aaagggccaa
36481 gtgcagagcg agtatatata ggactaaaaa atgacgtaac gggttaaagtc cacaaaaaac
36541 acccagaaaa ccgcacgcga acctacgcc agaaacgaaa gccaaaaaac ccacaacttc
36601 ctcaaatcgt cacttccgtt ttcccacgtt acgtcacttc ccattttaag aaaactacaa
36661 ttccaacac atacaagtta ctccgcccta aaacctacgt caccgcgcc gttcccacgc
36721 cccgcgccac gtcacaaact ccacccctc attatcatat tggcttcaat ccaaaataag
36781 gtatattatt gatgatg (SEQ ID NO: 16)

FIG. 18A-12

35/126

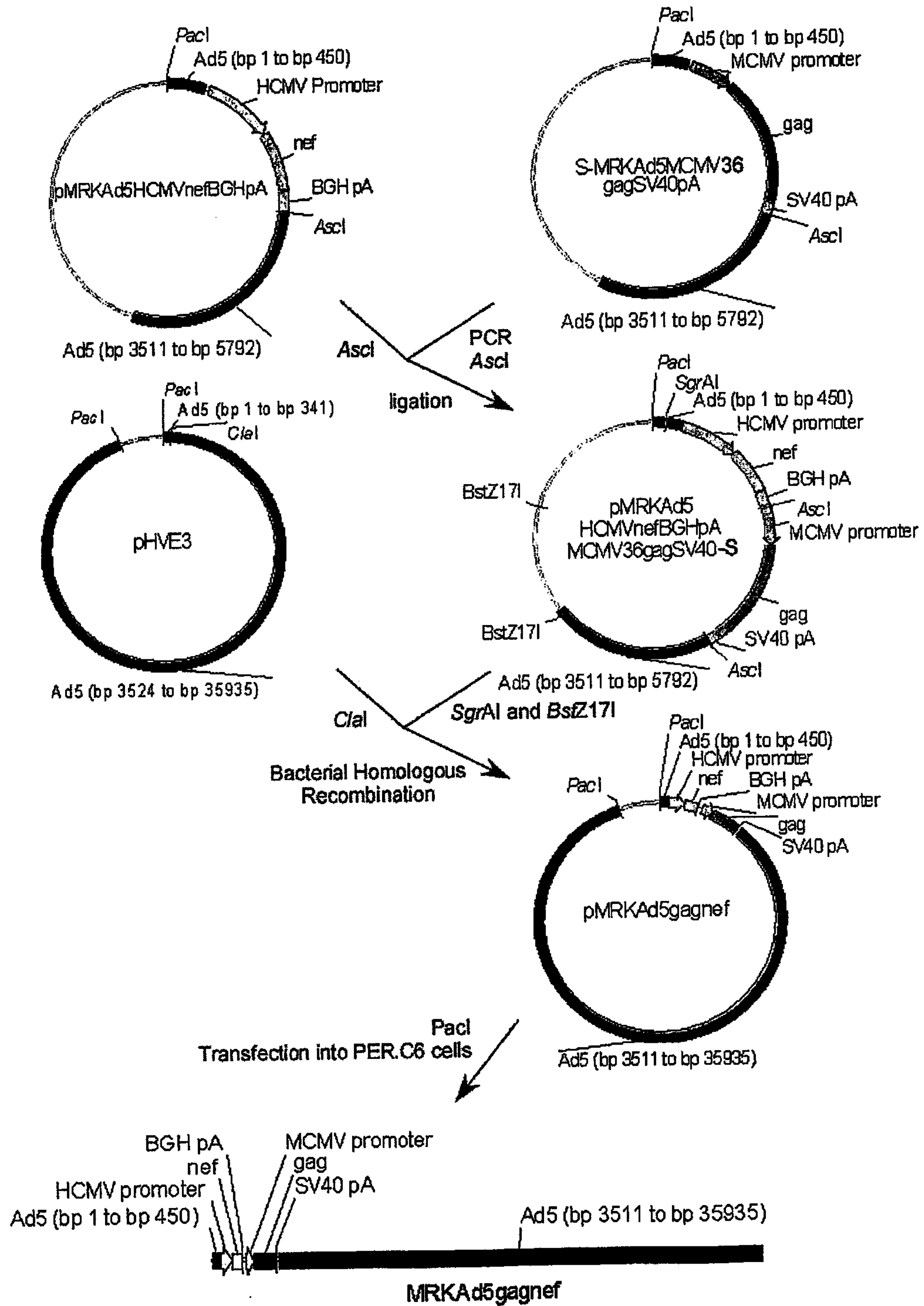


FIG. 19

36/126

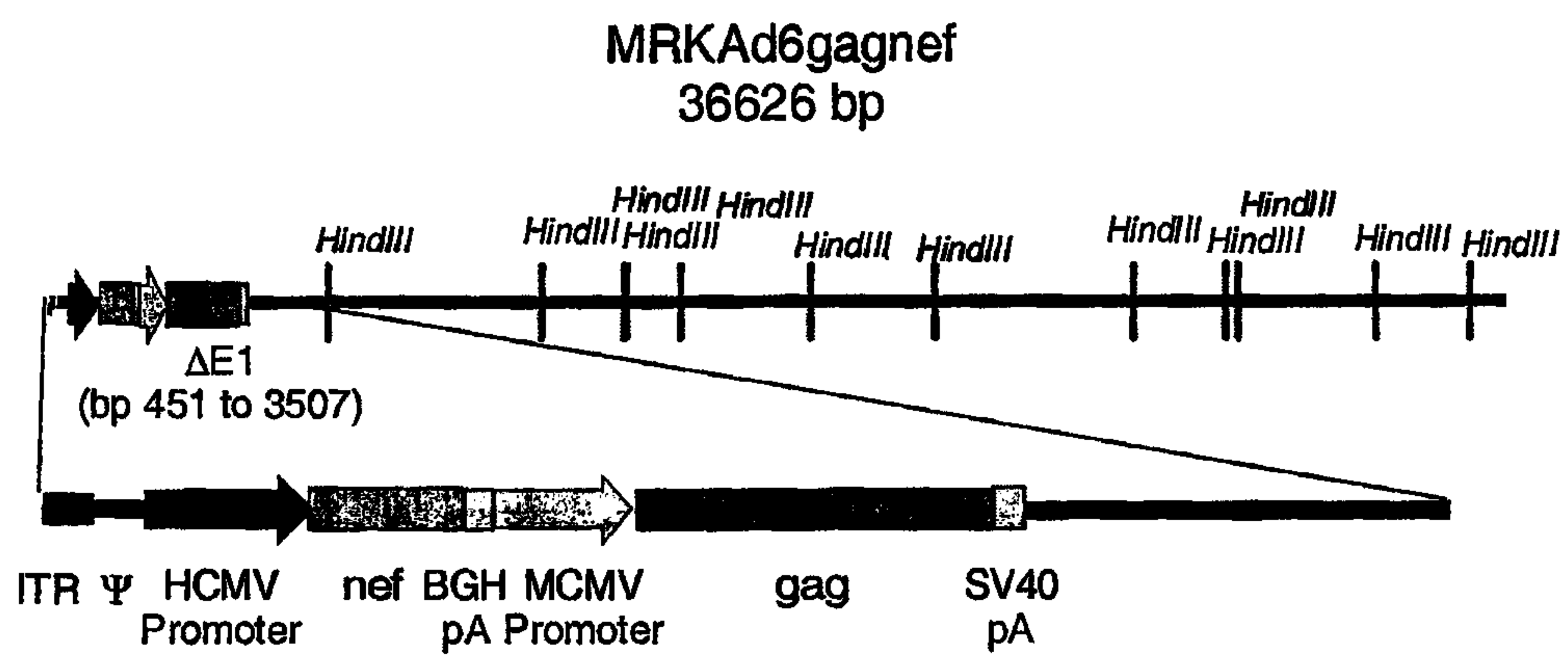


FIG. 20

WO 2006/020480

PCT/US2005/027658

37/126

MRKAd6gagnef

KEY:	_____ HCMV promoter	_____ Nef	_____ BGH pA	 MCMV promoter	 Gag	 SV40 pA
------	---------------------	-----------	--------------	---------------------	-----------	---------------

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgtaa gtgtggcgga acacatgtaa gcgccggatg tggtaaaagt gacgtttttg
181 gtgtgcgcgg gtgtacacgg gaagtgacaa ttttcgcgcg gttttaggcg gatgttgtag
241 taaatttggg cgtaaccaag taatatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataattct gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgcgc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcgtttt attattatag cggccgcgat ccattgcata cgttgtatcc
481 atatcataat atgtacattt atattggctc atgtccaaca ttaccgccat gttgacattg
541 attattgact agttattaat agtaatcaat tacgggggtca ttagttcata gcccatatat
601 ggagttccgc gttacataac ttacggtaaa tggcccgctt ggctgaccgc ccaacgacct
661 ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag ggactttcca
721 ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtac atcaagtgtg
781 tcatatgccg agtacgccc ctattgacgt caatgacggg aaatggcccg cctggcatta
841 tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg tattagtcac
901 cgctattacc atggtgatgc ggttttggca gtacatcaat gggcgtggat agcggtttga
961 ctcacgggga tttccaagtc tccaccccat tgacgtcaat gggagtttgt tttggcacca
1021 aaatcaacgg gactttccaa aatgtcgtaa caactccgcc ccattgacgc aaatggcgcg
1081 taggcgtgta cgggtgggagg tctatataag cagagctcgt ttagtgaacc gtcagatcgc
1141 ctggagacgc catccacgct gttttgacct ccatagaaga caccgggacc gatccagcct
1201 ccgcgcccg gaaacggtgca ttggaacgcg gattccccgt gccaaagagt agatctgccg
1261 ccattggccg caagtggctc aagaggtccg tgcccggtc gtcaccctg agggagagga
1321 tgaggagggc cgaagccccc gccgacaggg tgaggaggac cgaagccccc gcaagtggcg
1381 tgggcggcgt gtccagggac ctgagagaag acggcgccat cactcctcc aacaccggcg
1441 ccaccaacgc cgaactgcgc tgactggagg ccagaggaga cgaaggagtg ggcctccccg
1501 tgaggcccca ggtgcccctg aggcccatga cctacaaggg cgcggtggac ctgtcccact
1561 tcttgaagga gaagggcgcc ctgaggggcc tgatccactc ccagaagagg caggacatcc
1621 tggacctgtg ggtgtaccac acccagggct acttccccga ctggcagaac tacacccccc
1681 gcccggcat caggttcccc ctgaccttcg gctggtgctt caagctggtg cccgtggagc
1741 ccgagaaggt ggaggaggcc aacgagggcg agaacaactg cctgctgcac cccatgtccc
1801 agcacggcat cgaagacccc gagaaggagg tgctggagtg gaggttcgac tccaagctgg
1861 ccttccacca cgtgagcagg gaagctgacc ccgagtacta caaggactgc taaagcccg
1921 gcagatctgc tgtgccttct agttgccagc catctgttgt ttgccctcc cccgtgcctt
1981 ccttgacctt ggaaggtgcc actcccactg tcccttccta ataaaatgag gaaattgcac
2041 cgcattgtct gagtaggtgt cattctattc tggggggtgg ggtggggcag gacagcaagg
2101 gggaggattg ggaagacaat agcaggcatt ctggggatgc ggtgggctct atggccgac
2161 ggcgcgccat atactgagtc attagggact ttccaatggg ttttggccag tacataaggt
2221 caataggggt gaatcaacag gaaagtccca ttggagccaa gtacactgag tcaatagggg
2281 ctttccattg ggttttggcc agtacaaaag gtcaataggg ggtgagtcac tgggtttttc
2341 ccattattgg cacgtacata aggtcaatag ggtgagtcac ttgggttttt ccagccaatt
2401 tataaaacgc catgtacttt cccaccattg acgtcaatgg gctattgaaa ctaatgcaac
2461 gtgaccttta aacggtactt tcccatagct gattaatggg aaagtaccgt tctcgagcca
2521 atacacgtca atgggaagtg aaagggcagc caaacgtaa caccgccccg gttttccctt
2581 ggaattcca tattggcacg cattctattg gctgagctgc gttctacgtg ggtataagag
2641 gcgcgaccag cgtcgggtacc gtcgcagtct tcggtctgac caccgtagaa cgcagatcga
2701 gatctaccat ggtgcttagg gcttctgtgc tctctggtgg tgagctggac aagtgggaga
2761 agatcagcct gaggcctggt ggcaagaaga agtacaagct aaagcacatt gtgtggcctt
2821 ccagggagct ggagaggttt gctgtgaacc ctggcctgct ggagacctct gagggtgca
2881 ggcagatcct gggccagctc cagccctccc tgcaaacagg ctctgaggag ctgaagctcc

```

FIG. 21A-1

WO 2006/020480

PCT/US2005/027658

38/126

```

2941 tgtacaacac agtggctacc ctgtactgtg tgcaccagaa gattgatgtg aaggacacca
3001 aggaggccct ggagaagatt gaggaggagc agaacaagtc caagaagaag gccagcagg
3061 ctgctgctgg cacaggcaac tccagccagg tgtcccagaa ctacccatt gtgcagaacc
3121 tccagggccca gatggtgcac caggccatct ccccccggac cctgaatgcc tgggtgaagg
3181 tgggtggagga gaaggccttc tcccctgagg tgatcccat gttctctgcc ctgtctgagg
3241 gtgccacccc ccaggacctg aacaccatgc tgaacacagt ggggggcat caggctgcca
3301 tgcagatgct gaaggagacc atcaatgagg aggtgctga gtgggacagg ctgcatcctg
3361 tgcacgctgg cccattgcc cccggccaga tgagggagcc caggggctct gacattgctg
3421 gcaccacctc caccctccag gaggagattg gctggatgac caacaacccc cccatccctg
3481 tgggggaaat ctacaagagg tggatcatcc tgggctgaa caagattgtg aggatgtact
3541 cccccacctc catcctggac atcaggcagg gcccaagga gcccttcagg gactatgtgg
3601 acaggttcta caagaccctg agggctgagc aggcctcca ggaggtgaag aactggatga
3661 cagagaccct gctggtgcag aatgccaac ctgactgcaa gaccatcctg aaggccctgg
3721 gccctgctgc caccctggag gagatgatga cagcctgcca gggggtgggg gccctggtc
3781 acaaggccag ggtgctggct gaggccatgt cccaggtgac caactccgc accatcatga
3841 tgcagagggg caacttcagg aaccagagga agacagtga gtgcttcaac tgtggcaagg
3901 tgggccacat tgccaagaac tgtagggcc ccaggaagaa gggctgctgg aagtgtggca
3961 aggagggccca ccagatgaag gactgcaatg agaggcaggc caacttcctg gcaaaatct
4021 gccctccca caaggcagg cctggcaact tcctccagtc caggcctgag cccacagccc
4081 ctcccagga gtccttcagg tttggggagg agaagaccac cccagccag aagcaggagg
4141 ccattgacaa ggagctgtac cccctggcct ccctgaggtc cctgtttggc aacgacccct
4201 cctcccagta aaataaagcc cgggcagatc taacttgttt attgcagctt ataattggtta
4261 caaataaagc aatagcatca caaatttcac aaataaagca tttttttcac tgcattctag
4321 ttgtggtttg tccaaactca tcaatgtatc ttatcatgtc tggatcgggc cgccgtactg
4381 aaatgtgtgg gcggtggctta aggggtggga agaatatata aggtgggggt ctcatgtagt
4441 tttgtatctg ttttgacgca gccgccgcca tgagcgccaa ctcgtttgat ggaagcattg
4501 tgagctcata tttgacaacg cgcctgccc catgggcccg ggtgcgtcag aatgtgatgg
4561 gctccagcat tgatggctgc cccgtcctgc ccgcaaactc tactaccttg acctacgaga
4621 ccgtgtctgg aacgccgttg gagactgcag cctccgccc cgtttcagcc gctgcagcca
4681 ccgcccgcg gattgtgact gactttgctt tcctgagccc gcttgcaagc agtgcagctt
4741 cccgttcata cggcccgcat gacaagtga cggctctttt ggcacaattg gattctttga
4801 cccgggaact taatgtcgtt tctcagcagc tgttggtatc gcgccagcag gtttctgccc
4861 tgaaggcttc ctccctccc aatgcggttt aaaacataaa taaaaccag actctgtttg
4921 gatthggatc aagcaagtgt cttgctgtct ttatttaggg gttttgcgcg cgcggtaggc
4981 ccgggaccag cggctctcgt cgttgagggt cctgtgtatt tttccagga cgtggtaaag
5041 gtgactctgg atgttcagat acatgggcat aagcccgtct ctggggtgga ggtagacca
5101 ctgcagagct tcatgctgcg ggggtggtgt gtatgatgac cagtcgtagc aggagcgtg
5161 ggcgtggtgc ctaaaaatgt ctttcagtag caagctgatt gccaggggca ggcccttgg
5221 gtaagtgttt acaaagcgg taagctggga tgggtgcata cgtggggata tgagatgcat
5281 cttggactgt atttttaggt tggctatgtt cccagccata tccctccggg gattcatgtt
5341 gtgcagaacc accagcacag tgtatccggt gcacttgga aatttgtcat gtagcttaga
5401 aggaaatgcg tggagaact tggagacgcc cttgtgacct ccaagatttt ccatgcattc
5461 gtccataatg atggcaatgg gccacgggc ggcggcctgg gcgaagatat ttctgggatc
5521 actaacgtca tagttgtgtt ccaggatgag atcgatcatg gccattttta caaagcgcg
5581 gcggagggtg ccagactgcg gtataatggt tccatccggc ccaggggctg agttaccctc
5641 acagatttgc atttcccacg ctttgagttc agatgggggg atcatgtcta cctgcggggc
5701 gatgaagaaa accgtttccg gggtagggga gatcagctgg gaagaaagca ggttectaag
5761 cagctgcgac ttaccgcagc cgggtggccc gtaaatcaca cctattaccg gctgcaactg
5821 gtagttaaga gagctgcagc tgccgtcatc cctgagcagg ggggccactt cgttaagcat
5881 gtccctgact tgcattgttt cctgaccaa atccgccaga aggcgctcgc cggccagcga
5941 tagcagttct tgcaaggaag caaagttttt caacggtttg aggcgctccg ccgtaggcat
6001 gcttttgagc gtttgaccaa gcagttccag gcggtccac agctcggtca cgtgctctac
6061 ggcattctga tccagcatat ctctcgttt cgcgggttgg ggcggcttcc gctgtacggc
6121 agtagtcggt gctcgtccag acgggccagg gtcattgtct tccacgggcg cagggtcctc
6181 gtcagcgtag tctgggtcac ggtgaagggg tgcgtcccg gttgcgcgct ggccagggtg

```

FIG. 21A-2

WO 2006/020480

PCT/US2005/027658

39/126

6241 cgcttgaggc tggtcctgct ggtgctgaag cgctgcccgt cttcgccctg cgcgtcggcc
 6301 aggtagcatt tgaccatggt gtcatagtcc agccccctccg cggcgtggcc cttggcgcgc
 6361 agcttgccct tggaggaggc gccgcacgag gggcagtgca gacttttaag ggcgtagagc
 6421 ttgggcgcga gaaataccga ttccggggag taggcatccg cggcgcaggc cccgcagacg
 6481 gtctcgcatt ccacgagcca ggtgagctct ggccgttcgg ggtcaaaaac caggtttccc
 6541 ccatgctttt tgatgcgttt cttacctctg gtttccatga gccggtgtcc acgctcgggtg
 6601 acgaaaaggc tgtccgtgtc cccgtatata gacttgagag gcctgtcctc gagcgggtgtt
 6661 ccgcggtcct cctcgtatag aaactcggac cactctgaga cgaaggctcg cgtccaggcc
 6721 agcacgaagg aggctaagtg ggaggggtag cggctcgttg ccactagggg gtccactcgc
 6781 tccagggtgt gaagacacat gtcgccctct tcggcatcaa ggaagggtgat tggtttatag
 6841 gtgtaggcca cgtgaccggg tgttcctgaa ggggggctat aaaagggggg gggggcgcgt
 6901 tcgtcctcac tctcttccgc atcgtgtctc gcgagggcca gctgttgggg tgagtactcc
 6961 ctctcaaaag cgggcatgac ttctgcgcta agattgtcag tttccaaaaa cgaggaggat
 7021 ttgatattca cctggcccg cgtgatgcct ttgagggtgg ccgctccat ctggtcagaa
 7081 aagacaatct ttttgttgtc aagcttggtg gcaaacgacc cgtagagggc gttggacagc
 7141 aacttggcga tggagcgcag ggtttggttt ttgtcgcgat cggcgcgctc cttggccgcg
 7201 atgttttagc gcacgtatcc gcgcgcaacg caccgccatt cgggaaagac ggtggtgcgc
 7261 tcgtcgggca ctaggtgcac gcgccaaccg cggttgtgca gggtgacaag gtcaacgctg
 7321 gtggctacct ctccgcgtag gcgctcgttg gtccagcaga ggcggccgcc cttgcgcgag
 7381 cagaatggcg gtagtgggtc tagctgcgtc tcgtccgggg ggtctgcgtc cacggtaaag
 7441 accccgggca gcaggcgcgc gtcgaagtag tctatcttgc atccttgcaa gtctagcgc
 7501 tgctgccatg cgcgggcggc aagcgcgcgc tcgtatgggt tgagtggggg accccatggc
 7561 atgggggtggg tgagcgcgga ggcgtacatg ccgcaaattg cgtaaacgta gaggggctct
 7621 ctgagtattc caagatatgt agggtagcat cttccaccgc ggatgctggc gcgcacgtaa
 7681 tcgtatagtt cgtgcgaggg agcagaggag tcgggaccga ggttgctacg ggcgggctgc
 7741 tctgctcgga agactatctg cctgaagatg gcattgtagt tggatgatat ggttgagcgc
 7801 tgggaagacgt tgaagctggc gtctgtgaga cctaccgcgt cacgcacgaa ggaggcgtag
 7861 gagtgcgcga gcttgttgac cagctcggcg gtgacctgca cgtctagggc gcagtagtcc
 7921 agggtttcc tcatgatgtc atacttatcc tgtccctttt ttttccacag ctgcggttg
 7981 aggacaaact cttcgcggtc tttccagtac tcttgatcg gaaaccgctc ggcctccgaa
 8041 cggtaagagc ctagcatgta gaactgggtg acggcctggt aggcgcagca tcccttttct
 8101 acgggtagcg cgtatgcctg cgcggccttc cggagcagag tgtgggtgag cgcaaagggtg
 8161 tccctaacca tgactttgag gtactggtat ttgaagtcag tgtcgtcgca tccgccctgc
 8221 tcccagagca aaaagtccgt gcgctttttg gaacgcgggt ttggcagggc gaagggtgaca
 8281 tcgttgaaga gtatctttcc cgcgcgaggc ataaagtgtc gtgtgatgcg gaagggtccc
 8341 ggcacctcgg aacggttgtt aattacctgg gcggcgagca cgatctcgtc aaagccgttg
 8401 atgttgtggc ccacaatgta aagttccaag aagcgcggga tgcccttgat ggaaggcaat
 8461 tttttaagtt cctcgtaggt gagctcttca ggggagctga gcccggtgctc tgaaagggcc
 8521 cagtctgcaa gatgagggtt ggaagcgacg aatgagctcc acaggtcacg ggccattagc
 8581 atttgcaggt ggtcgcgaaa ggtcctaacc tggcgacctt tggccatttt ttctgggggtg
 8641 atgcagtaga aggtaagcgg gtcttgttcc cagcggctcc atccaaggctc cgcggctagg
 8701 tctcgcgcgg cggtcactag aggtcatct cccccaact tcatgaccag catgaagggc
 8761 acgagctgct tcccaaaggc ccccatccaa gtataggtct ctacatcgta ggtgacaaag
 8821 agacgctcgg tgcgaggatg cgagccgatc ggaagaact ggatctcccg ccaccagttg
 8881 gaggagtggc tgttgatgtg gtgaaagtag aagtccctgc gacgggcccga aactcgtgc
 8941 tggcttttgt aaaaacgtgc gcagtactgg cagcgggtgca cgggctgtac atcctgcacg
 9001 aggttgacct gacgaccgcg cacaaggaag cagagtggga atttgagccc ctgcctggc
 9061 gggtttggtt ggtggtcttc tacttcggct gcttgtcctt gaccgtctgg ctgctcaggg
 9121 ggagttacgg tggatcggac caccacgccg cgcgagccca aagtccagat gtccgcgcgc
 9181 ggcggtcggg gcttgatgac aacatcgcgc agatgggagc tgtccatggt ctggagctcc
 9241 cgcggcgtca ggtcaggcgg gagctcctgc aggtttacct cgcatagcgg ggtcaggggc
 9301 cgggctaggt ccaggtgata cctgatttcc aggggctggt tggtaggggc gtcgatggct
 9361 tgcaagaggc cgcacccccg cggcgcgact acggtagccg gcggcggggc gtgggcccgc
 9421 ggggtgtcct tggatgatgc atctaaaagc ggtgacgcgg gcgggccccg ggaggtaggg
 9481 ggggctcggg acccgccggg agaggggggca ggggcacgct ggcgcgcgcg gcgggcagga

FIG. 21A-3

WO 2006/020480

PCT/US2005/027658

40/126

```

9541 gctgggtgctg cgcgcgaggg ttgctggcga acgcgacgac gcggcggttg atctcctgaa
9601 tctggcgccct ctgcgtgaag acgacggggc cggtagagctt gaacctgaaa gagagtctga
9661 cagaatcaat ttcgggtgtcg ttgacggcgg cctggcgcaa aatctcctgc acgtctcctg
9721 agttgtcttg ataggcgatc tcggccatga actgctcgat ctcttctctc tggagatctc
9781 cgcgctccggc tcgctccacg gtggcgggcga ggtcgttgga gatgcggggc atgagctgcg
9841 agaaggcggt gaggcctccc tcgttccaga cgcggtgtga gaccacggcc ccttcggcat
9901 cgcgggcgcg catgaccacc tgcgcgagat tgagctccac gtgcccggcg aagacggcgt
9961 agtttcgcag gcgctgaaag aggtagttga gggtaggtggc ggtgtgttct gccacgaaga
10021 agtacataac ccagcgccgc aacgtggatt cgttgatatc cccaaggcc tcaaggcgct
10081 ccatggcctc gtagaagtcc acggcgaagt tgaaaaactg ggagttgcgc gccgacacgg
10141 ttaactctc ctccagaaga cggatgagct cggcgacagt gtcgcgcacc tcgcgtcaa
10201 aggctacagg ggctctctt tcttcttcaa tctcctcttc cataagggcc tccccttctt
10261 cttcttcttg cgcggtggg ggagggggga cacggcgggc acgacggcgc accgggaggg
10321 ggtcgacaaa gcgctcgatc atctccccgc ggcgacggcg catggtctcg gtgacggcgc
10381 ggccgttctc gcggggggcg agttggaaga cgccggccgt catgtcccgg ttatgggttg
10441 gcggggggct gccgtgcggc agggatacgg cgctaacgat gcattctaac aattgttgtg
10501 taggtactcc gccaccgagg gacctgagcg agtccgcac gaccggatcg gaaaacctct
10561 cgagaaaggc gtctaaccag tcacagtcgc aaggtaggct gagcacgtg gcggcgggca
10621 gcggcgggcg gtcgggggtg tttctggcgg aggtgctgct gatgatgtaa ttaaagtagg
10681 cggctctgag acggcggatg gtcgacagaa gcaccatgtc cttgggtccg gcctgctgaa
10741 tgcgcaggcg gtcggccatg cccaggtct cgttttgaca tcggcgagg tctttgtagt
10801 agtcttgcat gagcctttct accggcactt cttcttcttc ttcctcttgt cctgcatctc
10861 ttgcatctat cgctgcggcg gcggcgagg ttggccgtag gtggcgccct cttcctccca
10921 tgcgtgtgac cccgaagccc ctcatcggct gaagcagggc caggtcggcg acaacgcgt
10981 cggctaatat ggctgtctgc acctgcgtga gggtagactg gaagtcgtcc atgtccacaa
11041 agcgggtggt tgcgcccgtg ttgatgggtg aagtgcagtt ggccataacg gaccagttaa
11101 cggctctggt acccggtctg gagagctcgg tgtacctgag acgcgagtaa gcccttgagt
11161 caaagacgta gtcgttgcaa gtccgcacca ggtactggt tcccaccaa aagtgcggcg
11221 gcggctggcg gtagaggggc cagcgtaggg tggccggggc tccggggcg aggtcttcca
11281 acataaggcg atgatatccg tagatgtacc tggacatcca ggtgatgccg gcggcggtgg
11341 tggaggcgcg cggaaagtca cggacgcgg tccagatgtt gcgcagcggc aaaaagtgt
11401 ccatggtcgg gacgtcttgg ccggtcagg gcgcgcagtc gttgacgtc tagaccgtgc
11461 aaaaggagag cctgtaagcg ggcactcttc cgtggtctgg tggataaatt cgcaagggtg
11521 tcatggcgga cgaccgggt tccaacccg gatccggcg tccgcccgtg tccatgcgtt
11581 taccgcccgc gtgtcgaacc caggtgtgcg acgtcagaca acgggggagc gctccttttg
11641 gcttccttcc aggcgcggcg gatgctgcgc tagctttttt ggccactggc cgcgcgcggc
11701 gtaagcgggt aggttgaaa gcgaaagcat taagtggctc gctccctgta gccggagggt
11761 tattttccaa gggttgagtc gcgggacccc cggttcgagt ctcgggccgg ccggactgcg
11821 gcgaacgggg gtttgcctcc ccgtcatgca agaccccgt tgcataattc tccggaacaa
11881 gggacgagcc ccttttttgc ttttccaga tgcattccgt gctgcggcag atgcgcccc
11941 ctctcagca gcggcaagag caagagcagc ggcagacatg cagggcacc tcccctctc
12001 ctaccgcgtc aggaggggca acatccgcgg ctgacgcggc ggcagatggt gattacgaac
12061 ccccgcgcg ccggaccgg cactacttgg acttgaggga gggcgagggc ctggcgcggc
12121 taggagcgcc ctctcctgag cgacacccaa ggggtgcagct gaagcgtgac acgcgcgagg
12181 cgtacgtgcc gcggcagaac ctgtttcgcg accgcgagg agaggagccc gaggagatgc
12241 gggatcgaaa gttccatgca gggcgcgagt tgcggcatgg cctgaaccgc gagcggttgc
12301 tgcgcgagga ggactttgag cccgacgcgc ggaccgggat tagtcccgc cgcgcacacg
12361 tggcgggcgc cgacctggt accgcgtac agcagacggt gaaccaggag attaactttc
12421 aaaaaagctt taacaaccac gtgcgcacgc ttgtggcgcg cgaggagggt gctataggac
12481 tgatgcatct gtgggacttt gtaagcgcg tggagcaaaa ccaaatagc aagccgctca
12541 tggcgcgagt gttccttata gtgcagcaca gcagggacaa cgaggcattc agggatgcgc
12601 tgctaaacat agtagagccc gagggccgct ggctgctcga tttgataaac attctgcaga
12661 gcatagtggg gcaggagcgc agcttgagcc tggctgacaa ggtggccgcc attactatt
12721 ccatgctcag tctgggcaag ttttacgccc gcaagatata ccataccct tacgttccca
12781 tagacaagga ggtaaagatc gaggggttct acatgcgcac ggcgtgaag gtgcttacct

```

FIG. 21A-4

WO 2006/020480

PCT/US2005/027658

41/126

12841 tgagcgacga cctgggcggtt tatcgcaacg agcgcatcca caaggccgtg agcgtgagcc
12901 ggcggcgcgga gctcagcgac cgcgagctga tgcacagcct gcaaagggcc ctggctggca
12961 cgggcagcgg cgatagagag gccgagtcct actttgacgc gggcgctgac ctgcgctggg
13021 cccaagccg acgcgccctg gaggcagctg gggccggacc tgggctggcg gtggcaccgc
13081 cgcgcgctgg caacgtcggc ggcgtggagg aatatgacga ggacgatgag tacgagccag
13141 aggacggcga gtactaagcg gtgatgtttc tgatcagatg atgcaagacg caacggaccc
13201 ggcggtgcgg gcggcgctgc agagccagcc gtccggcctt aactccacgg acgactggcg
13261 ccaggtcatg gaccgcatca tgtcgctgac tgcgcgcaac cctgacgcgt tccggcagca
13321 gccgcaggcc aaccggctct ccgcaattct ggaagcgggtg gtcccggcgc gcgcaaacc
13381 cacgcacgag aaggtgctgg cgatcgtaaa cgcgctggcc gaaaacaggg ccatccggcc
13441 cgatgaggcc ggcctggtct acgacgcgt gcttcagcgc gtggctcgtt acaacagcag
13501 caacgtgcag accaacctgg accggctggg gggggatgtg cgcgaggccg tggcgacgcg
13561 tgagcgcgcg cagcagcagg gcaacctggg ctccatgggt gactaaacg ccttcctgag
13621 tacacagccc gccaacgtgc cgcggggaca ggaggactac accaactttg tgagcgact
13681 gcggctaata gtgactgaga caccgcaaag tgagggtgat cagtccgggc cagactatct
13741 tttccagacc agtagacaag gcctgcagac cgtaaacctg agccaggctt tcaagaactt
13801 gcaggggctg tgggggggtg gggctcccac aggcgaccgc gcgaccgtgt ctagcttgct
13861 gacgccaac tcgcgcctgt tgctgctgct aatagcgccc ttcacggaca gtggcagcgt
13921 gtcccgggac acatacctag gtcacttgct gacactgtac cgcgaggcca taggtcaggc
13981 gcatgtggac gagcatactt tccaggagat tacaagtgtt agccgcgcgc tggggcagga
14041 ggacacgggc agcctggagg caacctgaa ctacctgtg accaaccggc ggcaaaaaat
14101 cccctcgttg cacagttaa acagcgagga ggagcgcat ttcgctatg tgcagcagag
14161 cgtgagcctt aacctgatgc gcgacggggt aacgccagc gtggcgctgg acatgaccgc
14221 gcgcaacatg gaaccgggca tgtatgcctc aaaccggccg tttatcaatc gcctaattga
14281 ctacttgcac cgcgcggcgc ccgtgaacct cgagtatttc accaatgcca tcttgaacct
14341 gcaactggcta ccgccccctg gtttctacac cgggggattc gaggtgcccg agggtaacga
14401 tggattcctc tgggacgaca tagacgacag cgtgttttcc ccgcaaccgc agacctgct
14461 agagttgcaa caacgcgagc aggcagaggc ggcgctgcga aaggaaagct tccgcaggcc
14521 aagcagcttg tccgatctag gcgctgcggc cccgcggtca gatgctagta gccatttcc
14581 aagcttgata ggggtctctta ccagcactcg caccacccgc ccgcgcctgc tgggcgagga
14641 ggagtaccta aacaactcgc tgctgcagcc gcagcgcgaa agaacctgc ctccggcgtt
14701 tccaacaac gggatagaga gcctagtggg caagatgagt agatggaaga cgtatgcgca
14761 ggagcacagg gatgtgcccg gccgcgccc gccacccgt cgtcaaaggc acgaccgtca
14821 gcgggggtctg gtgtgggagg acgatgactc ggcagacgac agcagcgtct tggatttggg
14881 agggagtggc aaccctgttg cacaccttcg cccaggctg gggagaatgt tttaaaaaa
14941 gcatgatgca aaataaaaaa ctcaccaagg ccatggcacc gagcgttggg tttcttgat
15001 tccccttagt atgcggcgcg cggcgatgta tgaggaaagg cctcctccct cctacgagag
15061 cgtggtgagc gcggcgccag tggcgggcgg gctgggttca cccttcgatg ctcccctgga
15121 cccgcggttc gtgcctccgc ggtacctgcg gcctaccggg gggagaaaca gcatccgtta
15181 ctctgagttg gcacccctat tcgacaccac ccgtgtgtac cttgtggaca acaagtcaac
15241 ggatgtggca tccctgaact accagaacga ccacagcaac tttctaacca cggtcattca
15301 aaacaatgac tacagcccgg gggaggcaag cacacagacc atcaatcttg acgaccgtc
15361 gcaactggggc ggcgacctga aaaccatcct gcataccaac atgcaaatg tgaacgagtt
15421 catgtttacc aataagttta aggcgcgggt gatggtgtcg cgctcgctta ctaaggacaa
15481 acaggtggag ctgaaatacg agtgggtgga gttcacgctg cccgagggca actactccga
15541 gaccatgacc atagacctta tgaacaacgc gatcgtggag cactacttga aagtgggag
15601 gcagaacggg gttctggaaa gcgacatcgg ggtaaagttt gacacccgca acttcagact
15661 ggggtttgac ccagtcactg gtcttgtcat gcctggggta tatacaaacg aagccttcca
15721 tccagacatc attttgctgc caggatgcgg ggtggacttc accacagacc gcctgagcaa
15781 cttgttgggc atccgcaagc ggcaaccctt ccaggagggc tttaggatca cctacgatga
15841 cctggagggt ggtaacattc ccgcaactgt ggatgtggac gcctaccagg caagcttgaa
15901 agatgacacc gaacagggcg ggggtggcgc aggcggcggc aacaacagtg gcagcgcgcc
15961 ggaagagAAC tccaacgcgg cagctgcggc aatgcagccg gtggaggaca tgaacgatca
16021 tgccattcgc ggcgacacct ttgccacacg ggcggaggag aagcgcgctg aggcgaggc
16081 agcggccgaa gctgccgccc ccgctgcgga ggctgcacaa cccgagggtcg agaagcctca

FIG. 21A-5

42/126

```

16141 gaagaaaccg gtgattaaac ccctgacaga ggacagcaag aaacgcagtt acaacctaata
16201 aagcaatgac agcaccttca cccagtaccg cagctggtac cttgcataca actacggcga
16261 ccctcaggcc gggatccgct catggaccct gctttgcact cctgacgtaa cctgaggctc
16321 ggagcaggta tactgggtcgt tgcccacat gatgcaagac cccgtgacct tccgctccac
16381 ggcgcagatc agcaactttc cgggtggtggg cgcgcagctg ttgcccgtgc actccaagag
16441 cttctacaac gaccaggccg tctactccca gctcatccgc cagtttacct ctctgaccca
16501 cgtgttcaat cgctttcccg agaaccagat tttggcgcgc ccgccagccc ccaccatcac
16561 caccgtcagt gaaaacgttc ctgctctcac agatcacggg acgctaccgc tgcgcaacag
16621 catcggagga gtccagcgag tgaccattac tgacgccaga cgccgcacct gccctacgt
16681 ttacaaggcc ctgggcatag tctcgccgcg cgtcctatcg agccgcactt tttgagcaag
16741 catgtccatc cttatatcgc ccagcaataa cacaggctgg ggcctgcgct tcccaagcaa
16801 gatgtttggc ggggccaaga agcgtccga ccaacaccca gtgcgcgtgc gcgggcaacta
16861 ccgcgcgccc tggggcgcgc acaaacgcgg ccgactggg cgaccaccg tcgatgacgc
16921 catcgacgcg gtggtggagg aggcgcgcaa ctacacgccc acgcgcgcgc cagtgtccac
16981 cgtggacgcg gccattcaga ccgtggtgcg cggagcccg cgctacgcta aatgaagag
17041 acggcggagg cgcgtagcac gtgcgccacc ccgcccagccc ggcactgccg cccaacgcgc
17101 ggcggcggcc ctgcttaacc gcgcacgtcg caccggccga cgggcggcca tgcgagccgc
17161 tcgaaggctg gccgcgggta ttgtcactgt gccccccagg tccaggcgac gagcggccgc
17221 cgcagcagcc gcggccatta gtgctatgac tcagggtcgc aggggcaacg tgtactgggt
17281 gcgcgactcg gttagcggcc tgcgcgtgcc cgtgcgcacc cgccccccgc gcaactagat
17341 tgcaataaaa aactacttag actcgtactg ttgtatgtat ccagcggcgg cggcgcgcac
17401 cgaagctatg tccaagcgca aaatcaaaga agagatgctc caggtcatcg cgccggagat
17461 ctatggcccc ccgaagaagg aagagcagga ttacaagccc cgaaagctaa agcgggtcaa
17521 aaagaaaaag aaagatgatg atgatgatga acttgacgac gaggtggaac tgttgacgc
17581 gaccgcgccc aggcgacggg tacagtggaa aggtcgacgc gtaagacgtg ttttgcgacc
17641 cggcaccacc gtagtcttta cgcccgggtg gcgctccacc cgcacctaca agcgcgtgta
17701 tgatgaggtg tacggcgacg aggacctgct tgagcaggcc aacgagcgcc tcggggagtt
17761 tgcctacgga aagcggcata aggacatgct ggcgttgccg ctggacgagg gcaaccaaac
17821 acctagccta aagcccgtga cactgcagca ggtgctgccc gcgcttgac cgtccgaaga
17881 aaagcgcggc ctaaagcgcg agtctggtga cttggcacc accgtgcagc tgatggtacc
17941 caagcgtcag cgactggaag atgtcttgga aaaaatgacc gtggagcctg ggctggagcc
18001 cgaggtccgc gtgcggccaa tcaagcaggt ggcaccggga ctgggcgtgc agaccgtgga
18061 cgttcagata cccaccacca gtagcactag tattgccact gccacagagg gcatggagac
18121 acaaacgtcc ccggttgctt cggcggtggc agatgccgcg gtgcaggcgg ccgctgcggc
18181 cgcgtccaag acctctacgg aggtgcaaac ggaccctgg atgtttcgtg tttcagcccc
18241 ccggcgtccg cgccgttcaa ggaagtacgg cgccgccagc gcgctactgc ccgaatatgc
18301 cctacatcct tccatcgcg ctaaccccg ctatcgtggc tacacctacc gccccagaag
18361 acgagcaact acccgacgccc gaaccaccac tggaaaccgc cgccgcccgc gccgtcgcca
18421 gcccggtgctg gccccgattt ccgtgcgcag ggtggctcgc gaaggaggca ggaccctggt
18481 gctgccaaca gcgcgtacc accccagcat cgtttaaaag ccggtctttg tggttcttgc
18541 agatatggcc ctcacctgcc gcctccgttt cccgggtgcc ggattccgag gaagaatgca
18601 ccgtaggagg ggcattggcc gccacggcct gacgggcggc atgcgtcgtg cgcaccaccg
18661 gcggcggcgc gcgtgcacc gtgcgatgcg cggcggtatc ctgccccctc ttattccact
18721 gatcgccgcg gcgattggcg ccgtgcccgg aattgcatcc gtggccttgc aggcgcagag
18781 aactgatta aaaacaagtt acatgtggaa aaatcaaaat aaaagtctgg actctcacgc
18841 tcgcttggtc ctgtaactat tttgtagaat ggaagacatc aactttgct cactggcccc
18901 gcgacacggc tcgcgcccgt tcatgggaaa ctggcaagat atcggcacca gcaatatgag
18961 cgggtggcgc ttcagctggg gctcgtgtg gagcggcatt aaaaatttcg gttccgcccgt
19021 taagaactat ggcagcaaag cctggaacag cagcacaggc cagatgctga gggacaagtt
19081 gaaagagcaa aatttccaac aaaagggtgg agatggcctg gcctctggca ttagcggggt
19141 ggtggacctg gccaaaccagg cagtgcacaa taagattaac agtaagcttg atccccgccc
19201 tcccgtagag gagcctccac cggccgtgga gacagtgtct ccagaggggc gtggcgaaaa
19261 gcgtccgcga cccgacaggg aagaaactct ggtgacgcaa atagacgagc ctccctcgta
19321 cgaggaggca ctaaagcaag gcctgccacc caccgtccc atcgcgcca tggctaccgg
19381 agtgcgtggc cagcacacac ccgtaacgct ggacctgcct cccccgcgc acaccagca

```

FIG. 21A-6

WO 2006/020480

PCT/US2005/027658

43/126

```

19441 gaaacctgtg ctgccagggc cgtccgccgt tgttgtaacc cgtcctagcc gcgcgtccct
19501 gcgcccgcgc gccagcggtc cgcgatcggt gcggcccgtg gccagtggca actggcaaag
19561 cacactgaac agcatcgtgg gtttgggggt gcaatccctg aagcgccgac gatgcttctg
19621 atagctaacg tgtcgatatg gtgtcatgta tgcgtccatg tcgccgccag aggagctgct
19681 gagccgcccgc gcgcccgcct tccaagatgg ctaccccttc gatgatgccg cagtggctct
19741 acatgcacat ctccgggccag gacgcctcgg agtacctgag ccccgggctg gtgcagttcg
19801 cccgcgccac cgagacgtac ttcagcctga ataacaagtt tagaaacccc acggtggcgc
19861 ctacgcacga cgtgaccaca gaccggtctc agcgtttgac gctgcggttc atccccgtgg
19921 accgcgagga tactgcgtag tcgtacaagg cgcggttcac cctagctgtg ggtgataacc
19981 gtgtgctaga catggcttcc acgtactttg acatccgcgg cgtgctggac agggggcccta
20041 cttttaagcc ctactctggc actgcctaca acgcactggc cccaaggggt gcccacaact
20101 cgtgcgagtg ggaacaaaat gaaactgcac aagtggatgc tcaagaactt gacgaagagg
20161 agaatgaagc caatgaagct caggcgcgag aacaggaaca agctaagaaa acccatgtat
20221 atgcccaggc tccactgtcc ggaataaaaa taactaaaga aggtctacaa ataggaactg
20281 ccgacgccac agtagcaggt gccggcaaag aaattttcgc agacaaaact tttcaacctg
20341 aaccacaagt aggagaatct caatggaacg aagcggatgc cacagcagct ggtggaaggg
20401 ttcttaaaaa gacaactccc atgaaaccct gctatggctc atacgctaga cccaccaatt
20461 ccaacggcgg acagggcggt atgggtgaac aaaatggtaa attggaaagt caagtcgaaa
20521 tgcaattttt ttccacatcc acaaatgcc acaatgaagt taacaatata caaccaacag
20581 ttgtattgta cagcgaagat gtaaaccatg aaactccaga tactcatctt tcttataaac
20641 ctaaaatggg ggataaaaat gccaaagtca tgcttggaac acaagcaatg ccaaacagac
20701 caaattacat tgctttttaga gacaatttta ttggtctcat gtattacaac agcacaggta
20761 acatgggtgt ccttgctggg caggcatcgc agttgaacgc tgttgtagat ttgcaagaca
20821 gaaacacaga gctgtcctac cagcttttgc ttgattcaat tggcgacaga acaagatact
20881 tttcaatgtg gaatcaagct gttgacagct atgatccaga tgtcagaatt attgagaacc
20941 atggaactga ggatgagttg ccaaattatt gctttcctct tgggtggaatt gggattactg
21001 acacttttca agctgttaaa acaactgctg ctaacgggga ccaaggcaat actacctggc
21061 aaaaagattc aacatttgca gaacgcaatg aaataggggt gggaaataac tttgccatgg
21121 aaattaacct gaatgccaac ctatggagaa atttccttta ctccaatatt gcgctgtacc
21181 tgccagacaa gctaaaatac aaccccacca atgtggaaat atctgacaac cccaacacct
21241 acgactacat gaacaagcga gtgggtggctc ctgggcttgt agactgctac attaaccttg
21301 gggcgcgctg gtctctggac tacatggaca acgttaatcc ctttaaccac caccgcaatg
21361 cgggcctgcg ttaccgctcc atgttggttg gaaacggccg ctacgtgccc tttcacattc
21421 aggtgcccc aaggtttttt gccattaaaa acctcctcct cctgccaggc tcatacacat
21481 atgaatggaa cttcaggaag gatgttaaca tgggtctgca gagctctctg ggaaacgacc
21541 ttagagttga cggggctagc attaagtttg acagcatttg tctttacgcc accttcttcc
21601 ccatggccca caacacggcc tccacgctgg aagccatgct cagaaatgac accaacgacc
21661 agtcctttaa tgactacctt tccgcgcga acatgctata tcccataccc gccaacgcca
21721 ccaacgtgcc catctccatc ccatcgcgca actgggcagc atttcgcggt tgggccttca
21781 cacgcttgaa gacaaaaggaa accccttccc tgggatcagg ctacgacctt tactacacct
21841 actctggctc cataccatac cttgacggaa ccttctatct taatcacacc tttagaagg
21901 tggccattac ttttgactct tctgttagct ggccgggcaa cgaccgcctg cttactccca
21961 atgagtttga gattaagcgc tcagttgacg gggagggcta taacgtagct cagtgaaca
22021 tgacaaagga ctggttccta gtgcagatgt tggccaacta caatattggc taccagggct
22081 tctacattcc agaaagctac aaagaccgca tgtactcgtt cttcagaaac ttccagccca
22141 tgagccggca agtggtggac gatactaaat acaaagatta tcagcaggtt ggaattatcc
22201 accagcataa caactcaggc ttcgtaggct acctcgctcc caccatgcgc gagggacaag
22261 cttaccccg c taatgttccc taccactaa taggcaaaac cgcggttgat agtattacc
22321 agaaaaagtt tctttgcgac cgcaccctgt ggcgcacccc cttctccagt aactttatgt
22381 ccatgggtgc gctcacagac ctgggccaac accttctcta cgcaaactcc gccacgcgc
22441 tagacatgac ctttgaggtg gatcccatgg acgagccac ccttctttat gttttgtttg
22501 aagtctttga cgtggtccgt gtgcaccagc cgcaccgcgg cgtcatcgag accgtgtacc
22561 tgcgcacgcc cttctcggcc ggcaacgcca caacataaag aagcaagcaa catcaacaac
22621 agctgccgcc atgggctcca gtgagcagga actgaaagcc attgtcaaag atcttggttg
22681 tgggccatat tttttgggca cctatgacaa gcgcttccca ggctttgttt cccacacaa

```

FIG. 21A-7

44/126

22741 gctcgcctgc gccatagtta acacggccgg tcgcgagact gggggcggtac actggatggc
22801 ctttgcctgg aaccgcgct caaaaacatg ctacctcttt gagccctttg gcttttctga
22861 ccaacgtctc aagcaggttt accagtttga gtacgagtca ctcctgcgcc gtagcgccat
22921 tgcctcttcc cccgaccgct gtataacgct ggaaaagtcc acccaaagcg tgcaggggcc
22981 caactcggcc gcctgtggcc tattctgctg catgtttctc cagccctttg ccaactggcc
23041 ccaaactccc atggatcaca accccacat gaaccttatt accggggtac ccaactccat
23101 gcttaacagt cccaggtac agcccaccct gcgcgcgaac caggaacagc tctacagctt
23161 cctggagcgc cactcgcctt acttccgcag ccacagtgcg caaattagga gcgccacttc
23221 tttttgtcac ttgaaaaaca tgtaaaaata atgtactagg agacactttc aataaaggca
23281 aatgttttta tttgtacact ctccgggtgat tatttaccct cacccttgcc gtctgcgccg
23341 tttaaaaatc aaaggggttc tgccgcgcat cgctatgcgc cactggcagg gacacgttgc
23401 gatactggtg tttagtgtc cacttaaaact caggcacaac catccgcggc agctcgggtga
23461 agtttttact ccacaggctg cgcaccatca ccaacgcgtt tagcaggctg ggcgccgata
23521 tcttgaagtc gcagttgggg cctccgccct gcgcgcgcga gttgcgatac acagggttac
23581 agcactggaa cactatcagc gccgggtggt gcacgctggc cagcacgctc ttgtcggaga
23641 tcagatccgc gtccaggctc tccgcgttgc tcagggcgaa cggagtcaac tttggtagct
23701 gccttcccaa aaaggggtgca tgcccaggct ttgagttgca ctgcgaccgt agtggcatca
23761 gaaggtgacc gtgcccagtc tgggcgttag gatacagcgc ctgcatgaaa gccttgatct
23821 gcttaaaagc cacctgagcc tttgcgcctt cagagaagaa catgccgcaa gacttgccgg
23881 aaaactgatt ggccggacag gccgcgtcat gcacgcagca ccttgcgctc gtgttgagga
23941 tctgcaccac atttcggccc caccggttct tcacgatctt ggccttgcta gactgtcctt
24001 tcagcgcgcg ctgcccgttt tcgctcgtca catccatttc aatcacgtgc tccttattta
24061 tcataatgct cccgtgtaga cacttaagct cgccttcgat ctcagcgcag cgggtgcagcc
24121 acaacgcgca gcccggtggc tcgtggtgct tgtaggttac ctctgcaaac gactgcaggt
24181 acgcctgcag gaatcgcccc atcatcgtca caaaggtctt gttgctggtg aaggtcagct
24241 gcaaccgcgc gtgctcctcg tttagccagg tcttgcatat ggcgcgcaga gcttccactt
24301 ggtcaggcag tagcttgaag tttgccttta gatcgttatc cacgtggtac ttgtccatca
24361 acgcgcgcgc agcctccatg ccttctctcc acgcagacac gatcggcagg ctcagcgggt
24421 ttatcacctg gctttcactt tccgcttcac tggactcttc ctttctctct tgcacccgca
24481 taccgcgcgc cactgggtcg tcttcattca gccgcgcac cgtgcgctta cctcccttgc
24541 cgtgcttgat tagcacgggt ggttgctga aaccacatc ttgtagcgc acatcttctc
24601 tttcttctc gctgtccacg atcacctctg gggatggcgg gcgctcgggc ttgggagagg
24661 ggcgcttctt tttctttttg gacgcaatgg ccaaateccg cgtcgaggtc gatggccgcg
24721 ggctgggtgt gcgcggcacc agcgcctctt gtgacgagtc ttcttcgtcc tcggactcga
24781 gacgcgcctt cagccgcttt tttgggggcg cgcggggagg cggcggcgac ggcgacgggg
24841 acgagacgtc ctccatgggt ggtggacgtc gcgcgcacc gcgtccgcgc tcgggggtgg
24901 tttcgcgctg ctctcttctc cgactggcca tttcttctc ctataggcag aaaaagatca
24961 tggagtcagt cgagaaggag gacagcctaa ccgccccctt tgagttcgcc accaccgctt
25021 ccaccgatgc cgccaacgcg cctaccacct tccccgtcga ggcacccccg cttgaggagg
25081 aggaagtgat tatcgagcag gaccaggtt ttgtaagcga agacgacgaa gatcgtcag
25141 taccaacaga ggataaaaag caagaccagg acgacgcaga ggcaaacgag gaacaagtgc
25201 ggcgggggga ccaaaggcat ggcgactacc tagatgtggg agacgacgtg ctggtgaagc
25261 atctgcagcg ccagtgcgcc attatctgct acgcgttgca agagcgcagc gatgtgcccc
25321 tcgccatagc ggatgtcagc cttgcctacg aacgccacct gttctcaccg cgcgtacccc
25381 ccaaacgcca agaaaacggc acatgcgagc ccaaccgcg cctcaacttc taccctgtat
25441 ttgccgtgcc agaggtgctt gccacctatc acatcttttt ccaaaactgc aagatacccc
25501 tatcctgccg tgccaaccgc agccgagcgg acaagcagct ggccttgccg cagggcgctg
25561 tcatacctga tatcgctcgt ctgcaggaag tgccaaaaat ctttgagggt cttggacgcg
25621 acgagaagcg cgcggcaaac gctctgcaac aagaaaacag cgaaaatgaa agtcactgtg
25681 gagtgctggt ggaacttgag ggtgacaacg cgcgcctagc cgtgctgaaa cgcagcatcg
25741 aggtcaccca ctttgcctac ccggcactta acctaccccc caaggttatg agcacagtca
25801 tgagcgagct gatcgtgcgc cgtgcacgac ccctggagag ggatgcaaac ttgcaagaac
25861 aaaccgagga gggcctaccc gcagttggcg atgagcagct ggcgcgctgg cttgagacgc
25921 gcgagcctgc cgacttggag gagcgacgca agctaataat ggccgcagtg cttgttaccg
25981 tggagcttga gtgcatgcag cggttctttg ctgacccgga gatgcagcgc aagctagagg

FIG. 21A-8

45/126

```

26041 aaacgttgca ctacaccttt cgccagggct acgtgcgcca ggccctgcaaa atttccaacg
26101 tggagctctg caacctgggc tcctaccttg gaattttgca cgaaaaccgc cttgggcaaa
26161 acgtgcttca ttccacgctc aaggcgagg cgccgcgca ctacgtccgc gactgctttt
26221 acttatttct gtgctacacc tggcaaaccg ccatgggcgt gtggcagcag tgcctggagg
26281 agcgcaacct gaaggagctg cagaagctgc taaagcaaaa cttgaaggac ctatggacgg
26341 ccttcaacga gcgctccgtg gccgcgcacc tggcggacat tatcttcccc gaacgcctgc
26401 ttaaaacctt gcaacagggg ctgccagact tcaccagtca aagcatgttg caaaacttta
26461 ggaactttat cctagagcgt tcaggaattc tgcccgcac ctgctgtgcg cttcctagcg
26521 actttgtgcc cattaagtac cgtgaatgcc ctccgcgct ttggggtcac tgctaccttc
26581 tgcagctagc caactacctt gcctaccact ccgacatcat ggaagacgtg agcggtgacg
26641 gcctactgga gtgtcactgt cgctgcaacc tatgcacccc gcaccgctcc ctgggtctgca
26701 attcacaact gcttagcgaa agtcaaatta tcggtacctt tgagctgcag ggtccctcgc
26761 ctgacgaaaa gtccgcggct ccgggggtga aactcactcc ggggctgtgg acgtcggctt
26821 accttcgcaa atttgtacct gaggactacc acgcccacga gattaggttc tacgaagacc
26881 aatccccgcc gccaaatgcg gagcttaccg cctgcgtcat taccaggggc cacatccttg
26941 gccaattgca agccattaac aaagcccgcc aagagtttct gctacgaaag ggacgggggg
27001 tttacttgga ccccagtcg ggcgaggagc tcaacccaat cccccgcgc ccgcagccct
27061 atcagcagcc gcgggcccct gcttcccagg atggcaccca aaaagaagct gcagctgccg
27121 ccgcccgcac ccacggacga ggaggaatac tgggacagtc aggcagagga ggttttggac
27181 gaggaggagg agatgatgga agactgggac agcctagacg aggaagcttc cgaggccgaa
27241 gaggtgtcag acgaaacacc gtcaccctcg gtcgcattcc cctcgccggc gcccagaaa
27301 tcggcaaccg ttcccagcat tgctacaacc tccgctcctc aggcgcgcgc ggcaactgcc
27361 gttcgccgac ccaaccgtag atgggacacc actggaacca gggccggtaa gtctaagcag
27421 ccgcccgcgt tagcccaaga gcaacaacag cgccaaggct accgctcgtg gcgcgtgcac
27481 aagaacgcca tagttgcttg cttgcaagac tgtgggggca acatctcctt cgcccgcgc
27541 tttcttctct accatcacgg cgtggccttc ccccgtaaca tctgcatta ctaccgtcat
27601 ctctacagcc cctactgcac cggcggcagc ggcagcaaca gcagcgcca cgcagaagca
27661 aaggcgaccg gatagcaaga ctctgacaaa gcccaagaaa tccacagcgg cggcagcagc
27721 aggaggagga gcactgcgtc tggcgcccaa cgaacccgta tcgaccgcgc agcttagaaa
27781 caggattttt cccactctgt atgctatatt tcaacagagc aggggccaag aacaagagct
27841 gaaaataaaa aacaggcttc tgcgctccct caccgcagc tgctgtatc aaaaagcga
27901 agatcagctt cggcgcacgc tgggaagacg ggaggctctc ttcagcaa atctgcgcgt
27961 gactcttaag gactagtctt gcgcctttc tcaaatttaa gcgcgaaaac tacgtcatct
28021 ccagcgcca caccgcgc cagcacctgt cgtcagcgcc attatgagca aggaaattcc
28081 cacgccctac atgtggagtt accagccaca aatgggactt gcggctggag ctgccaaga
28141 ctactcaacc cgaataaact acatgagcgc gggacccac atgatatccc ggtcaacgg
28201 aatccgcgc caccgaaacc gaattctcct cgaacaggcg gctattacca ccacacctcg
28261 taataacctt aatccccgta gttggccgc tgccctggtg taccaggaaa gtcccgtcc
28321 caccactgtg gtacttcca gagacgcca ggccgaagtt cagatgacta actcaggggc
28381 gcagcttgcg ggcggctttc gtcacagggg gcggctcgcc gggcagggtg taactcacct
28441 gaaaatcaga gggcgaggta ttcagctcaa cgacgagtcg gtgagctcct ctcttggtct
28501 ccgtccggac gggacatttc agatcgcgcg cgctggccgc tcttcattta cgcccgtca
28561 ggcgatccta actctgcaga cctcgtcctc ggagccgcgc tccggaggca ttggaactct
28621 acaatttatt gaggagttcg tgccttcggt ttacttcaac ccttttctg gacctcccg
28681 ccactaccg gaccagttta tteccaactt tgacgcggta aaagactcgg cggacggcta
28741 cgactgaatg accagtggag aggcagagca actgcgcctg acacacctcg accactgccg
28801 ccgccacaag tgctttgccc gcggctccgg tgagttttgt tactttgaat tgcccgaaga
28861 gcatatcgag ggcccggcgc acggcgccg gctcaccacc caggtagagc ttacacgtag
28921 cctgattcgg gagtttacca agcgcacctt gctagtggag cgggagcggg gtccctgtgt
28981 tctgaccgtg gtttgcaact gtcctaacc tggattacat caagatcttt gttgtcatct
29041 ctgtgctgag tataataaat acagaaatta gaatctactg gggctcctgt cgccatcctg
29101 tgaacgccac cgtttttacc caccaaaagc agaccaaagc aaacctcacc tccggtttgc
29161 acaagcgggc caataagtac cttacctggt actttaacgg ctcttcattt gtaatttaca
29221 acagtttcca gcgagacgaa gtaagtttgc cacacaacct tctcggtctc aactacaccg
29281 tcaagaaaaa caccaccacc accctcctca cctgccggga acgtacgagt gcgtcaccgg

```

FIG. 21A-9

46/126

```

29341 ttgctgcgcc cacacctaca gcctgagcgt aaccagacat tactcccatt ttcccaaac
29401 aggaggtgag ctcaactccc ggaactcagg tcaaaaaagc attttgcggg gtgctgggat
29461 tttttaatta agtatatgag caattcaagt aactctacaa gcttgtctaa ttttctgga
29521 attggggtcg gggttatcct tactcttgta attctgttta ttcttatact agcacttctg
29581 tgccttaggg ttgccgcctg ctgcacgcac gtttgtacct attgtcagct ttttaaacgc
29641 tgggggcgac atccaagatg aggtacatga ttttaggctt gctcgccctt gcggcagtct
29701 gcagcgctgc caaaaagggt gagtttaagg aaccagcttg caatgttaca tttaaatcag
29761 aagctaata gaatgcactact cttataaaat gcaccacaga acatgaaaag cttattattc
29821 gccacaaaga caaaattggc aagtatgctg tatatgctat ttggcagcca ggtgacacta
29881 acgactataa tgtcacagtc ttccaagggtg aaaatcgtaa aacttttatg tataaatttc
29941 cattttatga aatgtgcgat attaccatgt acatgagcaa acagtacaag ttgtggcccc
30001 cacaaaagtg tttagagaac actggcacct tttgttccac cgctctgctt attacagcgc
30061 ttgcttttgt atgtacctta ctttatctca aatacaaaaag cagacgcagt tttattgatg
30121 aaaagaaaat gccttgattt tccgcttgct tgtattcccc tggacaattt actctatgtg
30181 ggatatgcgc caggcgggaa agattatacc cacaaccttc aaatcaaact ttctgggacg
30241 ttagcgcttg acttctgcca gcgctgcac tgcaaatttg atcaaacca gcttcagctt
30301 gcctgctcca gagatgaccg gctcaaccat cgcgcccaac acggactatc gcaacaccac
30361 tgctaccgga ctaaaatctg ccctaaattt accccaagtt catgcctttg tcaatgactg
30421 ggcgagcttg ggcattgtgt ggttttccat agcgcttatg tttgtttgcc ttattattat
30481 gtggcttatt tgttgcttaa agcgagacg cgccagacct cccatctata ggcctatcat
30541 tgtgctcaac ccacacaatg aaaaaattca tagattggac ggtctcaaac catgttctct
30601 tcttttacag tatgattaaa tgagacatga ttctctgagt ccttatatta ttgaccttg
30661 ttgcgctttt ctgtgcgtgc tctacattgg ctgcggtcgc tcacatcgaa gtagattgca
30721 tcccaccttt cacagtttac ctgctttacg gatttgtcac ccttatcttc atctgcagcc
30781 tcgtcactgt agtcatcgcc ttcattcagt tcattgactg gatttgtgtg cgcattgcgt
30841 accttaggca ccatccgcaa tacagagaca ggactatagc tgatcttctc agaattcttt
30901 aattatgaaa cggattgtca cttttgtttt gctgattttc tgcgccttac ctgtgctttg
30961 ctcccaaacc tcagcgcttc ccaaagaca tatttctctg agattcactc aaatatggaa
31021 cattcccagc tgctacaaca aacagagcga tttgtcagaa gcctgggtat acgccatcat
31081 ctctgtcatg gttttttgca gtaccatttt tgccctagcc atatacccat accttgacat
31141 tggttggaat gccatagatg ccatgaacca ccctactttc ccagcgccca atgtcatacc
31201 actgcaacag gttattgccc caatcaatca gcctcgcccc ccttctccca cccccactga
31261 gattagctac tttaatttga cagggtggaga tgactgaatc tctagatcta gaattggatg
31321 gaattaacac cgaacagcgc ctactagaaa ggcgcaaggc ggcgtccgag cgagaacgcc
31381 taaaacaaga agttgaagac atggttaacc tgcaccagtg taaaagaggt atcttttgtg
31441 tggtaagca ggccaaactt acctacgaaa aaaccactac cggcaaccgc cttagctaca
31501 agctaccac ccagcgccaa aaactgggtg ttatgggtgg agaaaaacct atcacgctca
31561 cccagcactc ggcagaaaca gaaggctgcc tgcacttccc ctatcagggt ccagaggacc
31621 tctgcactct tattaaaacc atgtgtggca ttagagatct tattccattc aactaacaat
31681 aaacacacaa taaattactt acttaaaatc agtcagcaaa tctttgtcca gcttattcag
31741 catcacctcc tttccctcct cccaactctg gtatttcage agccttttag ctgcgaactt
31801 tctccaaagt ctaaatggga tgtcaaattc ctcatgttct tgtccctccg caccactat
31861 cttcatattg ttgcagatga aacgcgccag accgtctgaa gacaccttca accctgtgta
31921 cccatattgac acggaaaccg gccctccaac tgtgcctttc cttacccttc cctttgtgtc
31981 gccaaatggg ttccaagaaa gtcccccg agtgctttct ttgcgtcttt cagaaccttt
32041 ggtaacctca caggcatgc ttgcgctaaa aatgggcagc ggcctgtccc tggatcaggc
32101 aggcaacctt acatcaaata caatcactgt ttctcaaccg ctaaaaaaa caaagtccaa
32161 tataactttg gaaacatccg cgcctcttac agtcagctca ggcgccttaa ccatggccac
32221 aacttcgctt ttggtggtct ctgacaacac tcttaccatg caatcacaag caccgctaac
32281 cgtgcaagac tcaaaactta gcattgctac caaagagcca cttacagtgt tagatggaaa
32341 actggccctg cagacatcag cccccctctc tgccactgat aacaacgccc tcactatcac
32401 tgcctcacct cctcttacta ctgcaaatgg tagtctggct gttaccatgg aaaaccact
32461 ttacaacaac aatggaaaac ttgggctcaa aattggcggt cctttgcaag tggccaccga
32521 ctcacatgca ctaacactag gtactgggtc gggggttgca gttcataaca atttgctaca
32581 tacaaaagtt acaggcgcaa tagggtttga tacatctggc aacatggaac ttaaaactgg

```

FIG. 21A-10

47/126

32641 agatggcctc tatgtggata ggcgcgggtcc taacccaaaa ctacatatta atctaaatac
32701 cacaaaaggc cttgctttttg acaacaccgc aataacaatt aacgctggaa aagggttgga
32761 atttgaaaca gactcctcaa acggaaatcc cataaaaaa aaaattggat caggcataca
32821 atataatacc aatggagcta tgggtgcaaa acttggaaca ggcctcagtt ttgacagctc
32881 cggagccata acaatgggca gcataaaca tgacagactt actcttttga caacaccaga
32941 cccatcccca aattgcagaa ttgcttcaga taaagactgc aagctaactc tggcgctaac
33001 aaaatgtggc agtcaaattt tgggcactgt ttcagctttg gcagtatcag gtaatatggc
33061 ctccatcaat ggaactctaa gcagtgtaaa cttgggttctt agatttgatg acaacggagt
33121 gcttatgtca aattcatcac tggacaaaca gtattggaac tttagaaacg gggactccac
33181 taacggtcaa ccatacactt atgctgttgg gtttatgcca aacctaaaag cttaccctaaa
33241 aactcaaagt aaaactgcaa aaagtaatat tgttagccag gtgtatctta atggtgacaa
33301 gtctaaacca ttgcatttta ctattacgct aaatggaaca gatgaaacca accaagtaag
33361 caaatactca atatcattca gttggctcctg gaacagtggg caatacacta atgacaaatt
33421 tgccaccaat tcctatacct tctcctacat tgcccaggaa taaagaatcg tgaacctgtt
33481 gcatgttatg tttcaacgtg tttatttttc aattgcagaa aatttcaagt catttttcat
33541 tcagtagtat agccccacca ccacatagct tatactaata accgtacctt aatcaaactc
33601 acagaaccct agtattcaac ctgccacctc cctcccaaca cacagagtac acagtccttt
33661 ctccccggct ggccttaaac agcatcatat catgggtaac agacatattc ttaggtgtta
33721 tattccacac ggtctcctgt cgagccaaac gctcatcagt gatgttaata aactccccgg
33781 gcagctcgct taagttcatg tcgctgtcca gctgctgagc cacaggctgc tgtccaactt
33841 gcggttgctc aacggggcggc gaaggagaag tccacgccta catgggggta gagtcataat
33901 cgtgcatcag gatagggcgg tgggtgctgca gcagcgcgcg aataaactgc tgccgcgcgc
33961 gctccgtcct gcaggaatac aacatggcag tgggtctctc agcgatgatt cgcaccgccc
34021 gcagcataag gcgccttgct ctccgggcac agcagcgcac cctgatctca cttaagtcag
34081 cacagtaact gcagcacagt accacaatat tgtttaaaat cccacagtgc aaggcgctgt
34141 atccaaagct catggcgggg accacagaac ccacgtggcc atcataccac aagcgcaggt
34201 agattaagtg gcgaccctc ataaacacgc tggacataaa cattacctct tttggcatgt
34261 tgtaattcac cacctcccg taccatataa acctctgatt aaacatggcg ccattccacca
34321 ccatectaaa ccagctggcc aaaacctgcc cgccggctat gcaactgcagg gaaccgggac
34381 tggacaatg acagtggaga gcccaggact cgtaacctat gatcatcatg ctcgatcatga
34441 tatcaatgtt ggcacaacac aggcacacgt gcatacactt cctcaggatt acaagctcct
34501 cccgcgtcag aaccatatac cagggaacaa cccattcctg aatcagcgta aatcccacac
34561 tgcagggaag acctcgcacg taactcacgt tgtgcattgt caaagtgtta cattcgggca
34621 gcagcggatg atcctccagt atggtagcgc gtgtctctgt ctcaaaagga ggtaggcgat
34681 ccctactgta cggagtgcgc cgagacaacc gagatcgtgt tggtcgtagt gtcatgcaa
34741 atggaacgcc ggacgtagtc atatttcctg aagcaaaacc aggtgcgggc gtgacaaaca
34801 gatctgcgtc tccggtctcg tcgcttagct cgctctgtgt agtagttgta gtatatccac
34861 tctctcaaag catccaggcg cccctgggt tggggttcta tgtaaactcc ttcattgcgc
34921 gctgccctga taacatccac caccgcagaa taagccacac ccagccaacc tacacattcg
34981 ttctgcgagt cacacacggg aggagcggga agagctggaa gaacctgtt tttttttttt
35041 attccaaaag attatccaaa acctcaaat gaagatctat taagtgaacg cgctccctc
35101 cgggtggcgtg gtcaaactct acagccaaag aacagataat ggcatttgta agatgttgca
35161 caatggcttc caaaaggcaa actgccctca cgtccaagtg gacgtaaagg cttaaaccctt
35221 cagggtgaat ctctctata aacattccag cacttcaac catgcccata taattttcat
35281 ctgcgccact tatcaatatg tctctaagca aatcccgaat attaatgta gcatgtgtaa
35341 aaatctgctc cagagcgccc tccaccttca gcctcaagca gcgaatcatg attgcaaaaa
35401 ttcaggttcc tcacagacct gtataagatt caaaagcgga acattaacaa aaataccgcg
35461 atcccgtagg tcccttcgca gggccagctg aacataatcg tgcaggctctg cacggaccag
35521 cgcggccact tccccgccag gaacctgac aaaagaacct acactgatta tgacacgcac
35581 actcggagct atgctaacca gcgtagcccc gatgtaagct tgttgcatgg gcggcgatat
35641 aaaatgcaag gtactgctca aaaaatcagg caaagcctcg cgcaaaaaag caagcacatc
35701 gtagtcatgc tcatgcagat aaaggcaggt aagttccgga accaccacag aaaaagacac
35761 catttttctc tcaaacatgt ctgcgggttc ctgcataaac acaaaataaa ataacaaaaa
35821 aaaaaaaca tttaaacatt agaagcctgt cttacaacag gaaaaacaac ccttataagc
35881 ataagacgga ctacggccat gccggcgtga ccgtaaaaaa actgggtcacc gtgattaaaa

FIG. 21A-11

WO 2006/020480

PCT/US2005/027658

48/126

35941 agcaccaccg acagttcctc ggtcatgtcc ggagtcataa tgtaagactc ggtaaacaca
36001 tcagggttgg taacatcggt cagtgtctaaa aagcgaccga aatagcccgg gggaatacat
36061 acccgagggc gtagagacaa cattacagcc cccataggag gtataacaaa attaatagga
36121 gagaaaaaca cataaacacc tgaaaaaccc tcctgcctag gcaaaatagc accctcccgc
36181 tccagaacaa catacagcgc ttccacagcg gcagccataa cagtcagcct taccagtaaa
36241 aaaacctatt aaaaaacacc actcgacacg gcaccagctc aatcagtcac agtgtaaaaa
36301 gggccaagta cagagcgagt atatatagga ctaaaaaatg acgtaacggg taaagtccac
36361 aaaaaccacc cagaaaaccg cagcggaacc tacgcccaga aacgaaagcc aaaaaacca
36421 caacttcctc aaatcttcac ttccgttttc ccacgatacg tcacttccca ttttaaaaaa
36481 aaactacaat tccaatata tgcaagttac tccgccctaa aacctacgtc acccgccccg
36541 ttcccacgcc ccgcccacg tcacaaactc cccccctca ttatcatatt ggcttcaatc
36601 caaaataagg tatattattg atgatg (SEQ ID NO: 17)

FIG. 21A-12

49/126

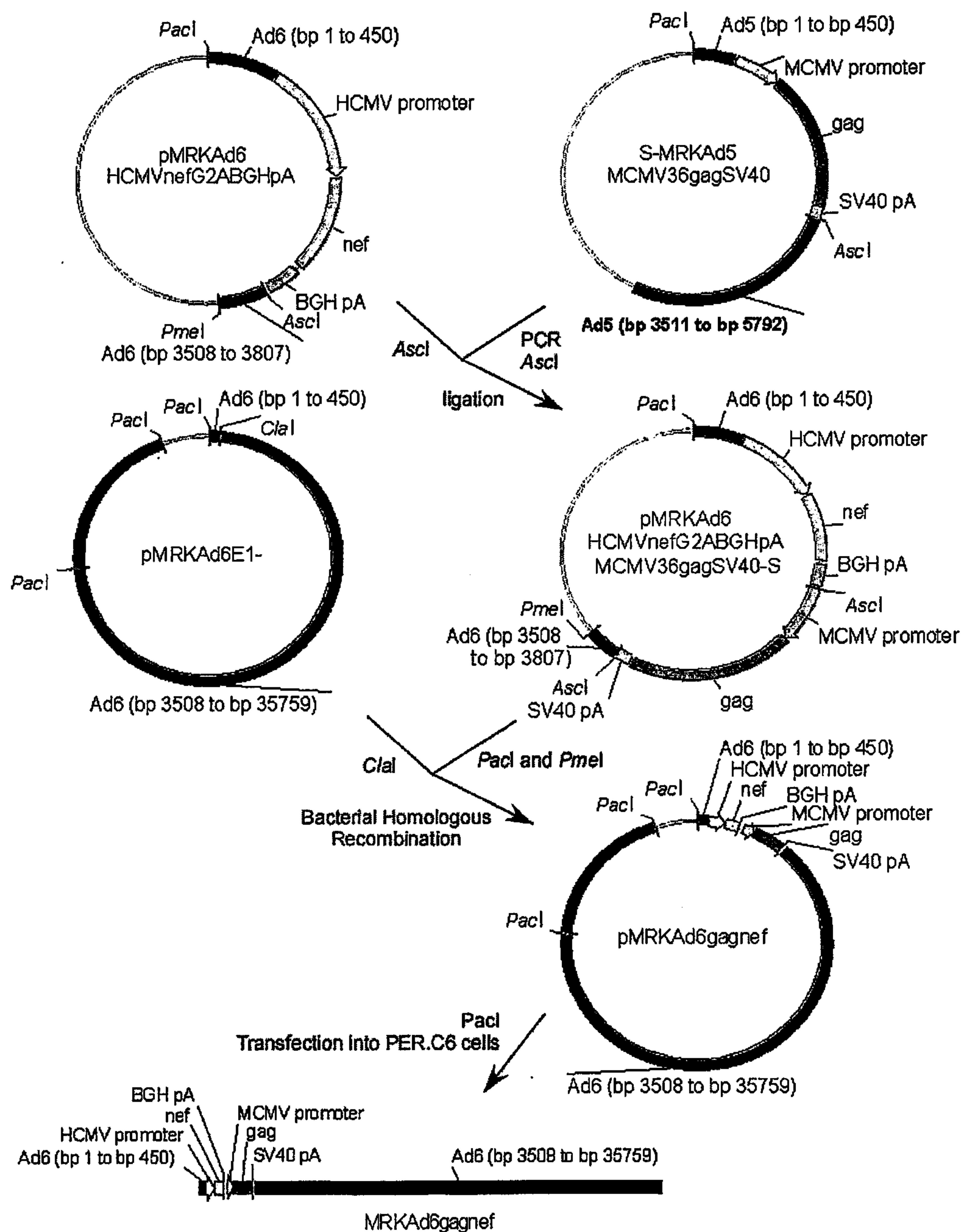


FIG. 22

50/126

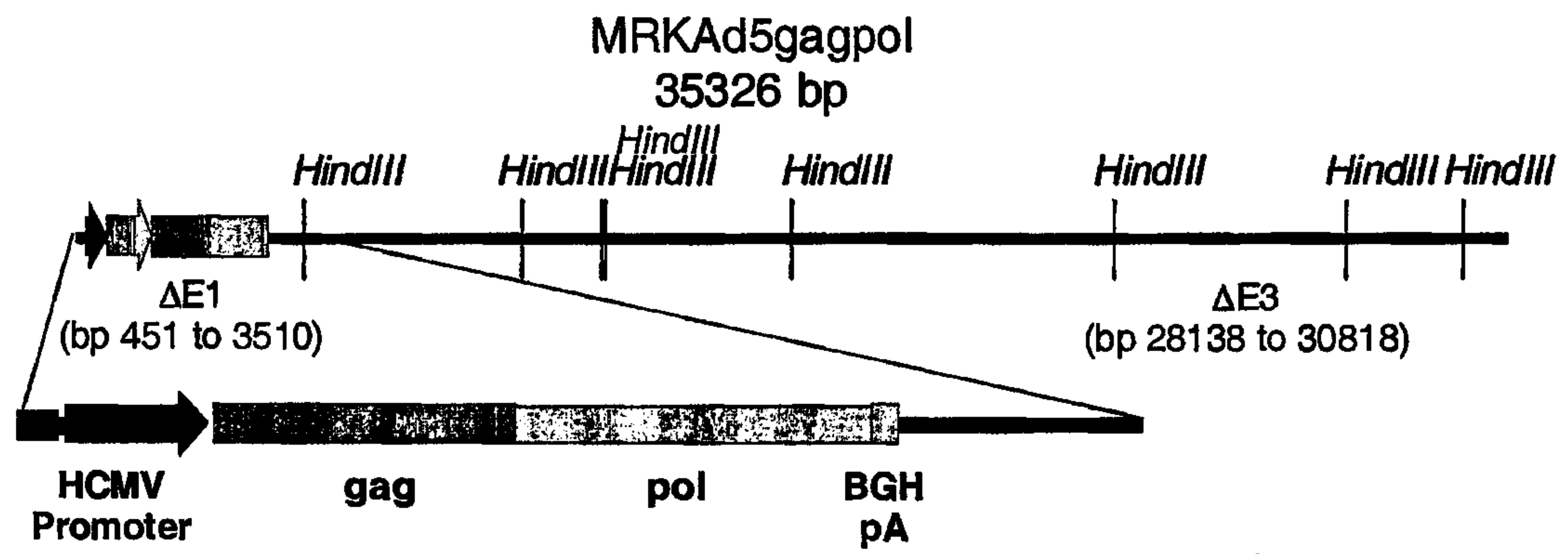


FIG. 23

51/126

MRKAd5gagpol

KEY: _____ HCMV promoter Gag _____ Pol _____ BGH pA

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgcaa gtgtggcggg acacatgtaa gcgacggatg tggcaaaagt gacgtttttg
181 gtgtgcgccg gtgtacacag gaagtgacaa ttttcgcgcg gttttaggcg gatgttgtag
241 taaatttggg cgtaaccgag taagatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataatttt gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcggttt attattatag gcggccgcga tccattgcat acgttgtatc
481 catatcataa tatgtacatt tatattggct catgtccaac attaccgcca tgttgacatt
541 gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata
601 tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc
661 cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc
721 attgacgtca atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt
781 atcatatgcc aagtacgcc cctattgacg tcaatgacgg taaatggccc gcctggcatt
841 atgccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca
901 tcgctattac catggtgatg cgtttttggc agtacatcaa tgggcgtgga tagcggtttg
961 actcacgggg atttccaagt ctccaccca ttgacgtcaa tgggagtttg ttttggcacc
1021 aaaatcaacg ggactttcca aaatgtcgta acaactccgc ccattgacg caaatgggcg
1081 gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgtcagatcg
1141 cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac cgatccagcc
1201 tccgcggccg ggaacggtgc attggaacgc ggattccccg tgccaagagt gagatctacc
1261 atgggtgcta ggccttctgt gctgtctggt ggtgagctgg acaagtggga gaagatcagg
1321 ctgagggcctg gtggcaagaa gaagtacaag ctaaagcaca ttgtgtgggc ctccagggag
1381 ctggagaggt ttgctgtgaa ccctggcctg ctggagacct ctgaggggtg caggcagatc
1441 ctgggccagc tccagccctc cctgcaaaac ggccttgagg agctgaggtc cctgtacaac
1501 acagtggcta ccctgtactg tgtgcaccag aagattgatg tgaaggacac caaggaggcc
1561 ctggagaaga ttgaggagga gcagaacaag tccaagaaga aggccagca ggctgctgct
1621 ggcacaggca actccagcca ggtgtcccag aactaccca ttgtgcagaa cctccagggc
1681 cagatggtgc accagggcat ctcccccccg accctgaatg cctgggtgaa ggtggtggag
1741 gagaaggcct tctccctga ggtgatcccc atgttctctg cctgtctga ggtgccacc
1801 cccagggacc tgaacaccat gctgaacaca gtggggggcc atcaggctgc catgcagatg
1861 ctgaaggaga ccatcaatga ggaggctgct gagtgggaca ggctgcatcc tgtgcacgct
1921 ggcgccattg ccccgccca gatgaggag cccaggggct ctgacattgc tggcaccacc
1981 tccaccctcc aggagcagat tggctggatg accaacaacc ccccatccc tgtggggaa
2041 atctacaaga ggtggatcat cctgggctg aacagattg tgaggatga ctccccacc
2101 tccatcctgg acatcaggca gggccccaag gagcccttca gggactatgt ggacaggttc
2161 tacaagaccc tgagggtgta gcaggcctcc caggaggtga agaactggat gacagagacc
2221 ctgctggtgc agaatgcaa ccctgactgc aagaccatcc tgaaggccct gggccctgct
2281 gccaccctgg aggagatgat gacagcctgc caggggtgga gggccctg tccacaaggcc
2341 aggtgctggt ctgagggcat gtcccagggt accaactccg ccaccatcat gatgcagagg
2401 ggcaacttca ggaaccagag gaagacagtg aagtgccttca actgtggcaa ggtgggccac
2461 attgccaaga actgtagggc cccaggaag aagggtgct ggaagtgtg caaggaggcc
2521 caccagatga aggactgcaa tgagaggcag gccacttcc tgggcaaat ctggccctcc
2581 cacaagggca ggcctggcaa ctctctccag tccaggcctg agcccacagc cctctccag
2641 gagtccttca ggtttgggga ggagaagacc acccccagcc agaagcagga gcccatggac
2701 aaggagctgt acccctgag ctccctgagg tccctgtttg gcaacgaccc ctctctccag
2761 cccatctccc ccattgagac tgtgctgtg aagctgaagc ctggcatgga tggccccaag
2821 gtgaagcagt ggccttgac tgaggagaag atcaaggccc tggtggaat ctgcactgag
2881 atggagaagg agggcaaat ctccaagatt ggcgccgaga accctacaa caccctgtg

```

FIG. 24A-1

52/126

2941 tttggccatca agaagaagga ctccaccaag tggaggaagc tgggtggactt cagggagctg
3001 aacaagagga cccaggactt ctgggaggtg cagctgggca tccccaccc cgtggcctg
3061 aagaagaaga agtctgtgac tgtgctggct gtgggggatg cctacttctc tgtggccctg
3121 gatgaggact tcaggaagta cactgccttc accatcccct ccatcaacaa tgagaccctt
3181 ggcatcaggt accagtacaa tgtgctgccc cagggctgga agggctcccc tgccatcttc
3241 cagtccctcca tgaccaagat cctggagccc ttcaggaagc agaaccctga cattgtgac
3301 taccagtaca tggctgccct gtatgtgggc tctgacctgg agattgggca gcacaggacc
3361 aagattgagg agctgaggca gcacctgctg aggtggggcc tgaccacccc tgacaagaag
3421 caccagaagg agccccctt cctgtggatg ggctatgagc tgacccccga caagtggact
3481 gtgcagccca ttgtgctgcc tgagaaggac tcctggactg tgaatgacat ccagaagctg
3541 gtgggcaagc tgaactgggc ctcccaaatc taccctggca tcaaggtgag gcagctgtgc
3601 aagctgctga ggggcaccaa ggcctgact gagggtatcc cctgactga ggagctgag
3661 ctggagctgg ctgagaacag ggagatcctg aaggagcctg tgcattgggt gtactatgac
3721 ccctccaagg acctgattgc tgagatccag aagcagggcc agggccaagt gacctaccaa
3781 atctaccagg agcccttcaa gaacctgaag actggcaagt atgccaggat gagggggggc
3841 cacaccaatg atgtgaagca gctgactgag gctgtgcaga agatcaccac tgagtccatt
3901 gtgatctggg gcaagacccc caagttcaag ctgcccattc agaaggagac ctgggagacc
3961 tgggtggactg agtactggca ggcacctgg atccctgagt gggagtttgt gaacacccc
4021 cccctggtga agctgtggtg ccagctggag aaggagccca ttgtgggggc tgagaccttc
4081 tatgtggctg gggctgcaa caggagacc aagctgggca agctggcta tgtgaccaac
4141 aggggcaggc agaaggtggt gacctgact gacaccacca accagaagac tgccctccag
4201 gccatctacc tggccctcca ggactctggc ctggaggtga acattgtgac tgccctccag
4261 tatgccctgg gcatcatcca gcccagcct gatcagtctg agtctgagct ggtgaaccag
4321 atcattgagc agctgatcaa gaaggagaag gtgtacctg cctgggtgcc tgcccacaa
4381 ggcattgggg gcaatgagca ggtggacaag ctggtgtctg ctggcatcag gaaggtgctg
4441 ttcctggatg gcattgacaa gcccaggat gaggatgaga agtaccactc caactggagg
4501 gctatggcct ctgacttcaa cctgccccct gtggtggcta aggagattgt ggctcctgt
4561 gacaagtgc agctgaagg gaggccatg catgggcagg tggactgctc cctggcatc
4621 tggcagctgg cctgcacca cctggagggc aagggtatcc tgggtgctgt gcatgtggc
4681 tccggctaca ttgaggctga ggtgatccct gctgagacag gccaggagac tgccctactc
4741 ctgctgaagc tggctggcag gtggcctgtg aagaccatcc acactgccaa tggctccaac
4801 ttcactgggg ccacagtga gctgcctgc tgggtggctg gcatcaagca ggagtttggc
4861 atccctaca accccagtc ccagggggtg gtggcctcca tgaacaagga cctgaagaag
4921 atcattgggc aggtgaggga ccaggctgag cacctgaaga cagctgtgca gatggtgtg
4981 ttcatccaca acttcaagag gaaggggggc atcggggct actccgctgg ggagaggatt
5041 gtggacatca ttgccacaga catccagacc aaggagctcc agaagcagat caccaagatc
5101 cagaacttca ggtgtacta caggactcc aggaacccc tgtggaagg ccctgccaa
5161 ctgctgtgga agggggagg gctgtgtgtg atccaggaca actctgacat caaggtggtg
5221 cccaggagga agccaagat catcaggac tatggcaagc agatggctgg gcatgactgt
5281 gtggcctcca ggcaggatga gactaacgg ggcagatctg ctgtgccttc tagttgccag
5341 ccatctgttg tttggccctc cccgtgcct tccttgacc tggaagggtg cactcccact
5401 gtcctttcct aataaaatga ggaattgca tcgcattgtc tgagtgggtg tcattctatt
5461 ctgggggggtg ggtgggggca gacagcaag ggggaggatt ggaagacaa tagcaggcat
5521 gctggggatg cgtggggctc tatggccgat cggcgcgccg tactgaaatg tgtggcggtg
5581 gcttaagggt ggaagaat atataagggt ggggtcttat gtagttttgt atctgttttg
5641 cagcagccgc cgccgccatg agcaccact cgtttgatgg aagcattgtg agctcatatt
5701 tgacaacgcg catgccccca tgggcggggg tgcgtcagaa tgtgatgggc tccagcattg
5761 atggtcgccc cgtcctgccc gcaaactcta ctaccttgac ctacgagacc gtgtctggaa
5821 cgccgttgga gactgcagcc tccgcggcgg cttcagccgc tgcagccacc gccgcggga
5881 ttgtgactga ctttgctttc ctgagccgc ttgcaagcag tgcagcttcc cgttcacccg
5941 cccgcgatga caagttgacg gctcttttgg cacaattgga ttctttgacc cgggaactta
6001 atgtcgtttc tcagcagctg ttggatctgc gccagcaggt ttctgccctg aaggcttct
6061 cccctcccaa tgcggtttta aacataaata aaaaaccaga ctctgttttg atttgatca
6121 agcaagtgtc ttgctgtctt tatttagggg ttttgcgcg gcggtaggcc cgggaccagc
6181 ggtctcggtc gttgagggtc ctgtgtattt tttccaggac gtggtaaagg tgactctgga

FIG. 24A-2

53/126

6241 tgttcagata catgggcata agcccgtctc tgggggtggag gtagcaccac tgcagagctt
6301 catgctgcgg ggtgggtgtg tagatgatcc agtcgtagca ggagcgctgg gcgtgggtgcc
6361 taaaaatgtc tttcagtagc aagctgattg ccaggggcag gcccttggtg taagtgttta
6421 caaagcgggt aagctgggat ggggtgcatac gtggggatat gagatgcac ttggactgta
6481 tttttagggt ggctatgttc ccagccatat ccctccgggg attcatgttg tgcagaacca
6541 ccagcacagt gtatccggtg cacttgggaa atttgtcatg tagcttagaa ggaaatgcgt
6601 ggaagaactt ggagacgccc ttgtgacctc caagattttc catgcattcg tccataatga
6661 tggcaatggg ccacagggcg gcggcctggg cgaagatatt tctgggatca ctaacgtcat
6721 agttgtgttc caggatgaga tctcatagg ccatttttac aaagcgcggg cggagggtgc
6781 cagactgcgg tataatggtt ccatccggcc caggggcgta gttaccctca cagatttgca
6841 tttcccacgc tttgagttca gatgggggga tcatgtctac ctgcggggcg atgaagaaaa
6901 cggtttccgg ggtaggggag atcagctggg aagaaagcag gttcctgagc agctgcgact
6961 taccgcagcc ggtgggcccc taaatcacac ctattaccgg ctgcaactgg tagttaagag
7021 agctgcagct gccgtcatcc ctgagcaggg gggccacttc gttagcatg tccctgactc
7081 gcatgttttc cctgaccaa tccgccagaa ggcgctcgcc gccagcgat agcagttctt
7141 gcaaggaagc aaagtttttc aacggtttga gaccgtccgc cgtaggcatg cttttgagcg
7201 tttgaccaag cagttccagg cggttcccaca gctcggtcac ctgctctacg gcatctcgat
7261 ccagcatatc tctcgttttc gcgggttggg gcggctttcg ctgtacggca gtagtcgggtg
7321 ctcgctccaga cgggccaggg tcatgtcttt ccacgggcgc agggctctcg tcagcgtagt
7381 ctgggtcacg gtgaaggggt gcgctccggg ctgcgcgctg gccagggtgc gcttgaggct
7441 ggtcctgctg gtgctgaagc gctgccggtc ttcgccctgc gcgtcggcca ggtagcattt
7501 gaccatggtg tcatagtcca gcccctccgc ggcgtggccc ttggcgcgca gcttgcctt
7561 ggaggaggcg ccgcacgagg ggcagtgcag acttttgagg gcgtagagct tgggcgcgag
7621 aaataccgat tccggggagt aggcacccgc gccgcaggcc ccgcagacgg tctcgcatc
7681 cacgagccag gtgagctctg gccgttcggg gtcaaaaacc aggtttcccc catgcttttt
7741 gatgcgtttc ttacctctgg tttccatgag ccggtgtcca cgctcgggtg cgaagggt
7801 gtccgtgtcc ccgtatacag acttgagagg cctgtcctcg agcgggtgtc cgcggctctc
7861 ctcgatataga aactcggacc actctgagac aaaggctcgc gtccaggcca gcacgaagga
7921 ggctaagtgg gaggggtagc ggtcgtttgt cactaggggg tccactcgct ccagggtgtg
7981 aagacacatg tcgccctctt cggcatcaag gaagggtgatt ggtttgtagg tgtaggccac
8041 gtgaccgggt gttcctgaag gggggctata aaagggggtg ggggcgcgtt cgtcctcact
8101 ctcttccgca tctgctgtctg cgagggccag ctggtggggg gactactccc tctgaaaagc
8161 gggcatgact tctgcgctaa gattgtcagt ttccaaaaac gaggaggatt tgatattcac
8221 ctggcccgcg gtgatgcctt tgagggtggc cgcattccatc tggtcagaaa agacaatctt
8281 tttgttgtca agcttgggtg caaacgacct gtagaggggc ttggacagca acttggcgat
8341 ggagcgcagg gtttggtttt tctcgcgac gccgcgctcc ttggccgca tgtttagctg
8401 cacgtattcg cgcgcaacgc accgccattc gggaaagacg gtggtgcgct cgtcgggcac
8461 cagggtgcac cgccaaccgc ggttgtgcag ggtgacaagg tcaacgctgg tggctacctc
8521 tccgcgtagg cgctcgttgg tccagcagag gcggccgccc ttgcgcgagc agaatggcgg
8581 taggggggtc agctgcgtct cgtccggggg gtctgcgtcc acggtaaaga ccccgggcag
8641 caggcgcgcg tcgaagtagt ctatcttgca tccttgcaag tctagcgcct gctgccatgc
8701 gcgggcggca agcgcgcgct cgtatgggtt gagtggggga ccccatggca tgggggtgggt
8761 gagcgcggag gcgtacatgc cgcaaagtgc gtaaaccgtg aggggctctc tgagtattcc
8821 aagatatgta gggtagcatc ttccaccgcg gatgctggcg gcacgtaat cgtatagtcc
8881 gtgcgaggga gcgaggaggt cgggaccgag gttgctacgg gcgggctgct ctgctcggaa
8941 gactatctgc ctgaagatgg catgtgagtt ggatgatag gttggacgct ggaagacgtt
9001 gaagctggcg tctgtgagac ctaccgcgtc acgcacgaag gaggcgtagg agtcgcgcag
9061 cttgttgacc agctcggcgg tgacctgcac gtctagggcg cagtagtcca gggtttctt
9121 gatgatgtca tacttatcct gtcccttttt tttccacagc tcgcggttga ggacaaactc
9181 ttcgcggtct ttccagtact cttggatcgg aaaccctcgc gcctccgaac ggtaagagcc
9241 tagcatgtag aactggttga cggcctggta ggcgcagcat cccttttcta cgggtagcgc
9301 gtatgcctgc gcggccttcc ggagcgaggt gtgggtgagc gcaaagggtg ccctgaccat
9361 gactttgagg tactggtatt tgaagtcagt gtcgtcgcat ccgccctgct ccagagcaa
9421 aaagtccgtg cgcttttttg aacgcggatt tggcaggggc aagggtgacat cgttgaagag
9481 tatctttccc gcgcgaggca taaagttgcg tgtgatgcgg aagggtcccc gcacctcgga

FIG. 24A-3

54/126

```

9541 acggttggtta attacctggg cggcgagcac gatctcgtca aagccgttga tgttggtggcc
9601 cacaatgtaa agttccaaga agcgcgggat gcccttgatg gaaggcaatt ttttaagttc
9661 ctcgtaggtg agctcttcag gggagctgag cccgtgctct gaaagggccc agtctgcaag
9721 atgaggggtg gaagcgacga atgagctcca caggtcacgg gccattagca tttgcagggtg
9781 gtcgcgaaag gtcctaaact ggcgacctat ggccattttt tctggggtga tgcagtagaa
9841 ggtaagcggg tcttggtccc agcgggtcca tccaagggtt cgggctaggt ctgcgcgggc
9901 agtcactaga ggctcatctc cgccgaactt catgaccagc atgaagggca cgagctgctt
9961 cccaaaggcc cccatccaag tataggtctc tacatcgtag gtgacaaaga gacgtcgggt
10021 gcgaggatgc gagccgatcg ggaagaactg gatctcccgc caccaattgg aggagtggct
10081 attgatgtgg tgaaagtaga agtccctgcg acgggcccga cactcgtgct ggcttttgta
10141 aaaacgtgcg cagtactggc agcgggtgcac gggctgtaca tcctgcacga ggttgacctg
10201 acgaccgcgc acaaggaagc agagtgggaa tttgagcccc tcgcctggcg ggtttggctg
10261 gtggtcttct acttcggctg cttgtccttg accgtctggc tgctcgaggg gagttacgggt
10321 ggatcggacc accacgccgc gcgagcccaa agtccagatg tccgcgcgcg gcggtcggag
10381 cttgatgaca acatcgcgca gatgggagct gtccatgggtc tggagctccc gcggcgctcag
10441 gtcaggcggg agctcctgca ggtttacctc gcatagacgg gtcagggcgc gggctagatc
10501 caggtgatac ctaatttcca ggggctgggt ggtggcggcg tcgatggctt gcaagaggcc
10561 gcatccccgc ggcgcgacta cggtagcgcg cggcgggccc tgggcccgcg ggggtgcctt
10621 ggatgatgca tctaaaagcg gtgacgcggg cgagcccccg gaggtagggg gggctccgga
10681 cccgccggga gagggggcag gggcacgtcg gcgcgcgcgc cgggcaggag ctggtgctgc
10741 gcgcgtaggt tgctggcgaa cgcgacgacg cggcgggtga tctcctgaat ctggcgcctc
10801 tgcgtgaaga cgacgggccc ggtgagcttg aacctgaaag agagtctgac agaataaatt
10861 tcggtgtcgt tgacggcggc ctggcgcaaa atctcctgca cgtctcctga gttgtcttga
10921 taggcgatct cggccatgaa ctgctcgatc tcttcctcct ggagatctcc gcgtccggct
10981 cgctccacgg tggcggcgag gtcgttgtaa atgcgggcca tgagctgcga gaaggcgttg
11041 aggcctccct cgttccagac gcggctgtag accacgcccc cttcggcatc gcgggcgcgc
11101 atgaccacct gcgcgagatt gagctccacg tgccgggcca agacggcgta gtttcgcagg
11161 cgctgaaaga ggtagttgag ggtggtggcg gtgtgttctg ccacgaagaa gtacataacc
11221 cagcgctcgca acgtggattc gttgatattc cccaaggcct caaggcgctc catggcctcg
11281 tagaagtcca cggcgaagtt gaaaaactgg gagttgcgcg ccgacacgggt taactcctcc
11341 tccagaagac ggatgagctc ggcgacagtg tcgcgcacct cgcgctcaaa ggctacaggg
11401 gcctcttctt cttcttcaat ctctcttccc ataagggcct ccccttcttc ttcttctggc
11461 ggcgggtggg gaggggggac acggcggcga cgacggcgca ccgggaggcg gtcgacaaaag
11521 cgctcgatca tctccccgcg gcgacggcgc atggtctcgg tgacggcgcg gccgttctcg
11581 cgggggcgca gttggaagac gccgccgctc atgtcccgggt tatgggttgg cggggggctg
11641 ccatgcggca gggatacggc gctaacgatg catctcaaca attgttgtgt aggtactccg
11701 ccgccgaggg acctgagcga gtccgcacgc accggatcgg aaaacctctc gagaaaggcg
11761 tctaaccagt cacagtcgca aggtaggctg agcaccgtgg cgggcggcag cgggcggcg
11821 tcgggggtgt ttctggcgga ggtgctgctg atgatgtaat taaagtaggc ggtcttgaga
11881 cggcggatgg tcgacagaag caccatgtcc ttgggtccgg cctgotgaat gcgcaggcg
11941 tcggccatgc cccaggcttc gttttgacat cggcgcagggt ctttgtagta gtcttgcatg
12001 agcctttcta ccggcacttc ttctctcctt tcctcttgct ctgcatctct tgcatctatc
12061 gctgcggcgg cggcggagtt tggccgtagg tggcgccctc ttcctcccat gcgtgtgacc
12121 ccgaagcccc tcacggctg aagcagggt aggtcggcga caacgcgctc ggctaataatg
12181 gcctgctgca cctgcgtgag ggtagactgg aagtcatcca tgtccacaaa gcggtggtat
12241 gcgcccgtgt tgatggtgta agtgagttg gccataacgg accagttaac ggtctggtga
12301 cccggctgcg agagctcgggt gtacctgaga cgcgagtaag ccctcgagtc aaatacgtag
12361 tcgttgcaag tccgcaccag gtactggtat cccacaaaaa agtgcggcgg cggctggcg
12421 tagaggggccc agcgtagggt ggccggggct ccgggggcga gatcttccaa cataaggcga
12481 tgatatccgt agatgtacct ggacatccag gtgatgccgg cggcgggtgt ggaggcgcgc
12541 ggaaagtcgc ggacgcgggt ccagatgttg cgcagcgcca aaaagtgtc catggtcggg
12601 acgctctggc cggtcaggcg cgcgcaatcg ttgacgctct agaccgtgca aaaggagagc
12661 ctgtaagcgg gcactcttcc gtggtctggt ggataaattc gcaagggtat catggcggac
12721 gaccgggggt cgagccccgt atccggccgt ccgcgctgat ccatgcgggt accgccgcgc
12781 tgtcgaaccc aggtgtgcga cgtcagacaa cgggggagtg ctccttttgg cttccttcca

```

FIG. 24A-4

WO 2006/020480

PCT/US2005/027658

55/126

```

12841 ggcgcgggcg ctgctgcgct agcttttttg gccactggcc gcgcgagcgc taagcgggta
12901 ggctggaaag cgaaagcatt aagtggctcg ctccctgtag ccggaggggt attttccaag
12961 gggtgagtcg cgggaccccc gggtcgagtc tcggaccggc cggactgcgc cgaacggggg
13021 ttgctctccc cgtcatgcaa gaccccgctt gcaaattcct ccggaacagc ggacgagccc
13081 cttttttgct tttcccagat gcatccgggt ctgcggcaga tgcgcccccc tcctcagcag
13141 cggcaagagc aagagcagcg gcagacatgc agggcaccct cccctcctcc taccgcgtca
13201 ggagggggcg catccgcggt tgacgcggca gcagatgggt attacgaacc cccgcggcgc
13261 cgggccccggc actacctgga cttggaggag ggcgagggcc tggcgcggtt aggagcgccc
13321 tctcctgagc ggcacccaag ggtgcagctg aagcgtgata cgcgtgaggg gtacgtgccg
13381 cggcagaacc tgtttcgcga ccgcgaggga gaggagcccc aggagatgcg ggatcgaaag
13441 ttccacgcag ggcgcgagct gcggcatggc ctgaatcgcg agcggttgct gcgcgaggag
13501 gacttttgagc ccgacgcgcg aaccgggatt agtcccgcgc gcgcacacgt ggcggccgcg
13561 gacctggtaa ccgcatacga gcagacgggt aaccaggaga ttaactttca aaaaagcttt
13621 aacaaccacg tgcgtacgct tgtggcgcgc gaggagggtg ctataggact gatgcatctg
13681 tgggactttg taagcgcgct ggagcaaaac ccaaatagca agccgctcat ggcgcagctg
13741 ttccttatag tgcagcacag cagggacaac gaggcattca gggatgcgct gctaaacata
13801 gtagagcccc agggccgctg gctgctcgat ttgataaaca tcctgcagag catagtgggtg
13861 caggagcgca gcttgagcct ggctgacaag gtggccgcca tcaactattc catgcttagc
13921 ctgggcaagt tttacgcccg caagatatac catacccctt acgttcccat agacaaggag
13981 gtaaagatcg aggggttcta catgcgcgat gcgctgaagg tgcttacctt gagcgacgac
14041 ctgggcggtt atcgcaacga gcgcacccac aaggccgtga gcgtgagccg gcggcgcgag
14101 ctacgagcacc gcgagctgat gcacagcctg caaagggccc tggctggcac gggcagcggc
14161 gatagagagg ccgagtccta ctttgacgcg ggcgctgacc tgcgctgggc cccaagccga
14221 cgcgccctgg aggcagctgg ggccggacct gggctggcgg tggcaccgcg gcgcgctggc
14281 aacgtcggcg gcgtggagga atatgacgag gacgatgagt acgagccaga ggacggcgag
14341 tactaagcgg tgatgtttct gatcagatga tgcaagacgc aacggacccg gcggtgcggg
14401 cggcgctgca gagccagccg tccggcctta actccacgga cgaactgggc caggtcatgg
14461 accgcatcat gtcgctgact gcgcgcaatc ctgacgcgtt ccggcagcag ccgcaggcca
14521 accggctctc cgcaattctg gaagcgggtg tcccggcgcg cgcaaacccc acgcacgaga
14581 aggtgctggc gatcgtaaac gcgctggccg aaaacagggc catccggccc gacgaggccg
14641 gcctggtcta cgacgcgctg cttcagcgcg tggctcgtta caacagcggc aacgtgcaga
14701 ccaacctgga ccggctgggt ggggatgtgc gcgaggccgt ggcgcagcgt gagcgcgcg
14761 agcagcaggg caacctgggc tccatgggtg cactaaacgc cttcctgagt acacagcccc
14821 ccaacgtgcc gcggggacag gaggactaca ccaactttgt gagcgcaact cggctaattg
14881 tgactgagac accgcaaagt gaggtgtacc agtctgggcc agactatttt ttccagacca
14941 gtagacaagg cctgcagacc gtaaacctga gccaggcttt caaaaacttg caggggctgt
15001 ggggggtgcg ggctcccaca ggcgaccgcg cgaccgtgtc tagcttgctg acgcccact
15061 cgcgcctggt gctgctgcta atagcgccct tcacggacag tggcagcgtg tcccgggaca
15121 catacctagg tcacttgctg acactgtacc gcgaggccat aggtcaggcg catgtggacg
15181 agcatacttt ccaggagatt acaagtgtca gccgcgcgct ggggcaggag gacacgggca
15241 gcctggaggc aaccctaaac tacctgctga ccaaccggcg gcagaagatc ccctcgttgc
15301 acagtttaaa cagcgaggag gagcgcatth tgcgctacgt gcagcagagc gtgagcctta
15361 acctgatgcg cgacggggta acgcccagcg tggcgctgga catgaccgcg cgcaacatgg
15421 aaccgggcat gtatgcctca aaccggccgt ttatcaaccg cctaattggac tacttgcatc
15481 gcgcggccgc cgtgaacccc gagtatttca ccaatgccat cttgaacccg cactggctac
15541 cgccccctgg tttctacacc gggggattcg aggtgcccgga gggtaacgat ggattcctct
15601 gggacgacat agacgacagc gtgttttccc cgcaaccgca gacctgcta gagttgcaac
15661 agcgcgagca ggcagaggcg gcgctgcgaa aggaaagctt ccgcaggcca agcagcttgt
15721 ccgatctagg cgctgcggcc ccgcggtcag atgctagtag cccatttcca agcttgatag
15781 ggtctcttac cagcactcgc accaccgcgc cgcgctgctt gggcgaggag gagtacctaa
15841 acaactcgct gctgcagccg cagcgcgaaa aaaacctgcc tccggcattt cccaacaacg
15901 ggatagagag cctagtggac aagatgagta gatggaagac gtacgcgcag gagcacaggg
15961 acgtgccagg cccgcgcccc cccaccgctc gtcaaaggca cgaccgtcag cggggtctgg
16021 tgtgggagga cgatgactcg gcagacgaca gcagcgtcct ggatttggga gggagtggca
16081 acccgtttgc gcaccttcgc cccaggctgg ggagaatggt ttaaaaaaaa aaaaagcatg

```

FIG. 24A-5

WO 2006/020480

PCT/US2005/027658

56/126

```

16141 atgcaaaata aaaaactcac caaggccatg gcaccgagcg ttggttttct tgtattcccc
16201 ttagtatgcg gcgcgcggcg atgtatgagg aaggtcctcc tccctcctac gagagtgtgg
16261 tgagcgcggc gccagtggcg gcggcgctgg gttctccctt cgatgctccc ctggaccgcg
16321 cgtttgtgcc tccgcggtac ctgcggccta ccggggggag aaacagcatc cgttactctg
16381 agttggcacc cctattcgac accacccgtg tgtacctggt ggacaacaag tcaacggatg
16441 tggcatccct gaactaccag aacgaccaca gcaactttct gaccacggtc attcaaaaca
16501 atgactacag cccggggggag gcaagcacac agaccatcaa tcttgacgac cggtcgcact
16561 ggggcggcga cctgaaaacc atcctgcata ccaacatgcc aaatgtgaac gagttcatgt
16621 ttaccaataa gtttaaggcg cgggtgatgg tgcgcgctt gcctactaag gacaatcagg
16681 tggagctgaa atacgagtgg gtggagttca cgctgcccgga gggcaactac tccgagacca
16741 tgaccataga ctttatgaac aacgcgatcg tggagcacta cttgaaagtg ggcagacaga
16801 acgggggttct ggaaagcgac atcggggtaa agtttgacac ccgcaacttc agactgggggt
16861 ttgaccccggt cactggtctt gtcatgcctg gggatatata aaacgaagcc ttccatccag
16921 acatcatttt gctgccagga tgcgggggtg acttcaccca cagccgcctg agcaacttgt
16981 tgggcatccg caagcggcaa ccttccagg agggctttag gatcacctac gatgatctgg
17041 aggggtggtaa cattcccgca ctgttggtat tggacgccta ccaggcgagc ttgaaagatg
17101 acaccgaaca gggcgggggt ggcgcaggcg gcagcaacag cagtggcagc ggcgcggaag
17161 agaactcaa cgcggcagcc gcggcaatgc agccggtgga ggacatgaac gatcatgcca
17221 ttcgcggcga cacctttgcc acacgggctg aggagaagcg cgctgaggcc gaagcagcgg
17281 ccgaagctgc cgccccgct gcgcaacccg aggtcgagaa gcctcagaag aaaccggtga
17341 tcaaaccctt gacagaggac agcaagaaac gcagttacaa cctaataagc aatgacagca
17401 ccttcaccca gtaccgcagc tggtagcttg catacaacta cggcgaccct cagaccggaa
17461 tccgctcatg gacctgctt tgcactcctg acgtaacctg cggctcggag caggtctact
17521 ggtcgttgcc agacatgatg caagaccccg tgaccttcg ctccacgcgc cagatcagca
17581 actttccggt ggtgggcgcc gagctgttgc ccgtgcactc caagagcttc tacaacgacc
17641 aggccgtcta ctcccaactc atccgccagt ttacctctct gaccacgtg ttcaatcgct
17701 ttcccagaaa ccagattttg gcgcgcccgc cagccccac catcaccacc gtcagtgaag
17761 acgttcctgc tctcacagat cacgggacgc taccgtgcg caacagcatc ggaggagtcc
17821 agcgagtgc cattactgac gccagacgcc gcacctgcc ctacgtttac aaggccctgg
17881 gcatagtctc gccgcgcgct ctatcgagcc gcactttttg agcaagcatg tccatcctta
17941 tatcgcagg caataacaca ggctggggcc tgcgcttccc aagcaagatg tttggcgggg
18001 ccaagaagcg ctccgaccaa caccagtgcc gcgtgcgcgg gcaactaccg gcgcccctgg
18061 gcgcgcacaa acgcggccgc actgggcgca ccaccgtcga tgacgccatc gacgcggtgg
18121 tggaggaggc gcgcaactac acgcccacgc cgccaccagt gtccacagtg gacgcggcca
18181 ttcagaccgt ggtgcgcgga gcccggcgct atgctaaaat gaagagacgg cggaggcgcg
18241 tagcacgtcg ccaccgcgcg cgaccgggca ctgccgccca acgcgcggcg gcggccctgc
18301 ttaaccgcgc acgtcgcacc ggccgacggg cggccatgcg ggccgctcga aggtggcccg
18361 cgggtattgt cactgtgccc ccaggtcca ggcgacgagc ggccgcccga gcagccgcgg
18421 ccattagtgc tatgactcag ggtcgcaggg gcaacgtgta ttgggtgcmc gactcggtta
18481 gcggcctgcm cgtgcccgtg cgcacccgcc cccgcgcgaa ctagattgca agaaaaaact
18541 acttagactc gtactgttgt atgtatccag cggcggcggc gcgcaacgaa gctatgtcca
18601 agcgcaaaat caaagaagag atgctccagg tcatcgcgcc ggagatctat ggccccccga
18661 agaaggaaga gcaggattac aagccccgaa agctaaagcg ggtcaaaaag aaaaagaaag
18721 atgatgatga tgaacttgac gacgaggtgg aactgctgca cgctaccgcg cccaggcgac
18781 gggtagagtg gaaaggctga cgcgtaaaac gtgttttgcm acccggcacc accgtagtct
18841 ttacgcccgg tgagcgctcc acccgcacct acaagcgcgt gtatgatgag gtgtacggcg
18901 acgaggacct gcttgagcag gccaacgagc gcctcgggga gtttgccctac ggaaagcggc
18961 ataaggacat gctggcgttg ccgctggacg agggcaaccc aacacctagc ctaaagcccc
19021 taacactgca gcaggtgctg cccgcgcttg caccgtcga agaaaagcgc ggcctaaagc
19081 gcgagtctgg tgacttgcca cccaccgtgc agctgatggg acccaagcgc cagcgactgg
19141 aagatgtctt ggaaaaaatg accgtggaac ctgggctgga gcccagggtc cgcgtgcggc
19201 caatcaagca ggtggcgccg ggactgggcm tgcagaccgt ggacgttcag ataccacta
19261 ccagtagcac cagtattgcm accgccacag agggcatgga gacacaaacg tccccggttg
19321 cctcagcggg ggcggatgcm gcgggtgcag cggctcgctg ggcccgctcc aagacctcta
19381 cggaggtgca aacggaccgc tggatgtttc gcgtttcagc ccccggcgcm ccgcgcgctt

```

FIG. 24A-6

WO 2006/020480

PCT/US2005/027658

57/126

```

19441 cgaggaagta cggcgccgcc agcgcgctac tgcccgaata tgccctacat ccttccattg
19501 cgcctacccc cggctatcgt ggctacacct accgcccag aagacgagca actacccgac
19561 gccgaaccac cactggaacc cgcgcgccgc gtcgcccgtc ccagcccgtg ctggccccga
19621 tttccgtgcg caggggtggc cgcgaaggag gcaggaccct ggtgctgcca acagcgcgct
19681 accaccccag catcgtttaa aagccggtct ttgtggttct tgcagatatg gccctcacct
19741 gccgcctccg tttcccggtg ccgggattcc gaggaagaat gcaccgtagg aggggcatgg
19801 ccggccacgg cctgacgggc ggcattgcgc gtgcgcacca ccggcggcgg cgcgcgtcgc
19861 accgtcgcac gcgcggcggc atcctgcccc tccttattcc actgatcgcc gcggcgattg
19921 gcgcctgccc cggaattgca tccgtggcct tgcaggcgca gagacactga ttaaaaacaa
19981 gttgcatgtg gaaaaatcaa aataaaaagt ctggactctc acgctcgctt ggtcctgtaa
20041 ctattttgta gaatggaaga catcaacttt gcgtctctgg ccccgcgaca cggctcgcgc
20101 ccgttcatgg gaaactggca agatatcggc accagcaata tgagcgggtg cgccttcagc
20161 tggggctcgc tgtggagcgg cattaaaaat ttcggttcca ccgttaagaa ctatggcagc
20221 aaggcctgga acagcagcac aggccagatg ctgagggata agttgaaaga gcaaaatttc
20281 caacaaaagg tggtagatgg cctggcctct ggcattagcg gggtggtgga cctggccaac
20341 caggcagtgc aaaataagat taacagtaag cttgatcccc gccctcccgt agaggagcct
20401 ccaccggccg tggagacagt gtctccagag gggcgtggcg aaaagcgtcc gcgccccgac
20461 agggaagaaa ctctggtgac gcaaatagac gagcctccct cgtacgagga ggcactaaag
20521 caaggcctgc ccaccaccg tcccatcgcg cccatggcta ccggagtgtt gggccagcac
20581 acaccgtaa cgctggacct gcctccccc gccgacacc agcagaaacc tgtgctgcca
20641 ggcccgaccg ccgttggtgt aaccgctct agccgcgct ccctgcgcgc cgcgcgcagc
20701 ggtccgcat cgctgaggcc cgtagccagt ggcaactggc aaagcacact gaacagcatc
20761 gtgggtctgg gggtgcaatc cctgaagcgc cgacgatgtt tctgatagct aacgtgtcgt
20821 atgtgtgtca tgtatgcgc catgtcgccg ccagaggagc tgctgagccg ccgcgcgcc
20881 gctttccaag atggctaccc cttcgatgat gccgcagtgg tcttacatgc acatctcggg
20941 ccaggacgcc tcggagtacc tgagccccgg gctggtgtag tttgcccgcg ccaccgagac
21001 gtacttcagc ctgaataaca agtttagaaa cccacgggtg gcgcctacgc acgacgtgac
21061 cacagaccgg tcccagcgtt tgacgctgcg gttcatccct gtggaccgtg aggatactgc
21121 gtactcgtac aaggcgcggc tcaccctagc tgtgggtgat aaccgtgtgc tggacatggc
21181 ttcacgtac tttgacatcc gcggcgtgct ggacaggggc cctactttta agccctactc
21241 tggcactgcc tacaacgccc tggctcccaa gggtgcccca aatccttgcg aatgggatga
21301 agctgctact gctcttgaaa taaacctaga agaagaggac gatgacaacg aagacgaagt
21361 agacgagcaa gctgagcagc aaaaaactca cgtatttggg caggcgcctt attctggtat
21421 aaatattaca aaggagggtt ttcaaatagg tgtcgaaggt caaacaccta aatatgccga
21481 taaaacattt caacctgaac ctcaaatagg agaactctag tggtagcaaa cagaaattaa
21541 tcatgcagct gggagagtcc taaaaaagac taccccaatg aaaccatgtt acggttcata
21601 tgcaaaaccc acaaatgaaa atggagggca aggcattctt gtaaagcaac aaaatggaaa
21661 gctagaaaagt caagtggaaa tgcaattttt ctcaactact gaggcagccg caggcaatgg
21721 tgataacttg actcctaaag tggatttgta cagtgaagat gtagatatag aaaccccaga
21781 cactcatatt tcttacatgc ccactattaa ggaaggtaac tcacgagaac taatgggcca
21841 acaatctatg cccaacaggc ctaattacat tgcttttagg gacaatttta ttggtotaat
21901 gtattacaac agcacgggta atatgggtgt tctggcgggc caagcatcgc agttgaatgc
21961 tgttgtagat ttgcaagaca gaaacacaga gctttcatac cagcttttgc ttgattccat
22021 tggatgata accaggtact tttctatgtg gaatcaggct gttgacagct atgatccaga
22081 tgtagaatt attgaaaatc atggaaactg agatgaactt ccaaattact gctttccact
22141 gggagggtgtg attaatacag agactcttac caaggtaaaa cctaaaacag gtcaggaaaa
22201 tggatgggaa aaagatgcta cagaattttc agataaaaat gaaataagag ttggaaataa
22261 ttttgccatg gaaatcaatc taaatgccaa cctgtggaga aatttcctgt actccaacat
22321 agcgtgtgat ttgcccga ca gctaaaagta cagtccttcc aacgtaaaaa tttctgataa
22381 cccaaacacc tacgactaca tgaacaagcg agtggtggct cccgggctag tggactgcta
22441 cattaacctt ggagcacgct ggtcccttga ctatatggac aacgtcaacc catttaacca
22501 ccaccgcaat gctggcctgc gctaccgctc aatgttgctg ggcaatggtc gctatgtgcc
22561 cttccacatc caggtgcctc agaagttctt tgccattaaa aacctccttc tctgcccggg
22621 ctcatacacc tacgagtggg acttcaggaa ggatgttaac atggttctgc agagctccct
22681 aggaaatgac ctaagggttg acggagccag cattaagttt gatagcattt gcctttacgc

```

FIG. 24A-7

58/126

22741 caccttcttc cccatggccc acaacaccgc ctccacgctt gaggccatgc ttagaaacga
22801 caccaacgac cagtccttta acgactatct ctccgccgcc aacatgctct accctatacc
22861 cgccaacgct accaacgtgc ccatatccat cccctccgcg aactgggcgg ctttccgcgg
22921 ctgggccttc acgcgcctta agactaagga aaccccatca ctgggctcgg gctacgaccc
22981 ttattacacc tactctggct ctatacccta cctagatgga accttttacc tcaaccacac
23041 ctttaagaag gtggccatta cctttgactc ttctgtcagc tggcctggca atgaccgcct
23101 gcttaccccc aacgagtttg aaattaagcg ctgagttgac ggggagggtt acaacgttgc
23161 ccagtgtaac atgaccaaaag actggttcct ggtacaaatg ctagctaact ataacattgg
23221 ctaccagggc ttctatatcc cagagagcta caaggaccgc atgtactcct tctttagaaa
23281 cttccagccc atgagccgtc aggtgggtgga tgatactaaa tacaaggact accaacaggt
23341 gggcatccta caccaacaca acaactctgg atttgttggc taccttgccc ccaccatgcg
23401 cgaaggacag gcctaccctg ctaacttccc ctatccgctt ataggcaaga ccgcagttga
23461 cagcattacc cagaaaaagt ttctttgcga tcgcaccctt tggcgcaccc cattctccag
23521 taactttatg tccatgggcg cactcacaga cctgggcca aaccttctct acgccaactc
23581 cgccacgcg ctagacatga cttttgaggt ggatcccatg gacgagccca ccttcttta
23641 tgttttgttt gaagtctttg acgtggtccg tgtgcaccag ccgcacgcgg gcgtcatcga
23701 aaccgtgtac ctgcgcacgc ccttctcggc cggcaacgcc acaacataaa gaagcaagca
23761 acatcaacaa cagctgccgc catgggctcc agtgagcagg aactgaaagc cattgtcaaa
23821 gatcttggtt gtgggccata ttttttgggc acctatgaca agcgctttcc aggctttgtt
23881 tctccacaca agctcgctg cgccatagtc aatacggccg gtcgcgagac tgggggcgta
23941 cactggatgg cctttgcctg gaaccgcac tcaaaaacat gctacctctt tgagcccttt
24001 ggcttttctg accagcgact caagcaggtt taccagtttg agtacgagtc actcctgcgc
24061 cgtagcgcca ttgcttcttc ccccgaccgc tgtataacgc tggaaaagtc cacccaaagc
24121 gtacaggggc ccaactcggc cgctgtgga ctattctgct gcatgtttct ccacgccttt
24181 gccaactggc cccaaactcc catggatcac aacccacca tgaaccttat taccggggta
24241 cccaactcca tgctcaacag tccccaggta cagccacccc tgcgtcgcaa ccaggaacag
24301 ctctacagct tcctggagcg ccactcgccc tacttccgca gccacagtgc gcagattagg
24361 agcgccactt ctttttgtca cttgaaaaac atgtaaaaat aatgtactag agacactttc
24421 aataaaggca aatgctttta tttgtacact ctccgggtgat tatttaccce cacccttgcc
24481 gtctgcgcgg tttaaaaatc aaaggggttc tgccgcgcac cgctatgcgc cactggcagg
24541 gacacgttgc gatactggtg tttagtgtc cacttaaact caggcacaac catccgcggc
24601 agctcgggtg agttttcact ccacaggctg cgcaccatca ccaacgcgtt tagcaggtcg
24661 ggcgcgcgata tcttgaagtc gcagttgggg cctccgcctt gcgcgcgcga gttgcgatac
24721 acaggggttg agcactggaa cactatcagc gccgggtggt gcacgctggc cagcacgctc
24781 ttgtcggaga tcagatccgc gtccagggtc tccgcgttgc tcagggcgaa cggagtcaac
24841 tttggtagct gccttcccaa aaagggcgcg tgcccaggct ttgagttgca ctgcaccgt
24901 agtggcatca aaaggtgacc gtgcccggtc tgggcgttag gatacagcgc ctgcataaaa
24961 gccttgatct gcttaaaagc cacctgagcc tttgcgcctt cagagaagaa catgccgcaa
25021 gacttgccgg aaaactgatt ggccggacag gccgcgtcgt gcacgcagca ccttgcgctc
25081 gtgttgagga tctgcaccac atttcggccc caccggttct tcacgatctt ggccttgcta
25141 gactgctcct tcagcgcgcg ctgcccgttt tcgctcgtca catccatttc aatcacgtgc
25201 tccttattta tcataatgct tccgtgtaga cacttaagct cgccttcgat ctgacgcgag
25261 cgggtgcagc acaacgcgca gcccggtggc tcgtgatgct tgtaggtcac ctctgcaaac
25321 gactgcaggt acgcctgcag gaatcgcccc atcatcgtca caaaggctct gttgctggtg
25381 aaggtcagct gcaaccgcg gtgctcctcg ttcagccagg tcttgcatat ggcgcgcaga
25441 gcttccactt ggtcaggcag tagtttgaag ttcgccttta gatcgttatc cacgtggtac
25501 ttgtccatca gcgcgcgcgc agcctccatg cccttctccc acgcagacac gatcggcaca
25561 ctgacgggtt tcatcaccgt aatttcaact tccgcttcgc tgggctcttc ctcttctct
25621 tgcgtccgca taccacgcgc cactgggtcg tcttcattca gccgcgcac tgtgcgtta
25681 cctcctttgc catgcttgat tagcacgggt ggggtgctga aaccaccat ttgtagcgcc
25741 acatcttctc tttcttctc gctgtccacg attacctctg gtgatggcgg gcgctcgggc
25801 ttgggagaag ggcgttctt tttcttctt ggcgcaatgg ccaaaccgc cgccgaggtc
25861 gatggcgcg ggctgggtgt gcgcggcacc agcgcgtctt gtgatgagtc ttctcgtcc
25921 tcggactcga tacgcgcct catccgctt tttggggcg cccggggagg cggcggcgac
25981 ggggacgggg acgacacgct cccatgggtt gggggacgct gcgcgcaccc gcgtccgcgc

FIG. 24A-8

59/126

26041 tcgggggtgg tttcgcgctg ctctcttcc cgactggcca tttccttctc ctataggcag
26101 aaaaagatca tggagtcagt cgagaagaag gacagcctaa ccgccccctc tgagttcgcc
26161 accaccgctt ccaccgatgc cgccaacgcg cctaccacct tccccgtcga ggcacccccg
26221 cttgaggagg aggaagtgat tatcgagcag gacccagggt ttgtaagcga agacgacgag
26281 gaccgctcag taccaacaga ggataaaaag caagaccagg acaacgcaga ggcaaacgag
26341 gaacaagtgc ggcgggggga cgaaaggcat ggcgactacc tagatgtggg agacgacgtg
26401 ctggttgaagc atctgcagcg ccagtgcgcc attatctgcg acgcgttgca agagcgcagc
26461 gatgtgcccc tcgccatagc ggatgtcagc cttgcctacg aacgccacct attctcaccg
26521 cgcgtacccc ccaaacgcca agaaaacggc acatgcgagc ccaaccgcg cctcaacttc
26581 taccocgtat ttgccgtgcc agaggtgctt gccacctatc acatcttttt ccaaaactgc
26641 aagatacccc tatcctgccg tgccaaccgc agccgagcgg acaagcagct ggccttgccg
26701 cagggcgctg tcatacctga tatcgccctc ctcaacgaag tgccaaaaat ctttgagggt
26761 cttggacgcg acgagaagcg cgcggcaaac gctctgcaac aggaaaacag cgaaaatgaa
26821 agtcactctg gagtgttggg ggaactcgag ggtgacaacg cgcgcctagc cgtactaaaa
26881 cgcagcatcg aggtcaccca ctttgcctac ccggcactta acctaccccc caaggtcatg
26941 agcacagtca tgagtgaagt gatcgtgcgc cgtgcgcagc ccctggagag ggatgcaaat
27001 ttgcaagaac aaacagagga gggcctaccc gcagttggcg acgagcagct agcgcgctgg
27061 cttcaaacgc gcgagcctgc cgacttgagg gagcgacgca aactaatgat ggccgcagtg
27121 ctcgttaccg tggagcttga gtgcatgcag cggttctttg ctgaccgga gatgcagcgc
27181 aagctagagg aaacattgca ctacaccttt cgacagggct acgtacgcca ggcctgcaag
27241 atctccaacg tggagctctg caacctggtc tcctaccttg gaattttgca cgaaaaccgc
27301 cttgggcaaa acgtgcttca ttccacgctc aagggcgagg cgcgccgca ctacgtccgc
27361 gactgcgttt acttattttt atgctacacc tggcagacgg ccatgggctt ttggcagcag
27421 tgcttgagg agtgcaacct caaggagctg cagaaactgc taaagcaaaa cttgaaggac
27481 ctatggacgg ccttcaacga gcgctcgtg gccgcgcacc tggcggacat cattttcccc
27541 gaacgcctgc ttaaaaccct gcaacagggt ctgccagact tcaccagtca aagcatgttg
27601 cagaacttta ggaactttat cctagagcgc tcaggaatct tgcccggcac ctgctgtgca
27661 cttcctagcg actttgtgcc cattaagtac cgcaatgcc ctccgcegt ttggggccac
27721 tgctaccttc tgcagctagc caactacctt gcctaccact ctgacataat ggaagacgtg
27781 agcggtgacg gtctactgga gtgtcactgt cgctgcaacc tatgcacccc gcaccgctcc
27841 ctggtttgca attcgcagct gcttaacgaa agtcaaatta tcggtacctt tgagctgcag
27901 ggtccctcgc ctgacgaaaa gtccgcggct ccggggttga aactcactcc ggggctgtgg
27961 acgtcggctt accttcgcaa atttgtacct gaggactacc acgcccacga gattaggttc
28021 tacgaagacc aatcccgccc gcctaattgc gagcttaccg cctgcgtcat taccagggc
28081 cacattcttg gccaatgca agccatcaac aaagcccgcc aagagtttct gctacgaaag
28141 ggacgggggg tttacttgga ccccagtc ccgagaggag tcaaccat acacccgccc
28201 ccgacgacct atcagcagca gccgcgggcc cttgcttccc aggatggcac ccaaaaagaa
28261 gctgcagctg ccgcccgcac ccacggacga ggaggaatac tgggacagtc aggcagagga
28321 ggttttggac gaggaggagg aggacatgat ggaagactgg gagagcctag acgaggaagc
28381 ttccgaggtc gaagagggtg cagacgaaac accgtcaccc tcggtcgcac tcccctcgcc
28441 ggcgccccag aaatcggcaa ccggttcag catggctaca acctccgctc ctacggcgcc
28501 gccggcactg cccgttcgcc gacccaaccg tagatgggac accactggaa ccaggggccg
28561 taagtccaag cagccgcccgc cgttagccca agagcaacaa cagcgccaag gctaccgctc
28621 atggcgcggg cacaagaacg ccatagttgc ttgcttgcaa gactgtgggg gcaacatctc
28681 cttcgccccg cgctttcttc tctaccatca cggcgtggcc tcccccgta acatcctgca
28741 ttactaccgt catctctaca gcccatactg caccggcgcc agcggcagca acagcagcgg
28801 ccacacagaa gcaaaggcga ccgcatagca agactctgac aaagcccaag aaatccacag
28861 cggcggcagc agcaggagga ggagcgtgct gtctggcgcc caacgaaccc gtatcgaccc
28921 gcgagcttag aaacaggatt tttccactc tgtatgctat atttcaacag agcaggggccc
28981 aagaacaaga gctgaaaata aaaaacagg ctctgcgac cctcaccgac agctgcctgt
29041 atcacaaaag cgaagatcag cttcggcgca cgctggaaga cgcggaggct ctcttcagta
29101 aatactgcgc gctgactctt aaggactagt ttccgcccct ttctcaaatt taagcgcgaa
29161 aactacgtca tctccagcgg ccacacccgg ccgcagcacc tgttgctcag gccattatga
29221 gcaaggaaat tcccacgccc tacatgtgga gttaccagcc acaaatggga cttgcggctg
29281 gagctgcccc agactactca acccgaataa actacatgag cgcgggaccc cacatgat

FIG. 24A-9

60/126

29341 cccgggtcaa cggaatacgc gccaccgaa accgaattct cctggaacag gcggctatta
29401 ccaccacacc tcgtaataac cttaatcccc gtagttggcc cgctgccctg gtgtaccagg
29461 aaagtcccg cccaccact gtggtacttc ccagagacgc ccaggccgaa gttcagatga
29521 ctaactcagg ggcgcagctt gcgggcggct ttcgtcacag ggtgcggtcg cccgggcagg
29581 gtataactca cctgacaatc agagggcgag gtattcagct caacgacgag tcggtgagct
29641 cctcgcttgg tctcgtccg gacgggacat ttcagatcgg cggcgccggc cgctcttcat
29701 tcacgcctcg tcaggcaatc ctaactctgc agacctcgtc ctctgagccg cgctctggag
29761 gcattggaac tctgcaattt attgaggagt ttgtgccatc ggtctacttt aacccttct
29821 cgggacctcc cggccactat cgggatcaat ttattcctaa ctttgacgcg gtaaaggact
29881 cggcggacgg ctacgactga atgttaagt gagaggcaga gcaactgcgc ctgaaacacc
29941 tgggccactg tcgccgccac aagtgccttg cccgcgactc cggtgagttt tgctactttg
30001 aattgcccga ggatcatatc gagggcccgg cgcacggcgt ccggcttacc gccaggggag
30061 agcttgcccg tagcctgatt cgggagttta cccagcgccc cctgctagtt gagcgggaca
30121 ggggacctg tgttctcact gtgatttgca actgtcctaa ccctggatta catcaagatc
30181 ctctagttat aactagagta cccggggatc ttattccctt taactaataa aaaaaataa
30241 taaagcatca cttacttaaa atcagttagc aaatttctgt ccagtttatt cagcagcacc
30301 tccttgccct cctccagct ctggtattgc agcttccctc tggctgcaaa ctttctccac
30361 aatctaaatg gaatgtcagt ttcctcctgt tcctgtccat ccgcaccac tatcttcatg
30421 ttgttgca gaagcgcg aagaccgtct gaagatacct tcaaccccg gtatccatat
30481 gacacggaaa ccggtcctcc aactgtgcct tttcttactc ctccctttgt atccccaat
30541 gggtttcaag agagtcccc tggggctactc tctttgcgcc tatccgaacc tctagttacc
30601 tccaatggca tgcttgcgct caaatgggc aacggcctct ctctggacga ggccggcaac
30661 cttacctccc aaaatgtaac cactgtgagc ccacctctca aaaaaacca gtcaaacata
30721 aacctggaaa tatctgcacc cctcacagtt acctcagaag ccctaactgt ggctgccgcc
30781 gcacctctaa tggctgcggg caacacactc accatgcaat cacaggcccc gctaaccgtg
30841 cacgactcca aacttagcat tgccacccaa ggaccctca cagtgtcaga aggaaagcta
30901 gccctgcaaa catcaggccc cctcaccacc accgatagca gtacccttac tatcactgcc
30961 tcacccctt taactactgc cactggtagc ttgggcattg acttgaaaga gccatttat
31021 acacaaaatg gaaaactagg actaaagtac ggggctcctt tgcagtgaac agacgacct
31081 aacactttga ccgtagcaac tgggtccagg gtgactatta ataatacttc cttgcaaact
31141 aaagttactg gagccttggg ttttgattca caaggcaata tgcaacttaa tgtagcagga
31201 ggactaagga ttgattctca aaacagacgc cttatacttg atgttagtta tccgtttgat
31261 gctcaaaacc aactaaatct aagactagga cagggccctc tttttataaa ctcagccac
31321 aacttgata ttaactacaa caaaggcctt tacttgttta cagcttcaaa caattccaaa
31381 aagcttgagg ttaacctaag cactgccaag ggggtgatgt ttgacgtac agccatagcc
31441 attaagcag gagatgggt tgaatttgg tccactaatg caccaaacac aaatcccctc
31501 aaaacaaaaa ttggccatgg cctagaattt gattcaaca aggctatgg tccataacta
31561 ggaactggcc ttagttttga cagcacaggt gccattacag taggaaacaa aaataatgat
31621 aagctaactt tgtggaccac accagctcca tctcctaact gtagactaaa tgcagagaaa
31681 gatgctaaac tcactttgg ttaacaaaaa tgtggcagtc aaatacttgc tacagtttca
31741 gttttggctg ttaaaggcag tttggctcca atatctggaa cagttcaaag tgctcatctt
31801 attataagat ttgacgaaaa tggagtgtca ctaaacaatt ccttcctgga cccagaatat
31861 tggaaacttta gaaatggaga tcttactgaa ggcacagcct atacaaacgc tgttggattt
31921 atgcctaacc tatcagctta tccaaaatct cacggtaaaa ctgcaaaaag taacattgtc
31981 agtcaagttt acttaaacgg agacaaaact aaacctgtaa cactaaccat tacactaaac
32041 ggtacacagg aaacaggaga cacaactcca agtgatact ctatgtcatt ttcattggac
32101 tggctctggc acaactacat taatgaaata tttgccacat cctcttacac tttttcatac
32161 attgcccaag aataaagaat cgtttgtgtt atgtttcaac gtgtttattt ttcaattgca
32221 gaaaatttca agtcattttt cattcagtag tatagcccca ccaccacata gcttatacag
32281 atcaccgtac cttaatcaaa ctcacagaac cctagtatc aacctgccac ctccctccca
32341 acacacagag tacacagtc tttctccccg gctggcctta aaaagcatca tatcatgggt
32401 aacagacata ttcttaggtg ttatatcca cacggtttcc tgtcgagcca aacgctcatc
32461 agtgatatta ataaactccc cgggcagctc acttaagtcc atgtcgctgt ccagctgctg
32521 agccacaggc tgctgtccaa cttgcggtt cttaacgggc ggcaaggag aagtccacgc
32581 ctacatgggg gtagagtc atcgtgcat caggataggg cgggtggtgt gcagcagcgc

FIG. 24A-10

WO 2006/020480

PCT/US2005/027658

61/126

```

32641 gcgaataaac tgctgccgcc gccgctccgt cctgcaggaa tacaacatgg cagtgggtctc
32701 ctcagcgatg attcgcaccg cccgcagcat aaggcgccctt gtcctccggg cacagcagcg
32761 caccctgatc tcacttaaatt cagcacagta actgcagcac agcaccacaa tattgttcaa
32821 aatcccacag tgcaaggcgc tgtatccaaa gctcatggcg gggaccacag aaccacgtg
32881 gccatcatac cacaagcgca ggtagattaa gtggcgaccc ctcataaaca cgctggacat
32941 aaacattacc tcttttggca tgttgtaatt caccacctcc cggtaccata taaacctctg
33001 attaaacatg gcgccatcca ccaccatcct aaaccagctg gccaaaacct gcccgccggc
33061 tatacactgc agggaaaccgg gactggaaca atgacagtgg agagcccagg actcgtaacc
33121 atggatcatc atgctcgtca tgatatcaat gttggcacia cacaggcaca cgtgcataca
33181 cttcctcagg attacaagct cctcccgcgt tagaaccata tcccaggga caaccattc
33241 ctgaatcagc gtaaatccca cactgcaggg aagacctcgc acgtaactca cgttgtgcat
33301 tgtcaaagtg ttacattcgg gcagcagcgg atgatcctcc agtatggtag cgcgggttc
33361 tgtctcaaaa ggaggtagac gatccctact gtacggagtg cgcgagaca accgagatcg
33421 tgttggtcgt agtgtcatgc caaatggaac gccggacgta gtcataattc ctgaagcaaa
33481 accaggtgcg ggcgtgacaa acagatctgc gtctccggtc tcgccgtta gatcgctctg
33541 tgtagtagtt gtagtatatc cactctctca aagcatccag gcgccccctg gcttcgggtt
33601 ctatgtaaac tccttcatgc gccgctgccc tgataacatc caccaccgca gaataagcca
33661 caccagcca acctacacat tcgttctgcy agtcacacac gggaggagcg ggaagagctg
33721 gaagaaccat gttttttttt ttattccaaa agattatcca aaacctcaa atgaagatct
33781 attaatgaa cgcgctccc tccggtggcg tggtaaaact ctacagcaa agaacagata
33841 atggcatttg taagatgttg cacaatggct tccaaaaggc aaacggccct cagtcceaag
33901 tggacgtaaa ggctaaaccc ttcagggtga atctcctcta taaacattcc agcaccttca
33961 accatgcca aataattctc atctcgccac cttctcaata tatctctaag caaatcccga
34021 atattaagtc cggccattgt aaaaatctgc tccagagcgc cctccacctt cagcctcaag
34081 cagcgaatca tgattgcaaa aattcaggtt cctcacagac ctgtataaga ttcaaaagcg
34141 gaacattaac aaaaataccg cgatcccgtg ggtcccttcg cagggccagc tgaacataat
34201 cgtgcaggte tgacaggacc agcgcgccca cttccccgcc aggaaccatg acaaaagaac
34261 ccacactgat tatgacacgc atactcggag ctatgctaac cagcgtagcc ccgatgtaag
34321 cttgttgcat gggcgcgcat ataaaatgca aggtgctgct caaaaaatca ggcaaagcct
34381 cgcgcaaaaa agaaagcaca tcgtagtcac gctcatgcag ataaaggcag gtaagctccg
34441 gaaccaccac agaaaaagac accatttttc tctcaaacat gtctgcgggt ttctgcataa
34501 acacaaaata aaataacaaa aaaacattta aacattagaa gcctgtctta caacaggaaa
34561 aacaaccctt ataagcataa gacggactac ggccatgccg gcgtgaccgt aaaaaaactg
34621 gtcaccgtga ttaaaaagca ccaccgacag ctctcgggtc atgtccggag tcataatgta
34681 agactcggta aacacatcag gttgattcac atcggtcagt gctaaaaagc gaccgaaata
34741 gcccggggga atacataccc gcaggcgtag agacaacatt acagcccca taggaggtat
34801 aacaaaatta ataggagaga aaaacacata aacacctgaa aaacctcct gcctaggcaa
34861 aatagcacc ccccgctcca gaacaacata cagcgcttcc acagcggcag ccataacagt
34921 cagccttacc agtaaaaaag aaaacctatt aaaaaaacac cactcgacac ggcaccagct
34981 caatcagtca cagtgtaaaa aagggccaa gtcagagcga gtatatatag gactaaaaaa
35041 tgacgtaacg gttaaagtcc acaaaaaaca cccagaaaac cgcacgcgaa cctacgcca
35101 gaaacgaaag ccaaaaaacc cacaacttcc tcaaatcgtc acttccgttt tcccacgtta
35161 cgtcacttcc cattttaaga aaactacaat tcccaacaca tacaagttac tccgccctaa
35221 aacctacgtc acccgccccg tccccacgcc ccgcgccacg tcacaaactc caccctctca
35281 ttatcatatt ggcttcaatc caaataagg tatattattg atgatg (SEQ ID NO: 18)

```

FIG. 24A-11

62/126

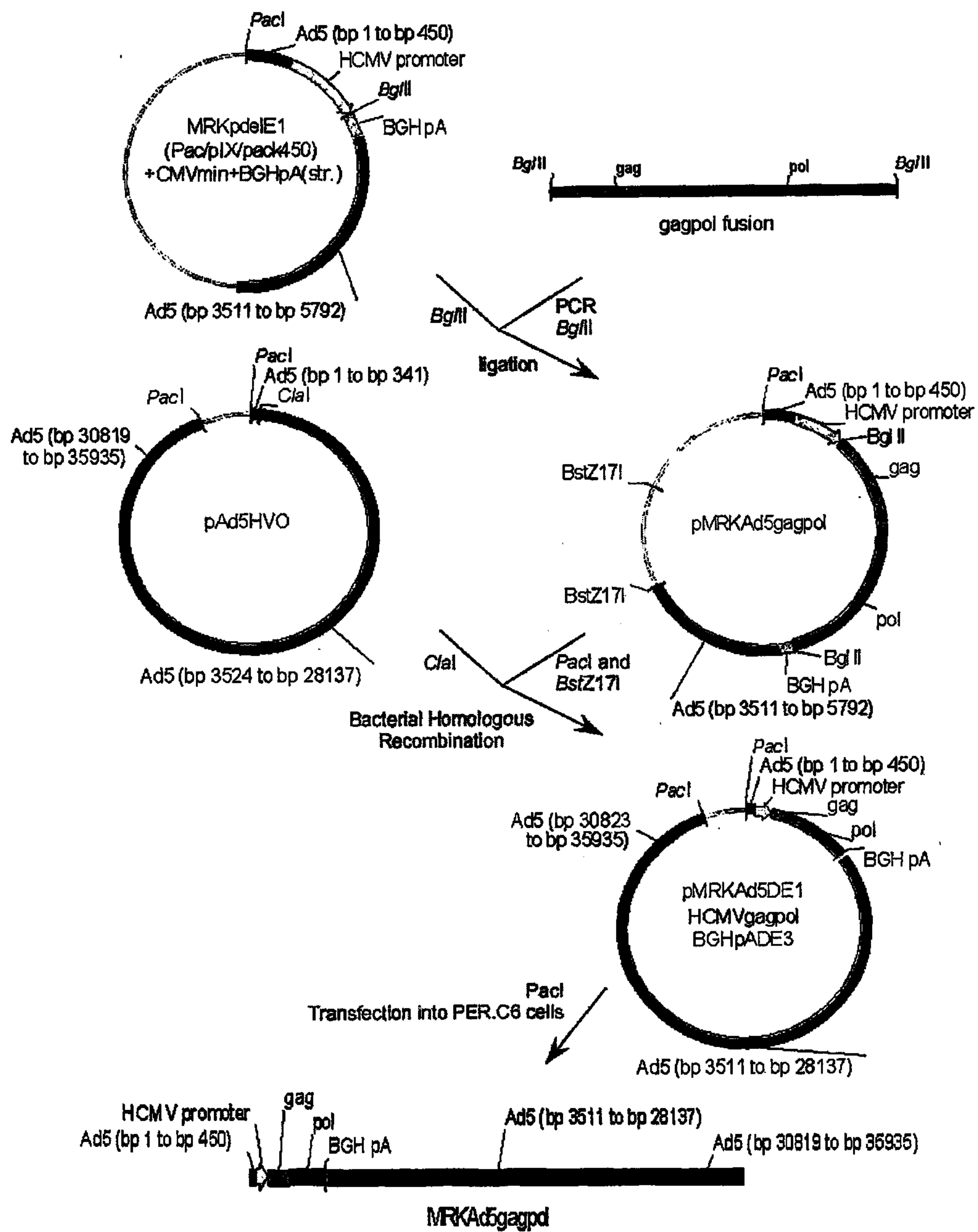


FIG. 25

63/126

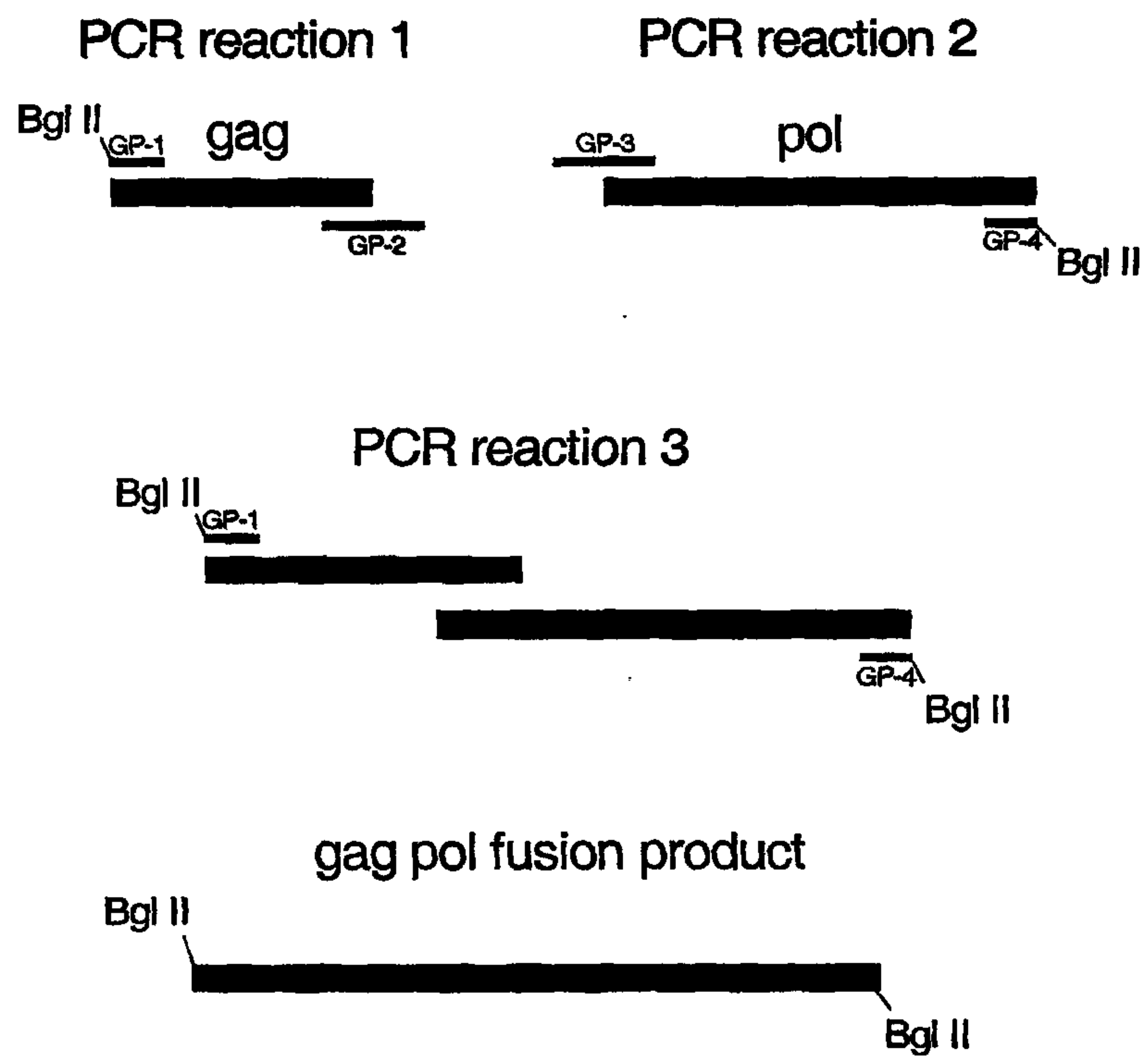


FIG. 26

64/126

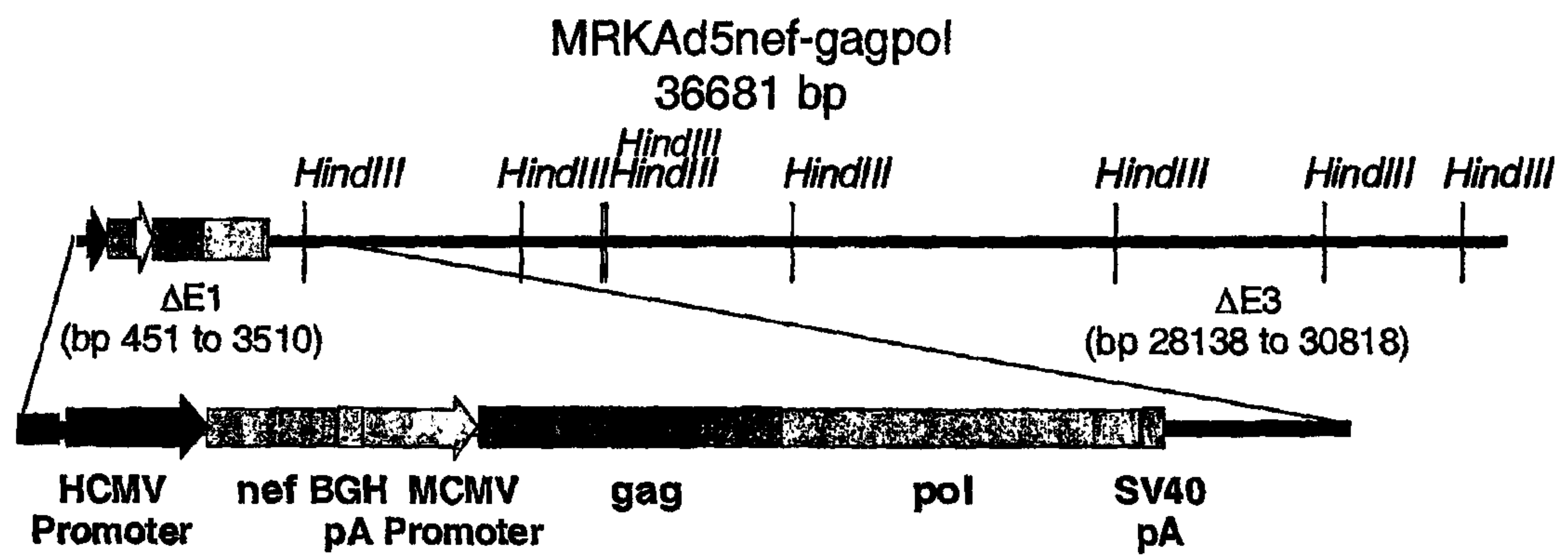


FIG. 27

WO 2006/020480

PCT/US2005/027658

65/126

MRKAd5nef-gagpol

KEY: HCMV promoter Nef BGH pA MCMV promoter Gag Pol SV40 pA

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg ggcgggggcg tgggaacggg gcggtgacg tagtagtggt gcggaagtgt
121 gatgttgcaa gtgtggcgga acacatgtaa gcgacggatg tggcaaaagt gacgtttttg
181 gtgtgcgcgc gtgtacacag gaagtgcaca ttttcgcgcg gttttaggcg gatgttgtag
241 taaatttggg cgtaaccgag taagatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataatttt gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcggttt attattatag gcggccgcga tccattgcat acgttgatc
481 catatcataa tatgtacatt tatattggct catgtccaac attaccgcca tgttgacatt
541 gattattgac tagttattaa tagtaataca ttacgggggc attagttcat agccatata
601 tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc
661 cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc
721 attgacgtca atgggtggag tatttacggg aaactgcccc cttggcagta catcaagtgt
781 atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt
841 atgcccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca
901 tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg
961 actcacgggg atttccaagt ctcaccccca ttgacgtcaa tgggagtttg ttttggcacc
1021 aaaatcaacg ggactttcca aaatgtcgta acaactccgc ccattgacg caaatgggcg
1081 gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgtcagatcg
1141 cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac ccatccagcc
1201 tccgcggccg ggaacgggtg attggaacgc ggattccccg tgccaagagt gagatctgcc
1261 accatggccc gcaagtggtc caagaggtcc gtgcccggct ggtccaccgt gaggagaggg
1321 atgaggaggg ccgagcccgc cgcgacagg gtgaggagga ccgagcccgc cgcagtgggc
1381 gtgggcggcg tgtccaggga cctggagaag cacggcgcca tcacctctc caacaccgcc
1441 gccaccaacg ccgactgcgc ctggctggag gccagggagg acgaggaggt gggcttcccc
1501 gtgaggcccc aggtgcccct gaggcccatg acctacaagg gcgccgtgga cctgtccac
1561 ttcctgaagg agaaggcgag cctggaggac ctgattccact ccagaagag gcaggacatc
1621 ctggacctgt ggtgtacca caccagggc tacttccccg actggcagaa ctacaccccc
1681 ggcggcgcca tcaggttccc cctgaccttc ggctggtgct tcaagctggt gccggtggag
1741 cccgagaagg tggaggaggg caacgagggc gagaacaact gcctgctgca cccatgtcc
1801 cagcacggca tcgaggaccc cgagaaggag gtgctggagt ggaagttcga ctccaagctg
1861 gccttccacc acgtggccag ggaactgcac cccgagtact acaaggactg ctaaagcccg
1921 ggcagatctg ctgtgacctc tagttgccag ccatctgttg tttgcccctc cccggtgctt
1981 tccttgaccc tgggaaggtg cactccact gtcctttcct aataaaatga ggaattgca
2041 tcgcattgtc tgagtagggt tcattctatt ctggggggtg ggtgggggca ggaagcaag
2101 ggggaggatt ggaagacaa tagcaggcat gctggggatg cgtgggctc tatggccgat
2161 cggcgcgcca tatactgagt cattagggac ttccaatgg gttttgcca gtacataagg
2221 tcaatagggg tgaatcaaca gaaagtccc attggagcca agtacactga gtcaataggg
2281 actttccatt gggttttgcc cagtacaaa ggtcaatagg ggtgagtc atgggttttt
2341 ccattattg gcacgtacat aaggtcaata ggggtgagtc attgggtttt tccagccaat
2401 ttataaaacg ccatgtactt tcccaccatt gacgtcaatg gctattgaa actaatgcaa
2461 cgtgaccttt aaacgggtact ttcccatagc tgattaatgg gaaagtaccg ttctcgagcc
2521 aatacacgtc aatgggaagt gaaagggcag ccaaacgta acaccgccc ggttttcccc
2581 tggaaattcc atattggcac gcattctatt gctgagctg cgttctacgt ggtataaga
2641 ggcgggacca gcgtcggtac cgtcgagtc ttccgtctga ccaccgtaga acgcagatcg
2701 agatctacca tgggtgctag ggcttctgt ctgtctggtg gtgagctgga caagtgggag
2761 aagatcaggg tgaggcctgg tggcaagaag aagtacaagg taaagcacat tgtgtgggcc
2821 tccagggagc tggagaggtt tgctgtgaac cctggcctgc tggagacctc tgagggtgc
2881 aggcagatcc tgggccagct ccagccctcc ctgcaaacag gctctgagga gctgaggtcc

```

FIG. 28A-1

66/126

2941 ctgtacaaca cagtggctac cctgtactgt gtgcaccaga agattgatgt gaaggacacc
3001 aaggaggccc tggagaagat tgaggaggag cagaacaagt ccaagaagaa gggccagcag
3061 gctgctgctg gcacaggcaa ctccagccag gtgtcccaga actaccccat tgtgcagaac
3121 ctccagggcc agatggtgca ccaggccatc tccccccgga cctgaatgc ctgggtgaag
3181 gtggtggagg agaaggcctt ctcccctgag gtgatccca tgttctctgc cctgtctgag
3241 ggtgccaccc cccaggacct gaacaccatg ctgaacacag tggggggcca tcaggctgcc
3301 atgcagatgc tgaaggagac catcaatgag gaggctgctg agtgggacag gctgcacctt
3361 gtgcacgctg gcccattgc cccgggccag atgaggaggc ccaggggctc tgacattgct
3421 ggcaccacct ccaccctcca ggagcagatt ggctggatga ccaacaacc ccccatccct
3481 gtgggggaaa tctacaagag gtggatcatc ctgggcctga acaagattgt gaggatgtac
3541 tccccacctt ccattctgga catcaggcag gggcccaagg agcccttcag ggactatgtg
3601 gacaggttct acaagacctt gagggctgag caggcctccc aggaagtgaa gaactggatg
3661 acagagaccc tgctggtgca gaatgccaac cctgactgca agaccatcct gaaggccctg
3721 ggcctgctg ccaccctgga ggagatgatg acagcctgcc agggggtggg gggcctggt
3781 cacaaggcca ggtgctggc tgaggccatg tcccaggta ccaactccgc caccatcatg
3841 atgcagaggg gcaacttcag gaaccagagg aagacagtga agtgcttcaa ctgtggcaag
3901 gtgggccaca ttgccaaaga ctgtagggcc cccaggaaga agggctgctg gaagtgtggc
3961 aaggaggccc accagatgaa ggaactgcaat gagaggcagg ccaacttcct gggcaaatc
4021 tggccctccc acaagggcag gctggcaac ttcctccagt ccaggcctga gcccacagcc
4081 cctcccaggg agtccttcag gtttggggag gagaagacca ccccagcca gaagcaggag
4141 cccattgaca aggagctgta cccctggcc tccctgaggt cctgtttgg caacgacccc
4201 tctcccagc ccattctccc cattgagact gtccctgta agctgaagcc tggcatggat
4261 gggcccaagg tgaagcagtg gcccctgact gaggagaaga tcaaggccct ggtggaaatc
4321 tgactgaga tggagaagga gggcaaatc tccaagattg gcccagaga cccctacaac
4381 accctgtgtt ttgcatcaa gaagaaggac tccaccaagt ggaggaaagt ggtggacttc
4441 agggagctga acaagaggac ccaggacttc tgggaggtgc agctggcat ccccacccc
4501 gctggcctga agaagaagaa gtctgtgact gtgctgctg tgggggatgc ctacttctct
4561 gtgcccctgg atgaggactt caggaagtac actgccttca ccattccctc catcaacaat
4621 gagaccctg gcattcagta ccagtacaat gtgctgccc agggctggaa gggctccct
4681 gccattctcc agtcctccat gaccaagatc ctggagccct tcaggaaqca gaacctgac
4741 attgtgatct accagtacat gctgcccctg tatgtgggt ctgacctga gattggcag
4801 cacaggacca agattgagga gctgaggcag cactgctga ggtggggcct gaccaccct
4861 gacaagaagc accagaagga gcccctctc ctgtggatgg gctatgagct gcacccgac
4921 aagtggactg tgcagcccat tgtgctgctt gagaaggact cctggactgt gaatgacatc
4981 cagaagctgg tgggcaagct gaactgggc tcccaaatct accctggcat caaggtgagg
5041 cagctgtgca agctgctgag gggcaccag gccctgactg aggtgatccc cctgactgag
5101 gaggctgagc tggagctggc tgagaacagg gagatcctga aggagcctgt gcatggggtg
5161 tactatgacc cctccaagga cctgattgct gagatccaga agcagggcca gggccagtgg
5221 acctaccaa tctaccagga gcccttcaag aacctgaaga ctggcaagta tggcaggatg
5281 aggggggccc acaccaatga tgtgaagcag ctgactgagg ctgtgcagaa gatcaccact
5341 gagtccattg tgatctgggg caagacccc aagttcaagc tggccatcca gaaggagacc
5401 tgggagacct ggtggactga gtactggcag gccacctga tccctgagt ggaagtttgt
5461 aacacccccc cctggtgaa gctgtgttac cagctggaga aggagcccat tgtggggct
5521 gagaccttct atgtggctgg gctgccaac agggagacca agctggcaa ggtgactat
5581 gtgaccaaca ggggcaggca gaaggtggtg accctgactg acaccacca ccagaagact
5641 gccctccagg ccattctacct gcccctccag gactctggcc tggaggtgaa cattgtgact
5701 gccctccagt atgccctggg catcatccag gccagcctg atcagttctga gtctgagctg
5761 gtgaaccaga tcattgagca gctgatcaag aaggagaagg tttacctggc ctgggtgctt
5821 gccacaagg gcattgggg caatgagcag gtggacaagc tgggtgtctg tggcatcagg
5881 aaggtgctgt tctgagatgg cattgacaag gccagagatg agcatgagaa gtaccactcc
5941 aactggaggg ctatggcctc tgaattcaac ctgcccctg tgggtgctaa ggagatttgt
6001 gccctctgtg acaagtcca gctgaagggg gaggccatgc atgggcaggt ggactgctcc
6061 cctggcatct ggcagctggc ctgacccac ctggaggcca aggtgatcct ggtggctgtg
6121 catgtggcct ccggtacat tgaggctgag gtgatccctg ctgagacagg ccaggagact
6181 gccacttcc tgctgaagct gctggcagg tggcctgtga agaccatcca cactgccaat

FIG. 28A-2

WO 2006/020480

PCT/US2005/027658

67/126

6241 ggctccaact tcaactggggc cacagtgaag gctgcctgct ggtgggctgg catcaagcag
 6301 gaqtttggca tccctacaa ccccaagtc cagggggtgg tggcctccat gaacaaggag
 6361 ctgaagaaga tcattgggca ggtgaggag caggctgagc acctgaagac agctgtgca
 6421 atggctgtgt tcatccacaa cttcaagagg aaggggggca tgggggcta ctccgctggg
 6481 gagaggattg tggacatcat tggcacagac atccagacca aggagctcca gaagcagatc
 6541 accaagatcc agaacttcag ggtgtactac agggactcca ggaacccctc gtggaagggc
 6601 cctgccaaag tctgtggaa gggggagggg gctgtggtga tccaggacaa ctctgacatc
 6661 aaggtggtgc ccaggaggaa ggccaagatc atcagggact atggcaagca gatggctggg
 6721 gatgactgtg tggcctccag gcaggatgag gactaaagcc cgggcagatc taacttgttt
 6781 attgcagctt ataatggtta caaataaagc aatagcatca caaatctcac aaataaagca
 6841 tttttttcac tgcattctag ttgtggtttg tccaaactca tcaatgtatc ttatcatgtc
 6901 tggatcggcg cgccgtactg aaatgtgtgg gcgtggctta aggggtggga agaataatata
 6961 aggtgggggt cttatgtagt tttgtatctg ttttgcagca gccgccgccg ccatgagcac
 7021 caactcgttt gatggaagca ttgtgagctc atatttgaca acgcgcagtc ccccatgggc
 7081 cggggtgctg cagaatgtga tgggctccag cattgatggg cggcccgctc tgcccgcaa
 7141 ctctactacc ttgacctag agaccgtgtc tggaaagccg ttggagactg cagcctccgc
 7201 cgccgcttca gccgtgcag ccaccgcccg cgggattgtg actgactttg ctttcctgag
 7261 cccgcttgca aacagtgcag cttcccgctc atccgccgcg gatgacaagt tgacggctct
 7321 tttggcacia ttggattctt tgaccggga actaatgtc gtttctcagc agctgttga
 7381 tctgcgccag caggtttctg cctgaagge ttcctccct cccaatgcgg tttaaaacat
 7441 aaataaaaaa ccagactctg tttggatttg gatcaagcaa gtgtcttgct gtctttattt
 7501 aggggttttg cgcgcgcggg agggccggga ccagcggctc cggtcggtga gggctcgtg
 7561 tattttttcc aggacgtggg aaaggtgact ctggatgttc agatacatgg gcataagccc
 7621 gtctctgggg tggaggtagc accactgcag agcttcatgc tgcggggtgg tgtgtgatg
 7681 gatccagtcg tagcaggagc gctgggctg gtgcctaaaa atgtctttca gtagcaagct
 7741 gattgccagg ggcaggccct tgggtgaagt gttacaaag cggttaagct gggatgggtg
 7801 catagctggg gatagtagat gcatcttga ctgtattttt aggttggcta tgttccagc
 7861 catatccctc cggggattca tgtgtgagc aaccaccagc acagtgtatc cgggtgactt
 7921 gggaaatttg tcatgtagct tagaaggaaa tgcgtggaag aacttggaga cgcccttgtg
 7981 acctccaaga ttttccatgc attcgtccat aatgatggca atgggcccac gggcggcggc
 8041 ctgggcgaag atatttctgg gatcactaac gtcatagttg tgttccagga tgagatcgtc
 8101 ataggccatt tttacaaagc gcgggcggag ggtgccagac tgcggtataa tggttccatc
 8161 cggcccaggg gcgtagttac cctcacagat ttgcatttcc cagccttga gttcagatgg
 8221 ggggatcatg tctacctgcg gggcgatgaa gaaaacgggt tccggggtag gggagatcag
 8281 ctgggaagaa agcagggtcc tgagcagctg cgacttaccg cagccgggtg gcccgtaa
 8341 cacacctatt accggctgca actggtagtt aagagagctg cagctgccgt catccctgag
 8401 cagggggggc acttcgttaa gcatgtccct gactcgcag ttttccctga ccaaatccgc
 8461 cagaaggcgc tcgcgcgcca gcgatagcag ttcttgcaag gaagcaaagt ttttcaacgg
 8521 tttgagaccg tccgcgtag gcatgctttt gagcgtttga ccaagcagtt ccaggcggtc
 8581 ccacagctcg gtcacctgct ctacggcatc tcgatccagc atatctctc gtttcgagg
 8641 ttggggcggc tttcgctgta cggcagtagt cgggtgctcg ccagacgggc cagggtcatg
 8701 tctttccacg ggcgcagggt cctcgtcagc gtagtctggg tcacggtgaa ggggtgcgct
 8761 ccgggctgcg cgctggccag ggtgcgcttg aggtggtcc tgggtgctg gaagcgtgc
 8821 cggctcttgc cctgcgcgtc ggccaggtag catttgacca tgggtgcata gtccagcccc
 8881 tccgcgcggt ggcccttggc gcgcagcttg cccttggagg aggcgcgca cgaggggag
 8941 tgcagacttt tgagggcgta gagcttgggc gcgagaaata ccgattccgg ggagtaggca
 9001 tccgcgcccgc aggcgccgca gacggtctcg cattccacga gccagggtgag ctctggccgt
 9061 tcgggggtcaa aaaccagggt tcccccatgc tttttgatgc gtttcttacc tctggtttcc
 9121 atgagccggt gtccacgctc ggtgacgaaa aggtgttccg tgtccccgta tacagacttg
 9181 agaggcctgt cctcgagcgg tgttcccgcg tctcctcgt atagaaactc ggaccactct
 9241 gagacaaagg ctgcgctcca ggccagcagc aaggaggcta agtgggaggg gtagcgggtc
 9301 ttgtccacta gggggtccac tcgctccagg gtgtgaagac acatgtcgcc ctcttcggca
 9361 tcaaggaagg tgattggttt gtaggtgtag gccacgtgac cgggtgttcc tgaagggggg
 9421 ctataaaagg ggggtggggc gcgttcgtcc tcaactctct ccgcacgtct gtctgcgagg
 9481 gccagctgtt ggggtgagta ctccctctga aaagcgggca tgacttctgc gctaagattg

FIG. 28A-3

68/126

9541 tcagttttcca aaaacgagga ggattttgata ttcacctggc ccgcggtgat gcctttgagg
9601 gtggccgcat ccatctgggtc agaaaagaca atctttttgt tgtcaagctt ggtggcaaac
9661 gacccgtaga gggcggttga cagcaacttg gcgatggagc gcagggtttg gtttttgtcg
9721 cgatcggcgc gctccttggc cgcgatgttt agctgcacgt attcgcgcgc aacgcaccgc
9781 cattcgggaa agacgggtgt gcgctcgtcg ggcaccaggt gcacgcgcca accgcggttg
9841 tgcagggtga caaggtaaac gctgggtggc acctctccgc gtaggcgctc gttggtccag
9901 cagaggcggc cgcccttgcg cgagcagaat ggcggtaggg ggtctagctg cgtctcgtcc
9961 ggggggtctg cgtccacggt aaagaccccg ggcagcaggc gcgcgtcgaa gtagtctatc
10021 ttgcatcctt gcaagtctag cgcctgctgc catgcgcggg cggcaagcgc gcgctcgtat
10081 ggggttgagt ggggacccca tggcatgggg tgggtgagcg cggaggcgta catgccgcaa
10141 atgtcgtaaa cgtagagggg ctctctgagt attccaagat atgtagggtg gcattctcca
10201 ccgcggtatg tggcgcgcac gtaatcgtat agttcgtgcg agggagcgag gaggtcggga
10261 ccgagggttg tacgggcggg ctgctctgct cggaaagacta tctgcctgaa gatggcatgt
10321 gagttggatg atatggttgg acgctggaag acgttgaagc tggcgtctgt gagacctacc
10381 gcgtcacgca cgaaggaggc gtaggagtcg cgcagcttgt tgaccagctc ggcggtgacc
10441 tgcacgtcta gggcgcagta gtccagggtt tccttgatga tgtcatactt atcctgtccc
10501 ttttttttcc acagctcgcg gttgaggaca aactcttcgc ggtctttcca gtactcttgg
10561 atcggaacc cgtcggcctc cgaacggtaa gagcctagca tgtagaactg gttgacggcc
10621 tggtaggcgc agcatccctt ttctacgggt agcgcgtatg cctgcgcggc cttccggagc
10681 gaggtgtggg tgagcgcaaa ggtgtccctg accatgactt tgaggtagtg gtatttgaag
10741 tcagtgtcgt cgcacccgcc ctgctcccag agcaaaaagt ccgtgcgctt tttggaacgc
10801 ggatttggca gggcgaagggt gacatcgttg aagagtatct tccccgcgcg aggcataaag
10861 ttgctgttga tgcggaagggt tcccgccacc tcggaacgggt tgttaattac ctgggcggcg
10921 agcacgatct cgtcaaagcc gttgatgttg tggcccacaa tgtaaagttc caagaagcgc
10981 gggatgccct tgatggaagg caatttttta agttcctcgt aggtgagctc ttcaggggag
11041 ctgagcccgt gctctgaaag ggcccagctc gcaagatgag ggttggaaag gacgaatgag
11101 ctccacagggt cacgggccat tagcatttgc aggtggtcgc gaaaggtcct aaactggcga
11161 cctatggcca ttttttctgg ggtgatgcag tagaaggtaa gcgggtcttg tcccagcgg
11221 tcccatccaa ggttcgcggc taggtctcgc gcggcagtcg ctagaggctc atctccgccg
11281 aacttcatga ccagcatgaa gggcagcagc tgcttcccaa agggcccat ccaagtatag
11341 gtctctacat cgtaggtgac aaagagacgc tcggtgcgag gatgcgagcc gatcgggaag
11401 aactggatct cccgccacca attggaggag tggctattga tgtggtgaaa gtagaagtcc
11461 ctgcgacggg ccgaacactc gtgctggctt ttgtaaaaac gtgcgcagta ctggcagcgg
11521 tgcacgggct gtacatcctg cacgaggttg acctgacgac cgcgcacaaag gaagcagagt
11581 gggaaattga gcccctcgcc tggcgggttt ggctggtggt cttctacttc ggctgcttgt
11641 ccttgaccgt ctggctgctc gaggggagtt acggtggatc ggaccaccac gccgcgcgag
11701 cccaaagtcc agatgtccgc gcgcggcggg cggagcttga tgacaacatc gcgcagatgg
11761 gagctgtcca tgggtctggag ctccccgcgc gtcaggteag gcgggagctc ctgcaggttt
11821 acctcgcata gacgggtcag ggcgcgggct agatccagggt gatacctaatt tccaggggc
11881 tggttggtgg cggcgtcgat ggcttgcaag aggcgcgac cccgcggcgc gactacggta
11941 ccgcgcggcg ggcgggtggg cgcgggggtg tccttggtat atgcatctaa aagcggtagc
12001 gcgggcgagc ccccgagggt agggggggct ccggacccgc cgggagaggg ggcaggggca
12061 cgtcggcgcc gcgcgcgggc aggagctggg gctgcgcgcg taggttgctg gcgaacgcga
12121 cgacgcggcg gttgatctcc tgaatctggc gcctctgcgt gaagacgacg ggcccggtag
12181 gcttgaacct gaaagagagt tcgacagaat caatttcggt gtcgttgacg gcggcctggc
12241 gcaaaatctc ctgcacgtct cctgagttgt cttgataggg gatctcggcc atgaactgct
12301 cgatctcttc ctccctggaga tctccgcgtc cggctcgtc caccgtggcg gcgaggctct
12361 tggaaatgcg ggccatgagc tgcgagaagg cgttgaggcc tccctcgttc cagacgcggc
12421 tgtagaccac gccccctcg gcacgcggg cgcgcgatgac cactgcgcg agattgagct
12481 ccacgtgccg ggcgaagacg gcgtagtttc gcaggcgtg aaagaggtag ttgagggtgg
12541 tggcgggtgt ttctgccacg aagaagtaca taaccacgcg tcgcaacgtg gattcgttga
12601 tatcccccaa ggcctcaagg cgctccatgg cctcgtagaa gtccacggcg aagttgaaaa
12661 actgggagtt gcgcgcgac acggttaact cctcctccag aagacggatg agctcggcga
12721 cagtgtcgcg cacctcgcgc tcaaaggcta caggggcctc ttctctctct tcaatctcct
12781 ctcccataag ggcctccctt tctctctctt ctggcggcgg tgggggaggg gggacacggc

FIG. 28A-4

69/126

12841 ggcgacgacg ggcgaccggg aggcgggtcga caaagcgctc gatcatctcc ccgcgggcgac
12901 ggcgcatggt ctccgtgacg gcgcggccgt tctcgcgggg gcgcagttgg aagacgcccgc
12961 ccgtcatgtc ccggttatgg gttggcgggg ggctgccatg cggcagggat acggcgctaa
13021 cgatgcatct caacaattgt tgtgtaggta ctccgcccgc gagggacctg agcgagtccg
13081 catcgaccgg atcggaaaac ctctcgagaa aggcgtctaa ccagtcacag tcgcaaggta
13141 ggctgagcac cgtggcgggc ggcagcgggc ggcggtcggg gttgtttctg gcggagggtgc
13201 tgctgatgat gtaattaaag taggcggtct tgagacggcg gatggtcgac agaagcacca
13261 tgtccttggg tccggcctgc tgaatgcgca ggcggtcggc catgccccag gcttcgtttt
13321 gacatcggcg cagggtctttg tagtagtctt gcatgagcct ttctaccggc acttcttctt
13381 ctcttctctc ttgtcctgca tctcttgcat ctatcgctgc ggcggcggcg gaggttggcc
13441 gtaggtggcg cctcttctct cccatgcgtg tgaccccgaa gccctcatc ggctgaagca
13501 gggctaggtc ggcgacaacg cgctcggcta atatggcctg ctgcacctgc gtgagggtag
13561 actggaagtc atccatgtcc acaaagcggg ggtatgcgcc cgtgttgatg gtgtaagtgc
13621 agttggccat aacggaccag ttaacgggtct ggtgaccggg ctgcgagagc tcggtgtacc
13681 tgagacgcga gtaagccctc gagtcaaata cgtagtcgtt gcaagtccgc accagggtact
13741 ggtatcccac caaaaagtgc ggcggcgggt ggcggtagag gggccagcgt aggggtggccg
13801 gggctccggg ggcgagatct tccaacataa ggcgatgata tccgtagatg tacctggaca
13861 tccagggtgat gccggcggcg gtggtggagg cgcgcgga aa gtcgcggacg cggttccaga
13921 tggtgcgcag cggcaaaaag tgctccatgg tcgggacgct ctggccggtc aggcgcgcgc
13981 aatcgttgac gctctagacc gtgcaaaagg agagcctgta agcgggcact cttccgtggt
14041 ctggtggata aattcgcaag ggtatcatgg cggacgaccg gggttcgagc cccgtatccg
14101 gccgtccgcc gtgatccatg cggttaccgc ccgcgtgtcg aaccaggtg tgcgacgtca
14161 gacaacgggg gagtgctcct tttggcttcc ttccaggcgc ggcggctgct gcgctagctt
14221 ttttggccac tggccgcgcg cagcgtaagc ggttaggctg gaaagcgaaa gcattaagtg
14281 gctcgctccc tgtagccgga gggttatttt ccaagggttg agtcgcggga ccccggttc
14341 gagtctcgga ccggccggac tgcggcgaac gggggtttgc ctcccgtca tgcaagacct
14401 cgcttgcaaa ttctccgga aacagggacg agccctttt ttgcttttcc cagatgcac
14461 cggtgctgcg gcagatgcgc cccctcctc agcagcggca agagcaagag cagcggcaga
14521 catgcagggc accctccct cctcctaccg cgtcaggagg ggcgacatcc gcggttgacg
14581 cggcagcaga tgggtgattac gaacccccgc ggcgcggggc ccggcactac ctggacttgg
14641 aggagggcga gggcctggcg cggctaggag cgccctctcc tgagcggcac ccaagggtgc
14701 agctgaagcg tgatacgct gaggcgtacg tgccgcggca gaacctgtt cgcgaccgcg
14761 agggagagga gcccaggag atgcgggatc gaaagtcca cgcagggcgc gagctgcggc
14821 atggcctgaa tcgcgagcgg ttgctgcgcg aggaggactt tgagcccagc gcgcgaaccg
14881 ggattagtcc cgcgcgcgca cacgtggcgg ccgccgacct ggtaaccgca tacgagcaga
14941 cggatgaacca ggagattaac tttcaaaaaa gctttaacaa ccacgtgct acgcttgtgg
15001 cgcgcgagga ggtggctata ggactgatgc atctgtggga ctttgtaagc gcgctggagc
15061 aaaacccaaa tagcaagccg ctcatggcgc agctgttctt tatagtgcag cacagcaggg
15121 acaacgaggc attcagggat gcgctgctaa acatagtaga gcccgagggc cgctggctgc
15181 tcgatttgat aaacatcctg cagagcatag tgggtgcagga gcgcagcttg agcctggctg
15241 acaagggtggc cgccatcaac tattccatgc ttagcctggg caagtthtac gcccgcaaga
15301 tataccatac cccttacgtt cccatagaca aggaggtaaa gatcgagggg ttctacatgc
15361 gcatggcgct gaagggtgctt acctgagcg acgacctggg cgtttatcgc aacgagcgca
15421 tccacaaggc cgtgagcgtg agccggcggc gcgagctcag cgaccgcgag ctgatgcaca
15481 gcctgcaaag ggcctggct ggcacgggca gcggcgatag agaggccgag tctactttg
15541 acgcggggcg tgacctgcgc tgggccccaa gccgacgcgc cctggaggca gctggggccg
15601 gacctgggct ggcgggtggca cccgcgcgcg ctggcaacgt cggcggcgtg gaggaatatg
15661 acgaggacga tgagtacgag ccagaggacg gcgagtacta agcgggtgatg tttctgatca
15721 gatgatgcaa gacgcaacgg acccgggcgt gcgggcggcg ctgcagagcc agccgtccgg
15781 ccttaactcc acggacgact ggcgcagggt catggaccgc atcatgtcgc tgactgcgcg
15841 caatcctgac gcgttccggc agcagccgca ggccaaccgg ctctccgcaa ttctggaagc
15901 ggtggtcccg gcgcgcgcaa accccacgca cgagaagggt ctggcgatcg taaacgcgct
15961 ggccgaaaac agggccatcc ggcccagca ggccggcctg gtctacgacg cgctgcttca
16021 gcgcgtggct cgttacaaca gcggcaacgt gcagaccaac ctggaccggc tgggtggggga
16081 tgtgcgcgag gccgtggcgc agcgtgagcg cgcgacgag cagggaacc tgggctccat

FIG. 28A-5

70/126

16141 gggttgacta aacgccttcc tgagtacaca gcccgcacaac gtgcccgcggg gacaggagga
16201 ctacaccaac tttgtgagcg cactgcggct aatgggtgact gagacaccgc aaagtgaggt
16261 gtaccagtct gggccagact attttttcca gaccagtaga caaggcctgc agaccgtaaa
16321 cctgagccag gctttcaaaa acttgcaggg gctgtggggg gtgcccgcctc ccacaggcga
16381 ccgcgcgacc gtgtctagct tgctgacgcc caactcgcgc ctgttgctgc tgctaatagc
16441 gcccttcacg gacagtggca gctgttcccg ggacacatac ctaggctact tgctgacact
16501 gtaccgcgag gccataggctc aggcgcagct ggacgagcat actttccagg agattacaag
16561 tgtcagccgc gcgctggggc agggaggacac gggcagcctg gaggcaacc taaactacct
16621 gctgaccaac cggcggcaga agatcccctc gttgcacagt ttaaacagcg agggaggcgc
16681 cattttgcgc tacgtgcagc agagcgtgag ccttaacctg atgcgcgacg gggtaacgcc
16741 cagcgtggcg ctggacatga ccgcgcgcaa catggaaccg ggcaggtatg cctcaaaccg
16801 gccgtttatc aaccgcctaa tggactactt gcacgcgcgc gccgcctga accccgagta
16861 tttcaccaat gccatcttga accgcactg gctaccgcc cctggtttct acaccggggg
16921 attcgaggtg cccgagggta acgatggatt cctctgggac gacatagacg acagcgtgtt
16981 ttccccgcaa ccgcagaccc tgctagagtt gcaacagcgc gagcaggcag aggcggcgct
17041 gcgaaaggaa agcttccgca ggccaagcag cttgtccgat ctaggcgctg cggccccgcg
17101 gtcagatgct agtagcccat ttccaagctt gatagggtct cttaccagca ctgcgaccac
17161 ccgcccgcgc ctgctggggc agggaggagta cctaaacaac tcgctgctgc agccgcagcg
17221 cgaaaaaaac ctgcctccgg catttcccaa caacgggata gagagcctag tggacaagat
17281 gagtagatgg aagacgtacg cgcaggagca cagggacgtg ccaggcccgc gcccgcccac
17341 ccgtcgtcaa aggcacgacc gtcagcgggg tctgggtgtg gaggacgatg actcggcaga
17401 cgacagcagc gtcctggatt tgggaggggag tggcaaccgc tttgcgcacc ttcgccccag
17461 gctggggaga atgtttttaa aaaaaaaaaa gcatgatgca aaataaaaaa ctcaccaagg
17521 ccatggcacc gagcgttggg tttcttgtat tccccttagt atgcggcgcg cggcgatgta
17581 tgaggaaggt cctcctccct cctacgagag tgtggtgagc gcggcgccag tggcgggcgc
17641 gctgggttct ccttcgatg ctcccctgga cccgcggtt gtgcctccgc ggtacctgcg
17701 gcctaccggg gggagaaaca gcatccgtta ctctgagttg gcaccctat tcgacaccac
17761 ccgtgtgtac ctggtggaca acaagtcaac ggatgtggca tccctgaact accagaacga
17821 ccacagcaac tttctgacca cggtcattca aaacaatgac tacagcccgg gggaggcaag
17881 cacacagacc atcaatcttg acgaccggtc gcaactggggc ggcgacctga aaacctcct
17941 gcataccaac atgccaaatg tgaacgagtt catgtttacc aataagttta aggcgcgggt
18001 gatgggtgtc cgcttgccca ctaaggacaa tcaggtggag ctgaaatacg agtgggtgga
18061 gttcacgctg cccgagggca actactccga gaccatgacc atagacctta tgaacaacgc
18121 gatcgtggag cactacttga aagtgggcag acagaacggg gttctggaaa gcgacatcgg
18181 ggtaaagttt gacaccgcga acttcagact ggggtttgac cccgtcactg gtcttgtcat
18241 gcctggggta tatacaaacg aagccttcca tccagacatc attttgctgc caggatgcgg
18301 ggtggacttc acccacagcc gcctgagcaa cttgttgggc atccgcaagc ggcaaccctt
18361 ccaggagggc tttaggatca cctacgatga tctggagggt ggtaacattc ccgactgtt
18421 ggatgtggac gcctaccagg cgagcttgaa agatgacacc gaacagggcg ggggtggcg
18481 aggcggcagc aacagcagtg gcagcggcg ggaagagaa tccaacgcgg cagccgcggc
18541 aatgcagccg gtggaggaca tgaacgatca tgccattcgc ggcgacacct ttgccacacg
18601 ggctgaggag aagcgcgctg aggcgaagc agcggccgaa gctgccgccc ccgctgcgca
18661 acccgaggtc gagaagcctc agaagaaacc ggtgatcaaa cccctgacag aggacagcaa
18721 gaaacgcagt tacaacctaa taagcaatga cagcaccttc acccagttac gcagctggta
18781 ccttgcatat aactacggcg accctcagac cggaatccgc tcatggacct tgctttgcac
18841 tcctgacgta acctgcggct cggagcaggt ctactggtcg ttgccagaca tgatgcaaga
18901 ccccgtagac ttccgctcca cgcgccagat cagcaacttt ccggtgggtg gcgcccagct
18961 gttgcccgtg cactccaaga gcttctacaa cgaccaggcc gtctactccc aactcatccg
19021 ccagttttacc tctctgacct acgtgttcaa tcgctttccc gagaaccaga ttttggcgcg
19081 cccgccagcc cccaccatca ccaccgtcag tgaaaacgtt cctgctctca cagatcacgg
19141 gacgctaccg ctgcgcaaca gcatcggagg agtccagcga gtgaccatta ctgacgccag
19201 acgcccaccc tgcccctacg tttacaaggc cctgggcata gtctcgccgc gcgtcctatc
19261 gagccgcact ttttgagcaa gcatgtccat ccttatatcg cccagcaata acacaggctg
19321 gggcctgcgc ttcccaagca agatgtttgg cggggccaag aagcgtccg accaacacc
19381 agtgcgcgtg cgcgggcact accgcgcgcc ctggggcgcg cacaacgcg gccgcactgg

FIG. 28A-6

WO 2006/020480

PCT/US2005/027658

71/126

```

19441 gcgccaccacc gtcgatgacg ccatcgacgc ggtggtggag gaggcgcgca actacacgcc
19501 cacgccgcca ccagtgtcca cagtggacgc ggccattcag accgtggtgc gcggagcccc
19561 gcgctatgct aaaatgaaga gacggcggag gcgcgtagca cgtcgccacc gccgccgacc
19621 cggcactgcc gcccaacgcg cggcggcgcc cctgcttaac cgcgcacgtc gcaccggccg
19681 acggggcgcc atgcggggcg ctcgaaggct ggccgcgggt attgtcactg tgcccccag
19741 gtccaggcga cgagcgggcg ccgcagcagc cgcggccatt agtgctatga ctcagggtcg
19801 caggggcaac gtgtattggg tgcgcgactc ggttagcggc ctgcgcgtgc ccgtgcgcac
19861 ccgccccccg cgcaactaga ttgcaagaaa aaactactta gactcgtact gttgtatgta
19921 tccagcggcg gcggcgcgca acgaagctat gtccaagcgc aaaatcaaag aagagatgct
19981 ccaggtcatc gcgccggaga tctatggccc ccgaagaag gaagagcagg attacaagcc
20041 ccgaaagcta aagcgggtca aaaagaaaaa gaaagatgat gatgatgaac ttgacgacga
20101 ggtggaactg ctgcacgcta ccgcgccag gcgacgggta cagtggaaag gtcgacgcgt
20161 aaaacgtgtt ttgcgacccg gcaccaccgt agtctttacg cccggtgagc gctccacccg
20221 cacctacaag cgcgtgtatg atgaggtgta cggcgacgag gacctgcttg agcaggccaa
20281 cgagcgccctc ggggagtttg cctacggaaa gcggcataag gacatgctgg cgttgccgct
20341 ggacgagggc aaccaacac ctagcctaaa gcccgtaaca ctgcagcagg tgctgcccg
20401 gcttgccaccg tccgaagaaa agcgcggcct aaagcgcgag tctggtgact tggcaccac
20461 cgtgcagctg atggtaccca agcgcagcgc actggaagat gtcttggaag aaatgaccgt
20521 ggaacctggg ctggagcccc aggtccgcgt gcggccaatc aagcagggtg cgcggggact
20581 gggcgtgcag accgtggacg ttcagatacc cactaccagt agcaccagta ttgccaccgc
20641 cacagagggc atggagacac aaacgtcccc ggttgccctca gcggtggcgg atgcccggt
20701 gcaggcggtc gctgcggccg cgtccaagac ctctacggag gtgcaaacgg acccgtggat
20761 gtttcgcgtt tcagcccccc ggcgcccgcg ccgttcgagg aagtacggcg ccgccagcgc
20821 gctactgcc gaatatgcc tacatccttc cattgcgcct acccccggt atcgtggcta
20881 cacctaccgc ccagaagac gagcaactac ccgacgccga accaccactg gaaccgcgcg
20941 ccgccgtcgc cgtcgccagc ccgtgctggc cccgatttcc gtgcgcaggg tggctcgcga
21001 aggaggcagg accctggtgc tgccaacagc gcgctaccac ccagcatcg tttaaaagcc
21061 ggtctttgtg gttcttgtag atatggccct cacctgccgc ctccgtttcc cggtgccggg
21121 attccgagga agaattgcac gtaggagggg catggccggc caccggcctga cgggcggcat
21181 gcgtcgtgcg caccaccggc ggcggcgcg cgtcgaccgt cgcgtgcgcg gcggtatcct
21241 gcccctcctt attccactga tcgcccgcg gattggcgcc gtgcccggaa ttgcatccgt
21301 ggccttgtag gcgcagagac actgattaaa aacaagttgc atgtggaaaa atcaaaataa
21361 aaagtctgga ctctcacgct cgcttggtcc tgtaactatt ttgtagaatg gaagacatca
21421 actttgcgtc tctggccccg cgacacggct cgcgcccggt catgggaaac tggcaagata
21481 tcggcaccag caatatgagc ggtggcgcc ctacgtgggg ctgctgttgg agcggcatta
21541 aaaatttcgg ttccaccgtt aagaactatg gcagcaaggc ctggaaacagc agcacaggcc
21601 agatgctgag ggataagttg aaagagcaaa atttccaaca aaaggtggta gatggcctgg
21661 cctctggcat tagcgggggt gtggacctgg ccaaccaggc agtgcaaaat aagattaaca
21721 gtaagcttga tccccgccct ccgtagagg agcctccacc ggccgtggag acagtgtctc
21781 cagagggggc tggcgaaaag cgtccgcgcc ccgacaggga agaaactctg gtgacgcaaa
21841 tagacgagcc tccctcgtag gaggaggcac taaagcaagg cctgcccacc acccgtccca
21901 tcgcgcccat ggctaccgga gtgctggggc agcacacacc cgtaacgctg gacctgcctc
21961 cccccgccga caccagcag aaacctgtgc tgccaggccc gaccgccgtt gttgtaacct
22021 gtcctagccg cgcgtccctg cgcgcgcgc ccagcggtcc gcgatcgttg cggcccgtag
22081 ccagtggcaa ctggcaagc acactgaaca gcctcgtggg tctgggggtg caatccctga
22141 agcggcgacg atgcttctga tagctaactg gtcgtatgtg tgcctatgat gcgtccatgt
22201 cgcggccaga ggagctgctg agcggccgc cgcggccttt ccaagatggc taccctctcg
22261 atgatgccgc agtggcttta catgcacatc tcggggcagg acgcctcgga gtacctgagc
22321 cccgggctgg tgcagtttgc ccgcgccacc gagacgtact tcagcctgaa taacaagttt
22381 agaaaccca cggtgggcgc tacgcacgac gtgaccacag accggtccca gcgtttgacg
22441 ctgcggttca tccctgtgga ccgtgaggat actgcgtact cgtacaaggc gcggttcacc
22501 ctagctgtgg gtgataaccg tgtgctggac atggcttcca cgtactttga catccgcggc
22561 gtgctggaca ggggccctac ttttaagccc tactctggca ctgcctacaa cgcctggct
22621 cccaagggtg ccccaaatcc ttgcgaatgg gatgaagctg ctactgctct tgaataaac
22681 ctagaagaag aggacgatga caacgaagac gaagtagacg agcaagctga gcagcaaaaa

```

FIG. 28A-7

72/126

22741 actcacgtat ttgggcaggc gccttattct ggtataaata ttacaaagga gggatttcaa
 22801 ataggtgtcg aaggtcaaac acctaaatat gccgataaaa catttcaacc tgaacctcaa
 22861 ataggagaat ctcaagtggta cgaaacagaa attaatacatg cagctgggag agtcctaaaa
 22921 aagactaccc caatgaaacc atgttacggc tcatatgcaa aaccacaaa tgaaaatgga
 22981 gggcaaggca ttcttgtaaa gcaacaaaat ggaaagctag aaagtcaagt ggaaatgcaa
 23041 tttttctcaa ctactgaggc agccgcaggc aatggtgata acttgactcc taaagtggta
 23101 ttgtacagtg aagatgtaga tatagaaacc ccagacactc atatttctta catgcccact
 23161 attaaggaag gtaactcacg agaactaatg ggccaacaat ctatgccccaa caggcctaata
 23221 tacattgctt ttagggacaa ttttattggc ctaatgtatt acaacagcac gggtaatatg
 23281 ggtgttcttg cgggccaagc atcgcagttg aatgctgttg tagatttgca agacagaaac
 23341 acagagcttt cataccagct tttgcttgat tccattgggtg atagaaccag gtacttttct
 23401 atgtggaatc aggtgttgga cagctatgat ccagatgtta gaattattga aaatcatgga
 23461 actgaagatg aacttccaaa ttactgcttt ccactgggag gtgtgattaa tacagagact
 23521 cttaccaagg taaaacctaa aacaggtcag gaaaatggat gggaaaaaga tgctacagaa
 23581 ttttcagata aaaatgaaat aagagttgga aataattttg ccatggaaat caatctaaat
 23641 gccaacctgt ggagaaattt cctgtactcc aacatagcgc tgtatttgcc cgacaagcta
 23701 aagtacagtc cttccaacgt aaaaatttct gataacccaa acacctacga ctacatgaac
 23761 aagcgagtgg tggctcccgg gctagtggac tgctacatta acctgggagc acgctggtcc
 23821 cttgactata tggacaacgt caaccattt aaccaccacc gcaatgctgg cctgcgctac
 23881 cgctcaatgt tgctgggcaa tggctgctat gtgcccctcc acatccaggt gcctcagaag
 23941 ttctttgcca ttaaaaacct ccttctcctg ccgggctcat acacctacga gtggaacttc
 24001 aggaaggatg ttaacatggt tctgcagagc tccctaggaa atgacctaa ggttgacgga
 24061 gccagcatta agtttgatag catttgctt tacgccacct tcttccccat ggcccacaa
 24121 accgcctcca cgcttgaggc catgcttaga aacgacacca acgaccagtc ctttaacgac
 24181 tatctctccg ccgccaacat gctctaccct ataccgcca acgctaccaa cgtgcccata
 24241 tccatccccct ccgcaactg ggcggcttcc cgcggctggg ccttcacgcg ccttaagact
 24301 aaggaaaccc catcactggg ctccggctac gacccttatt acacctactc tggctctata
 24361 ccctacctag atggaacctt ttacctcaac cacaccttta agaaggtggc cattaccttt
 24421 gactcttctg tcagctggcc tggcaatgac cgcctgctta cccccaacga gtttgaaatt
 24481 aagcgctcag ttgacgggga gggttacaac gttgcccagt gtaacatgac caaagactgg
 24541 ttcctggtag aaatgctagc taactataac attggctacc agggcttcta tatcccagag
 24601 agctacaagg accgcatgta ctcttcttt agaaacttcc agcccatgag ccgtcaggtg
 24661 gtggatgata ctaaatacaa ggactaccaa cagggtgggca tctacacca acacaacaac
 24721 tctggatttg ttggctacct tgccccacc atgcgcgaag gacaggccta ccctgctaac
 24781 ttcccctatc cgcttatagg caagaccgca gttgacagca ttaccagaa aaagtctctt
 24841 tgcgatcgca ccctttggcg catccattc tccagtaact ttatgtccat gggcgactc
 24901 acagacctgg gccaaaacct tctctacgcc aactccgcc acgcgctaga catgactttt
 24961 gaggtggatc ccatggacga gccaccctt ctttatgttt tgtttgaagt ctttgacgtg
 25021 gtccgtgtgc accagccgca ccgcggcgtc atcgaaaccg tgtacctgcg cacgcccctc
 25081 tcggccggca acgcccacac ataaagaagc aagcaacatc aacaacagct gccgccatgg
 25141 gctccagtga gcaggaactg aaagccattg tcaaagatct tggttgtggg ccatattttt
 25201 tgggcaccta tgacaagcgc tttccaggct ttgtttctcc acacaagctc gcctgcgcca
 25261 tagtcaatac ggccggctgc gagactgggg gcgtacactg gatggccttt gcctggaacc
 25321 cgcaactcaa aacatgctac ctctttgagc cctttggctt ttctgaccag cgactcaagc
 25381 aggtttacca gtttgagtac gagtcaactc tgcgccgtag cgccattgct tcttcccccg
 25441 accgctgtat aacgctggaa aagtcacccc aaagcgtaaa ggggcccacac tcggccgcct
 25501 gtggactatt ctgctgcatg tttctccacg cctttgcca ctggcccccac actcccatgg
 25561 atcacaaccc caccatgaac cttattaccg gggtagccaa ctccatgctc aacagtcccc
 25621 aggtacagcc caccctgcgt cgcaaccagg aacagctcta cagcttctct gagcgccact
 25681 cgccctactt ccgcagccac agtgccgaga ttaggagcgc cacttctttt tgtcacttga
 25741 aaaacatgta aaaataatgt actagagaca ctttcaataa aggcaaatgc ttttatttgt
 25801 acactctcgg gtgattattt acccccaccc ttgccgtctg cgccgtttta aaatcaaagg
 25861 gggtctgccc cgcatcgcta tgcgccactg gcagggacac gttgcgatac tgggtgttag
 25921 tgctccactt aaactcaggc acaaccatcc gcggcagctc ggtgaagttt tcaactccaca
 25981 ggctgcgcac catcaccaac gcgttttagc ggtcgggcgc cgatatcttg aagtcgcagt

FIG. 28A-8

WO 2006/020480

PCT/US2005/027658

73/126

26041 tggggcctcc gccctgcgcg cgcgagttgc gatacacagg gttgcagcac tggaaacta
 26101 tcagcgccgg gtggtgcacg ctggccagca cgctcttgtc ggagatcaga tccgcgtcca
 26161 ggtcctccgc gttgctcagg gcgaacggag tcaactttgg tagctgcctt cccaaaaagg
 26221 gcgcgtgccc aggcctttgag ttgcactcgc accgtagtgg catcaaaagg tgaccgtgcc
 26281 cggctctgggc gttaggatac agcgcctgca taaaagcctt gatctgctta aaagccacct
 26341 gagcctttgc gccttcagag aagaacatgc cgcaagactt gccggaaaac tgattggccg
 26401 gacaggccgc gtcgtgcacg cagcaccttg cgtcgggtgt ggagatctgc accacatttc
 26461 ggccccaccg gttcttcacg atcttggcct tgctagactg ctccctcagc gcgcgctgcc
 26521 cgttttctgt cgtcacatcc atttcaatca cgtgctcctt atttatcata atgcttcctg
 26581 gtagacactt aagctcgctt tcgatctcag cgcagcgggt cagccacaac gcgcagcccg
 26641 tgggctcgtg atgcttgtag gtcacctctg caaacgactg caggtacgcc tgcaggaaac
 26701 gccccatcat cgtcacaagg gtcttgttgc tgggtgaagg cagctgcaac ccgcggtgct
 26761 cctcgttcag ccaggctctt catacggccg ccagagcttc cacttgggtc ggcagtagtt
 26821 tgaagttcgc ctttagatcg ttatccacgt ggtacttgtc catcagcgcg cgcgcagcct
 26881 ccatgccctt ctcccacgca gacacgatcg gcacactcag cgggttcac accgtaattt
 26941 cactttccgc ttcgctgggc tcttctctt cctcttgcgt ccgcatacca cgcgccactg
 27001 ggtcgtcttc attcagccgc cgcactgtgc gcttacctcc tttgccatgc ttgattagca
 27061 ccggtggggt gctgaaaccc accatttcta ggcgcacatc ttctctttct tcctcgtgt
 27121 ccacgattac ctctgggtgat ggcgggcgct cgggcttggg agaaggcgcg ttctttttct
 27181 tcttgggcgc aatggccaaa tccgcgcgcg aggtcgatgg ccgcgggctg ggtgtgcgcg
 27241 gcaccagcgc gtcttgtgat gactcttct cgtcctcgga ctcgatacgc cgcctcatcc
 27301 gcttttttgg gggcgcccg gaggcgccg gcgacgggga cggggacgac acgtcctcca
 27361 tgggtggggg acgtcgcgcg gcaccgcgtc cgcgctcggg ggtggtttcg cgtgctcct
 27421 cttcccgact ggccatttcc ttctcctata ggcagaaaaa gatcatggag tcagtcgaga
 27481 agaaggacag cctaaccgcc cctctctagt tcgccaccac cgcctccacc gatgccgcca
 27541 acgcgcctac caccttcccc gtgcaggcac ccccgcttga ggaggaggaa gtgattatcg
 27601 agcaggaccc aggttttcta agcgaagacg acgaggaccg ctcagtacca acagaggata
 27661 aaaagcaaga ccaggacaac gcagaggcaa acgaggaaac agtcgggcgg ggggacgaaa
 27721 ggcattggcg ctacctagat gtgggagacg acgtgctgtt gaagcatctg cagcgccagt
 27781 gcgccattat ctgcgacgcg ttgcaagagc gcagcgatgt gccctcgcg atagcggatg
 27841 tcagccttgc ctacgaacgc cacctattct caccgcgcgt acccccaaaa cgccaagaaa
 27901 acggcacatg cgagcccaac ccgcgcctca acttctaccc cgtatttggc gtgccagagg
 27961 tgcttgccac ctatcacatc tttttccaaa actgcaagat acccctatcc tgccgtgcca
 28021 accgcagccg agcggacaag cagctggcct tgccggcagg cgtgtcata cctgatatcg
 28081 cctcgtctca cgaagtgcc aaaaatcttg aggtcttgg acgcgacgag aagcgcgcgg
 28141 caaacgctct gcaacaggaa aacagcgaaa atgaaagtca ctctggagtg ttggtggaac
 28201 tcgaggggtg caacgcgcgc ctagccgtac taaaacgcag catcgaggtc acccactttg
 28261 cctaccgggc acttaacctc cccccaagg tcatgagcac agtcatgagt gagctgatcg
 28321 tgcgcgctgc gcagcccctg gagagggatg caaatttgca agaacaaca gaggagggcc
 28381 taccgcgagt tggcgacgag cagctagcgc gctggcttca aacgcgcgag cctgccgact
 28441 tggaggagcg acgcaacta atgatggccg cagtgtcgtt taccgtggag cttgagtga
 28501 tgcagcgggt ctttgtgtac ccggagatgc agcgcaagct agaggaaaca ttgcactaca
 28561 cctttcgaca gggctacgta cgcagggcct gcaagatctc caacgtggag ctctgcaacc
 28621 tgggtctcta ccttgggaatt ttgcacgaaa accgccttgg gcaaaacgtg cttcattcca
 28681 cgctcaaggg cgaggcgcgc cgcgactacg tccgcgactg cgtttactta tttctatgct
 28741 acacctggca gacggccatg ggcgtttggc agcagtgtt ggaggagtgc aacctcaagg
 28801 agctgcagaa actgctaaag caaaacttga aggacctatg gacggccttc aacgagcgct
 28861 ccgtggccgc gcacctggcg gacatcattt tccccgaacg cctgcttaaa accctgcaac
 28921 agggctctgc agacttcacc agtcaaagca tggtgcagaa ctttaggaac tttatcctag
 28981 agcgtcagg aatcttgccc gccacctgct gtgcacttcc tagcgacttt gtgcccatta
 29041 agtaccgga atgcccctcg ccgctttggg gccactgcta ccttctgcag ctagccaact
 29101 accttgcta cactctgac ataattggaag acgtgagcgg tgacgggtcta ctggagtgtc
 29161 actgtcgtg caacctatgc accccgcacc gctccctggt ttgcaattcg cagctgctta
 29221 acgaaagtca aattatcggt acctttgagc tgcagggtcc ctcgcctgac gaaaagtcg
 29281 cggctccggg gttgaaactc actccggggc tgtggacgtc ggcttacctt cgcaaatctg

FIG. 28A-9

74/126

29341 tacctgagga ctaccacgcc cagcagatta ggttctacga agaccaatcc cgcccgcccta
29401 atgcgaggct taccgcctgc gtcattaccc agggccacat tcttggccaa ttgcaagcca
29461 tcaacaaagc ccgccaagag tttctgctac gaaagggacg gggggtttac ttggaccccc
29521 agtccggcga ggagctcaac ccaatcccc cgccgcccga gccctatcag cagcagccgc
29581 gggcccttgc ttcccaggat ggcacccaaa aagaagctgc agctgccgcc gccaccacg
29641 gacgaggagg aatactggga cagtcaggca gaggagggtt tggacgagga ggaggaggac
29701 atgatggaag actgggagag cctagacgag gaagcttccg aggtcgaaga ggtgtcagac
29761 gaaacaccgt caccctcggc cgcattcccc tcgcccggcg cccagaaatc ggcaaccggt
29821 tccagcatgg ctacaacctc cgctcctcag gcgcccggcg cactgcccggt tcgcccagcc
29881 aaccgtagat gggacaccac tggaaaccag gccggtaagt ccaagcagcc gccgcccgtta
29941 gcccaagagc aacaacagcg ccaaggctac cgctcatggc gcgggcacaa gaacgccata
30001 gttgcttgct tgcaagactg tgggggcaac atctccttcg cccgccgctt tcttctctac
30061 catcacggcg tggccttccc ccgtaacatc ctgcattact accgtcatct ctacagccca
30121 tactgcaccg gcggcagcgg cagcaacagc agcggccaca cagaagcaaa ggcgaccgga
30181 tagcaagact ctgacaaagc ccaagaaatc cacagcggcg gcagcagcag gaggaggagc
30241 gctgcgtctg gcgcccacg aaccgctatc gaccgcgag cttagaacaa ggatttttcc
30301 cactctgtat gctatatctc aacagagcag gggccaagaa caagagctga aaataaaaaa
30361 caggtctctg cgatccctca cccgcagctg cctgtatcac aaaagcgaag atcagcttcg
30421 gcgcacgctg gaagacgcgg aggtctctct cagtaaatac tgcgcgctga ctcttaagga
30481 ctagtttcgc gccctttctc aaatttaagc gcgaaaacta cgtcatctcc agcggccaca
30541 cccggcgcga gcacctgttg tcagcgcctat tatgagcaag gaaattccca cgccctacat
30601 gtggagttac cagccacaaa tgggacttgc ggctggagct gcccaagact actcaaccgg
30661 aataaactac atgagcgcgg gacccacat gatatcccgg gtcaacggaa tacgcgcccc
30721 ccgaaaccga attctcctgg aacaggcggc tattaccacc acacctcgta ataacctaa
30781 tccccgtagt tggcccgtg ccttggtgta ccaggaaagt cccgctccca ccactgtggt
30841 acttcccaga gacgcccagg ccgaagtcca gatgactaac tcaggggcg cagcttgcggg
30901 cggctttcgt cacagggtgc ggtcgcccgg gcagggtata actcacctga caatcagagg
30961 gcgaggtatt cagctcaacg acgagtcggt gagctcctcg cttggtctcc gtccggacgg
31021 gacatttcag atcggcggcg ccggccgctc ttcattcacg cctcgtcagg caatcctaac
31081 tctgcagacc tcgtcctctg agccgcgctc tggaggcatt ggaactctgc aatttatgtg
31141 ggagtttgtg ccatcgggtct actttaaccc cttctcggga cctcccggcc actatccgga
31201 tcaatttatt cctaactttg acgcggtaaa ggactcggcg gacggctacg actgaatgtt
31261 aagtggagag gcagagcaac tgcgcctgaa acacctggtc cactgtcgcc gccacaagtg
31321 ctttgcccgc gactccgggt agttttgcta ctttgaattg cccgaggatc atatcgaggg
31381 cccggcgcac ggcgtccggc ttaccgcca gggagagctt gcccgtagcc tgattcggga
31441 gtttaccag cgccccctgc tagttgagcg ggacagggga cctgtgttc tctgtgat
31501 ttgcaactgt cctaacctg gattacatca agatcctcta gttataacta gagtaccggg
31561 ggatcttatt ccctttaact aataaaaaaa aataataaag catcacttac ttaaaatcag
31621 ttagcaaatt tctgtccagt ttattcagca gcacctcctt gccctcctcc cagctctggt
31681 attgcagctt cctcctggct gcaaaccttc tccacaatct aaatggaatg tcagtttctt
31741 cctgttctctg tccatccgca cccactatct tcatgttgtt gcagatgaag cgcgcaagac
31801 cgtctgaaga taccttcaac cccgtgtatc catatgacac ggaaaccggt cctccaactg
31861 tgccttttct tactcctccc tttgtatccc ccaatgggtt tcaagagagt cccctgggg
31921 tactctcttt gcgcctatcc gaacctctag ttacctcaa tggcatgctt gcgctcaaaa
31981 tgggcaacgg cctctctctg gacgaggccg gcaaccttac ctcccaaat gtaaccactg
32041 tgagcccacc tctcaaaaaa accaagtcaa acataaacct ggaaatatct gcaccctca
32101 cagttacctc agaagcccta actgtggctg ccgcccgcac tctaattggtc gcgggcaaca
32161 cactcaccat gcaatcacag gccccgctaa ccgtgcacga ctccaaactt agcattgccca
32221 cccaaggacc cctcacagtg tcagaaggaa agctagccct gcaaacatca ggccccctca
32281 ccaccaccga tagcagtacc cttactatca ctgcctcacc cctctaaact actgccactg
32341 gtagcttggg cattgacttg aaagagccca tttatacaca aaatggaaaa ctaggactaa
32401 agtacggggc tcctttgcat gtaacagacg acctaaacac tttgaccgta gcaactgggtc
32461 caggtgtgac tattaataat acttccttgc aaactaaagt tactggagcc ttgggttttg
32521 attcacaagg caatatgcaa cttaatgtag caggaggact aaggattgat tctcaaaaca
32581 gacgccttat acttgatgtt agttatccgt ttgatgctca aaaccaacta aatctaagac

FIG. 28A-10

75/126

32641 taggacaggg ccctcttttt ataaactcag ccacaaactt ggatattaac tacaacaaag
32701 gcctttactt gtttacagct tcaaacaatt ccaaaaagct tgaggttaac ctaagcactg
32761 ccaaggggtt gatgtttgac gctacagcca tagccattaa tgcaggagat gggcttgaat
32821 ttggttcacc taatgcacca aacacaaatc ccctcaaaac aaaaattggc catggcctag
32881 aatttgattc aaacaaggct atggttccta aactaggaac tggccttagt tttgacagca
32941 caggtgccat tacagtagga aacaaaaata atgataagct aactttgtgg accacaccag
33001 ctccatctcc taactgtaga ctaaagtcag agaaagatgc taaactcact ttggtcttaa
33061 caaaatgtgg cagtcaaata cttgctacag tttcagtttt ggctgttaaa ggcagtttgg
33121 ctccaatatc tggaacagtt caaagtgtc atcttattat aagatttgac gaaaatggag
33181 tgctactaaa caattccttc ctggaccag aatattggaa ctttagaaat ggagatctta
33241 ctgaaggcac agcctataca aacgtgttg gatttatgcc taacctatca gcttatccaa
33301 aatctcacgg taaaactgcc aaaagtaaca ttgtcagtc agtttactta aacggagaca
33361 aaactaaacc tgtaacacta accattacac taaacggtac acaggaaaca ggagacacaa
33421 ctccaagtgc atactctatg tcattttcat gggactggtc tggccacaac tacattaatg
33481 aaatatttgc cacatcctct tacacttttt catacattgc ccaagaataa agaatcgttt
33541 gtgttatgtt tcaacgtgtt tatttttcaa ttgcagaaaa tttcaagtca tttttcattc
33601 agtagtatag cccaccacc acatagctta tacagatcac cgtacctta tcaaactcac
33661 agaaccctag tattcaacct gccacctccc tcccaacaca cagagtacac agtcctttct
33721 ccccggtgg ccttaaaaag catcatatca tgggtaacag acatattctt aggtgttata
33781 ttccacacgg tttcctgtcg agccaaacgc tcatcagtga tattaataaa ctccccgggc
33841 agctcactta agttcatgtc gctgtccagc tgctgagcca caggctgctg tccaacttgc
33901 ggttgcttaa cgggcgggcga aggagaagtc cacgcctaca tgggggtaga gtcataatcg
33961 tgcatacaga tagggcggtg gtgctgcagc agcgcgcgaa taaactgctg ccgcccgcgc
34021 tccgtcctgc aggaatacaa catggcagtg gtctcctcag cgatgattcg caccgcccgc
34081 agcataaggc gccttgtcct ccgggcacag cagcgcaccc tgatctcact taaatcagca
34141 cagtaactgc agcacagcac cacaatattg ttcaaaatcc cacagtgcga ggcgctgtat
34201 ccaaagctca tggcggggac cacagaaccc acgtggccat cataccacaa gcgcaggtag
34261 attaagtggc gacctctcat aaacacgctg gacataaaca ttacctctt tggcatgttg
34321 taattcacca cctcccggta ccatataaac ctctgattaa acatggcgcc atccaccacc
34381 atcctaaacc agctggccaa aacctgcccg ccggctatac actgcaggga accgggactg
34441 gaacaatgac agtggagagc ccaggactcg taacctatga tcatcatgct cgtcatgata
34501 tcaatgttgg cacaacacag gcacacgtgc atacacttcc tcaggattac aagctcctcc
34561 cgcgttagaa ccatatccca gggaacaacc cattcctgaa tcagcgtaaa tcccacactg
34621 cagggaagac ctgcacgta actcacgttg tgcatgttca aagtgttaca ttccggcagc
34681 agcggatgat cctccagtat ggtagcgcgg gtttctgtct caaaaggagg tagacgatcc
34741 ctactgtacg gagtgcgccc agacaaccga gatcgtgttg gtctagtgt catgccaaat
34801 ggaacgcccg acgtagtcac atttcctgaa gcaaaaccag gtgcgggctg gacaaacaga
34861 tctgcgtctc cgggtctcgcc gcttagatcg ctctgtgtag tagttgtagt atatccactc
34921 tctcaaagca tccaggcgcc ccctggcttc ggggttctatg taaactcctt catgcgcccgc
34981 tgccctgata acatccacca ccgcagaata agccacaccc agccaacctt cacattcggtt
35041 ctgcgagtca cacacgggag gagcgggaag agctggaaga accatgtttt tttttttatt
35101 ccaaaagatt atccaaaacc tcaaaatgaa gatctattaa gtgaacgcgc tcccctccgg
35161 tggcgtggtc aaactctaca gccaaagaac agataatggc atttgtaaga tgttgacaaa
35221 tggcttccaa aaggcaaacg gccctcacgt ccaagtggac gtaaaggcta aacccttcag
35281 ggtgaatctc ctctataaac attccagcac cttcaaccat gcccaataa ttctcatctc
35341 gccaccttct caatatatct ctaagcaaat cccgaatatt aagtccggcc attgtaaaaa
35401 tctgctccag agcgcctctc accttcagcc tcaagcagcg aatcatgatt gcaaaaattc
35461 aggttcctca cagacctgta taagattcaa aagcgggaaca ttaacaaaaa taccgcatc
35521 ccgtaggtcc cttcgcaggg ccagctgaac ataactgtgc aggtctgcac ggaccagcgc
35581 ggccacttcc ccgccaggaa ccatgacaaa agaaccaca ctgattatga cagcactact
35641 cggagctatg ctaaccagcg tagccccgat gtaagcttgt tgcattggcg gcgatataaa
35701 atgcaaggtg ctgctcaaaa aatcaggcaa agcctcgcg aaaaaagaaa gcacatcgta
35761 gtcattgctc tgcagataaa ggcaggtaag ctccggaacc accacagaaa aagacaccat
35821 ttttctctca aacatgtctg cgggtttctg cataaacaca aaataaaata acaaaaaaac
35881 atttaaacat tagaagcctg tcttacaaca ggaaaaacaa cccttataag cataagacgg

FIG. 28A-11

WO 2006/020480

PCT/US2005/027658

76/126

35941 actacggcca tgccggcgtg accgtaaaaa aactgggtcac cgtgattaaa aagcaccacc
36001 gacagtcctt cggtcattgtc cggagtcata atgtaagact cggtaaacac atcagggtga
36061 ttcacatcgg tcagtgtctaa aaagcgaccg aaatagcccg ggggaataca taccgcagg
36121 cgtagagaca acattacagc ccccatagga ggtataacaa aattaatagg agagaaaaac
36181 acataaacac ctgaaaaacc ctctgccta ggcaaatag caccctccc ctccagaaca
36241 acatacagcg cttccacagc ggcagccata acagtcagcc ttaccagtaa aaaagaaaac
36301 ctattaaaaa aacaccactc gacacggcac cagctcaatc agtcacagtg taaaaaggg
36361 ccaagtgcag agcgagtata tataggacta aaaaatgacg taacggttaa agtccacaaa
36421 aaacacccag aaaaccgcac gcgaacctac gcccagaaac gaaagccaaa aaaccacaaa
36481 cttcctcaaa tcgtcacttc cgttttccca cgttacgtca cttcccattt taagaaaact
36541 acaattcca acacatacaa gttactccgc cctaaaacct acgtcaccgc ccccgttccc
36601 acgccccgcg ccacgtcaca aactccacc cctcattatc atattggctt caatccaaaa
36661 taaggatat tattgatgat g (SEQ ID NO: 19)

FIG. 28A-12

77/126

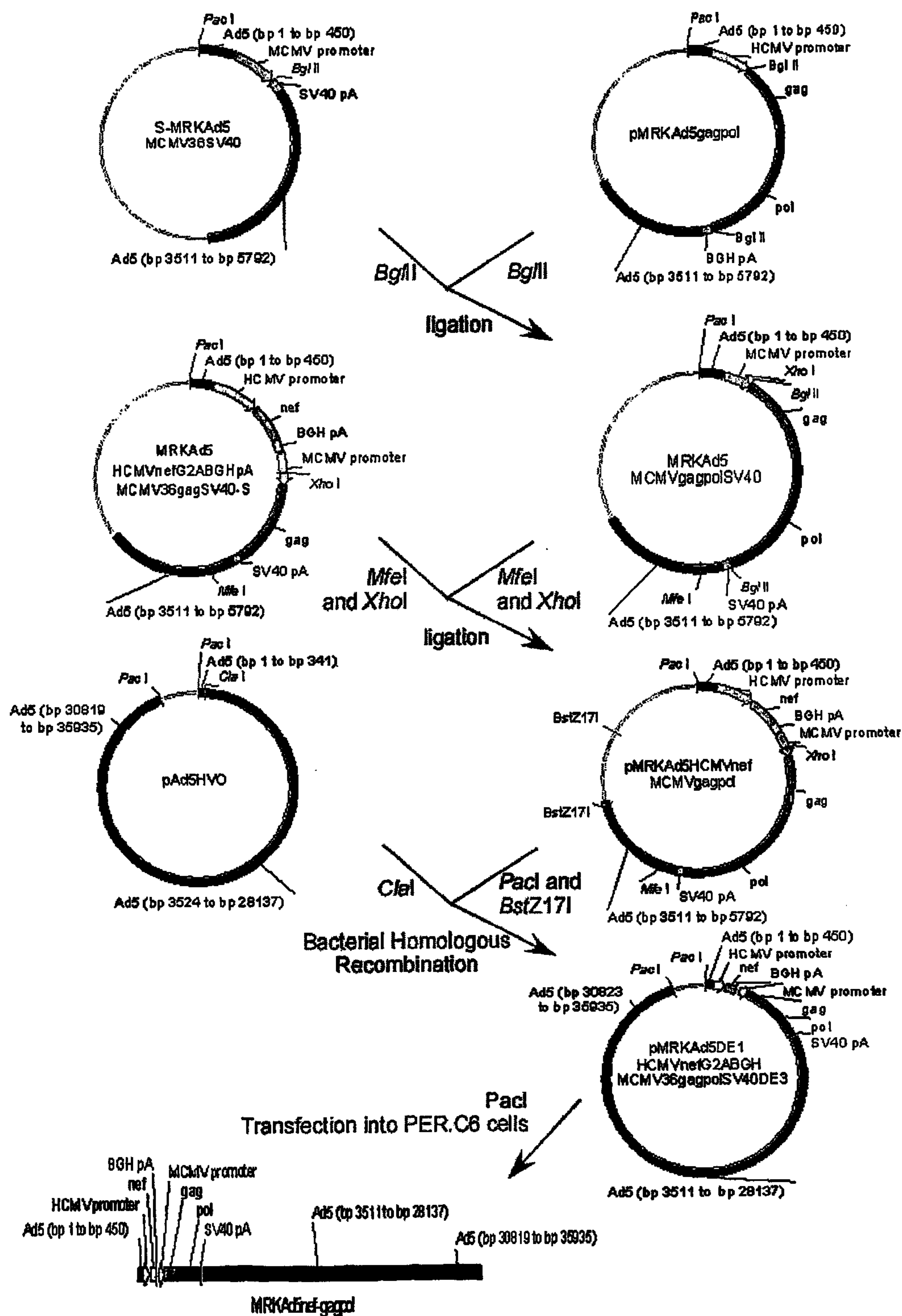


FIG. 29

78/126

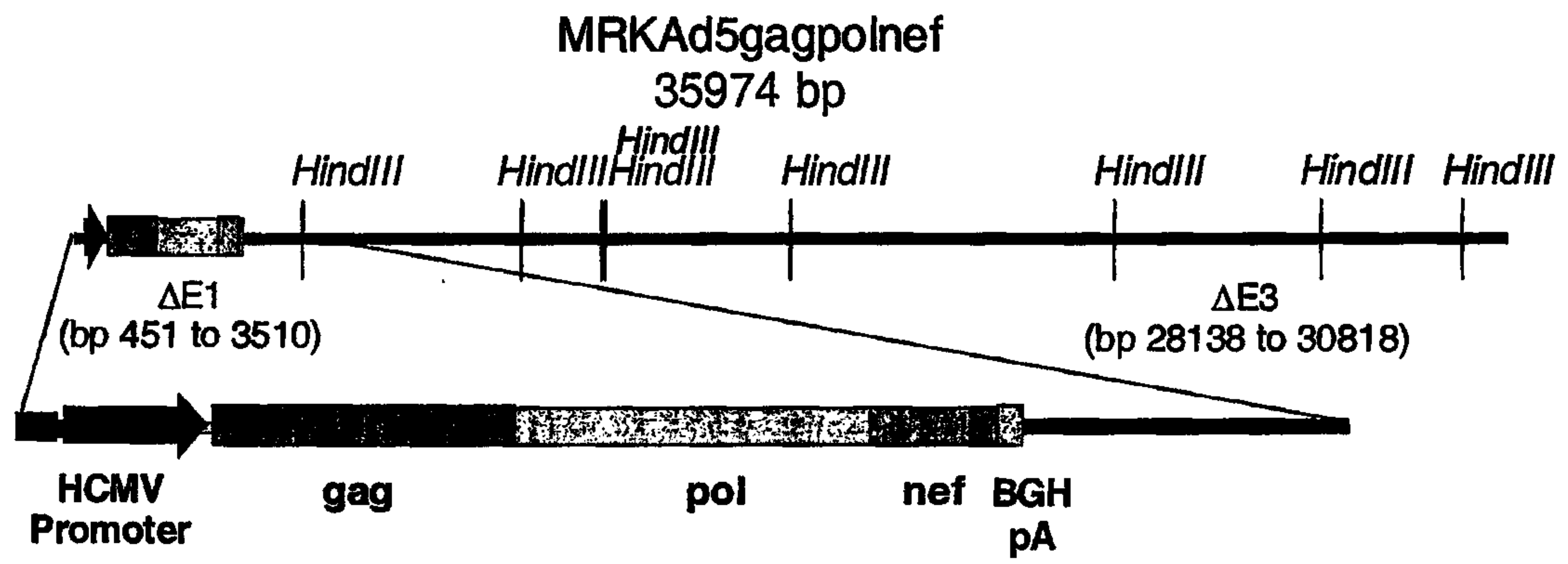


FIG. 30

79/126

MRKAd5gagpolnef

KEY: ____ HCMV promoter	 Gag	_____ Pol	_____ Nef	_____ BGH pA
-------------------------	-----------	-----------	-----------	--------------

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgcaa gtgtggcgga acacatgtaa gcgacggatg tggcaaaagt gacgtttttg
181 gtgtgcgccg gtgtacacag gaagtgacaa ttttcgcgcg gttttaggcg gatgttgtag
241 taaatttggg cgtaaccgag taagatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataatttt gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcgtttt attattatag gcggccgcga tccattgcat acgttgtatc
481 catatcataa tatgtacatt tatattggct catgtccaac attaccgcca tgttgacatt
541 gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata
601 tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc
661 cccgccattt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc
721 attgacgtca atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt
781 atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt
841 atggccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca
901 tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg
961 actcacgggg atttccaagt ctccaccca ttgacgtcaa tgggagtttg ttttggcacc
1021 aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg
1081 gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgtcagatcg
1141 cctggagacg ccatccacgc tgttttgacc tccatagaag acaccgggac cgatccagcc
1201 tccgcggccg ggaacggtgc attggaacgc ggattccccg tgccaagagt gagatctacc
1261 atgggtgcta gggcttctgt gctgtctggt ggtgagctgg acaagtggga gaagatcagg
1321 ctgagggcctg gtggcaagaa gaagtacaag ctaaaggaca ttgtgtgggc ctccagggag
1381 ctggagaggt ttgctgtgaa ccctggcctg ctggagacct ctgaggggtg caggcagatc
1441 ctgggcccagc tccagccctc cctgcaaaac ggctctgagg agctgaggtc cctgtacaac
1501 acagtggcta ccctgtactg tgtgcaccag aagattgatg tgaaggacac caaggaggcc
1561 ctggagaaga ttgaggagga gcagaacaag tccaagaaga aggccagca ggcctgctct
1621 ggcacaggca actccagcca ggtgtcccag aactaccca ttgtgcagaa cctccagggc
1681 cagatggtgc accagcccat ctccccccgg accctgaatg cctgggtgaa ggtggtgag
1741 gagaaggcct tctccctga ggtgatcccc atgttctctg ccctgtctga ggggtgccacc
1801 ccccaggacc tgaacaccat gctgaacaca gtggggggcc atcaggctgc catgcagatg
1861 ctgaaggaga ccatcaatga ggaggctgct gagtgggaca ggctgcatcc tgtgcacgct
1921 ggcgccattg ccccgccca gatgaggag cccaggggct ctgacattgc tggcaccacc
1981 tccaccctcc aggagcagat tggctggatg accaacaacc ccccatccc tgtgggggaa
2041 atctacaaga ggtggatcat cctgggcctg aacaagattg tgaggatgta ctccccacc
2101 tccatcctgg acatcaggca gggccccaag gagcccttca gggactatgt ggacaggttc
2161 tacaagaccg tgaggctga gcaggcctcc caggaggtga agaactggat gacagagacc
2221 ctgctggtgc agaatgccaa ccctgactgc aagaccatcc tgaaggccct gggccctgct
2281 gccaccctgg aggagatgat gacagcctgc cagggggtgg gggccctgg tcacaaggcc
2341 aggtgctgg ctgaggccat gtcccagggtg accaactccg ccaccatcat gatgcagagg
2401 ggcaacttca ggaaccagag gaagacagtg aagtgccttca actgtggcaa ggtggccac
2461 attgccaaga actgtagggc cccaggaag aagggtgctt ggaagtgtgg caaggaggcc
2521 caccagatga aggactgcaa tgagaggcag gccacttcc tgggcaaaat ctggccctcc
2581 cacaagggca ggcctggcaa cttcctccag tccaggcctg agcccacagc ccctcccagg
2641 gagtccttca ggtttgggga ggagaagacc acccccagcc agaagcagga gccattgac
2701 aaggagctgt accccctggc ctccctgagg tccctgtttg gcaacgaccc ctccctccag
2761 cccatctccc ccattgagac tgtgcctgtg aagctgaagc ctggcatgga tggccccaag

```

FIG. 31A-1

80/126

2821 gtgaagcaqt ggccttgac tgaggagaag atcaaggccc tggtagaat ctgcactgag
2881 atggagaagg agggcaaat ctccaagatt ggcctgaga accctacaa caccctgtg
2941 tttgcatca agaagaagga ctccaccaag tggaggagc tggtagactt caggagctg
3001 aacaagagga cccaggactt ctggagggtg cagctggga tccccaccc cgtggcctg
3061 aagaagaaga agtctgtgac tgtgctggct gtgggggatg cctacttctc tgtgcccctg
3121 gatgaggact tcaggaagta cactgccttc accatcccct ccatcaacaa tgagaccct
3181 ggcacaggt accagtacaa tgtgctgcc cagggtgga agggctccc tgcctcttc
3241 cagtcctcca tgaccaagat cctggagccc ttcaggaagc agaaccctga cattgtgatc
3301 taccagtaca tggctgcctt gtatgtggc tctgacctgg agattggga gcacaggacc
3361 aagattgag agctgaggca gcacctgtg aggtggggc tgaccaccc tgacaagaag
3421 caccagaag agccccctt cctgtgatg gctatgagc tgcacccga caagtggact
3481 gtgcagcca ttgtgctgcc tgagaaggac tctggactg tgaatgacat ccagaagctg
3541 gtgggcaagc tgaactggc ctcccaatc taccctgga tcaaggtgag gcagctgtc
3601 aagctgtga ggggaccaa ggcctgact aggtgatcc cctgactga ggagctgag
3661 ctggagctgg ctgagaacag ggagatcctg aaggagcctg tgcctgggt gtactatgac
3721 ccctccaag acctgattgc tgagatccag aagcaggcc agggccagt gacctacaa
3781 atctaccag agcccttcaa gaacctgaag actggcaagt atgccagat gaggggggc
3841 cacaccaatg atgtgaagc gctgactgag gctgtcaga agatcaccac tgagtccatt
3901 gtgactggg gcaagacccc caagttcaag ctgcccctc agaaggagac ctgggagacc
3961 tggtagactg agtactggc ggcacctg atccctgagt gggagttgt gaacacccc
4021 cccctggtga agctgtgta ccagctggag aaggagcca ttgtggggc tgagacctc
4081 tatgtgctg ggcctgcaa caggagacc aagctggga agctggcta tctgaccaac
4141 aggggaggg agaaggtgt gacctgact gacaccacca accagaagac tgcctccag
4201 gccatctacc tggcctcca gactctggc ctggaggta acattgtgac tgcctccag
4261 tatgcccctg gcatcatcca ggcagacct gatcagtct agtctgagct ggtgaaccag
4321 atcattgagc agctgatcaa gaaggagaag gtgtacctg cctgggtgc tcccacaa
4381 ggcattggg gcaatgagca ggtggacaag ctggtgtct ctggcatcag gaaggtgctg
4441 ttcttgatg gcatgacaa ggcaggat gacatgaga agtaccact caactggag
4501 gctatggcct ctgacttcaa cctgccccct gtggtgcta aggagattgt ggcctcctg
4561 gacaagtgc agctgaagg ggaggccatg catgggcagg tggactctc cctggcate
4621 tggcagctg cctgcacca cctggaggc aagtgatcc tggtagctgt gcatgtggc
4681 tccggtaca ttgaggctga ggtgatccct gctgagacag gccaggagac tgcctactc
4741 ctgctgaagc tggctggcag gtggcctgt aagaccatcc acactgcaa tggctccaa
4801 ttactggg ccacagtga gctgcctgc tggtagctg gcatcaagca ggaatttgg
4861 atcccctaca accccagtc ccaggggtg gtggcctcca tgaacaagga gctgaagaag
4921 atcattggg aggtgaggga ccagctgag cactgaaga cagctgtgca gatgctgtg
4981 ttcatccaca acttcaagag gaagggggc atcggggct actccgctg ggagaggatt
5041 gtggacatca ttgccacaga catccagacc aaggagctc agaagcagat caccaagatc
5101 cagaacttca ggtgtacta caggactcc aggaacccc tgtggaagg ccctgccaag
5161 ctgctgtgga aggggaggg gctgtgtgt atccaggaca actctgacat caaggtggtg
5221 cccaggagga aggcgaagat catcaggagc tatggcaagc agatggctg ggtgactgt
5281 gtggcctcca ggcaggatga ggcggcggc aagtggcca agaggtccgt gcccggctg
5341 tccaccgtga gggagagat gaggaggcc ggcggcggc ccacagggt gaggaggacc
5401 ggcggcggc cagtggcgt ggcggcgtg tccaggacc tggagaagca cggcggcatc
5461 acctcctca acacggcgc caccaacgc gactgcgct ggtggaggc ccaggaggac
5521 gaggaggtg gcttccccgt gaggcccgag gtgcccctga ggcctatgac ctacaaggc
5581 gccgtggacc tgtccactt cctgaaggag aaggcgggc tggaggcct gatccactc
5641 cagaagaggc aggacatcct gacctgtg gtgtaccaca ccagggcta ctccccgac
5701 tggcagaact acacccccg cccgggcatc aggttcccc tgaccttgg ctggtgctc
5761 aagctggtg ccgtggagc cgagaaggtg gaggaggcca accagggga gaacaactgc
5821 ctgctgcacc ccatgtcca gcacggcatc gaggacccc agaaggaggt gctggagtg
5881 aggttgcact ccaagctggc cttccaccac gtggcaggg agctgcacc caagtactac
5941 aaggactgct aaagccggg cagatctgct gtgccttcta gttgccagc atctgttgt
6001 tgcctctccc ccgtgcctc cttgacctg gaaggtgcca ctcccactgt ccttctctaa
6061 taaatgagg aattgcac gcattgtct agtaggtgtc attctattct ggggggtgg

FIG. 31A-2

81/126

```

6121 gtggggcagg acagcaaggg ggaggattgg gaagacaata gcaggcatgc tggggatgag
6181 gtgggctcta tggccgatcg gcgcgccgta ctgaaatgtg tgggcgtggc ttaagggtgg
6241 gaaagaatat ataagggtgg ggtcttatgt agttttgtat ctgttttgca gcagccgccg
6301 ccgccatgag caccaactcg tttgatggaa gcattgtgag ctcataattg acaacgcgca
6361 tgcccccatt ggccgggggtg cgtcagaatg tgatgggctc cagcattgat ggtcgccccg
6421 tcctgcccgc aaactctact accttgacct acgagaccgt gtctggaacg ccgttgagga
6481 ctgcagcctc cgccgccgct tcagccgctg cagccaccgc ccgcgggatt gtgactgact
6541 ttgctttcct gagcccgcct gcaagcagtg cagcttcccg ttcattccgc ccgatgaca
6601 agttgacggc tcttttggca caattggatt ctttgaccgg ggaacttaat gtcgtttctc
6661 agcagctgtt ggatctgcgc cagcaggttt ctgccctgaa ggcttcctcc cctcccaatg
6721 cggtttaaaa cataaataaa aaaccagact ctgtttggat ttggatcaag caagtgtctt
6781 gctgtcttta tttaggggtt ttgcgcgcgc ggtaggcccg ggaccagcgg tctcggtcgt
6841 tgagggtcct gtgtattttt tccaggacgt ggtaaagggt actctggatg ttcagataca
6901 tgggcataag cccgtctctg ggggtggagg agcaccactg cagagcttca tgctgcgggg
6961 tgggtgtgta gatgatccag tcgtagcagg agcgtggggc gtggtgccta aaaatgtctt
7021 tcagtagcaa gctgattgcc aggggcaggc ccttggtgta agtgtttaca aagcgggtta
7081 gctgggatgg gtgcatacgt ggggatatga gatgcattct ggactgtatt tttaggttgg
7141 ctatgttccc agccatatcc ctccggggat tcatgttgtg cagaaccacc agcacagtgt
7201 atccggtgca cttgggaaat ttgtcatgta gcttagaagg aaatgcgtgg aagaacttgg
7261 agacgccctt gtgacctcca agattttcca tgcattcgtc cataatgatg gcaatggggc
7321 cacggggcgg gccttggggc aagatatattc tgggatcact aacgtcatag ttgtgttcca
7381 ggatgagatc gtcataggcc atttttacaa agcgcggggc gaggggtgca gactgcggta
7441 taatggttcc atccggccca ggggcgtagt taccctcaca gatttgcatt tcccacgctt
7501 tgagttcaga tgggggggatc atgtctacct gcggggcgat gaagaaaacg gtttccgggg
7561 taggggagat cagctgggaa gaaagcaggt tcctgagcag ctgcgactta ccgcagccgg
7621 tgggcccgta aatcacacct attaccggct gcaactggta gtaagagag ctgcagctgc
7681 cgtcatccct gagcaggggg gccacttcgt taagcatgtc cctgactcgc atgttttccc
7741 tgaccaaate cgccagaagg cgctcggcgc ccagcgatag cagttcttgc aaggaagcaa
7801 agtttttcaa cggtttgaga ccgtccgccg taggcattgt tttgagcgtt tgaccaagca
7861 gttccaggcg gtcccacagc tcgggtcacct gctctacggc atctcgatcc agcatatctc
7921 ctggtttcgc gggttggggc ggctttcgtc gtacggcagt agtcgggtgt cgtccagacg
7981 ggccagggtc atgtctttcc acgggcgcag ggtcctcgtc agcgtagtct gggtcacggc
8041 gaaggggtgc gctccgggct gcgcgctggc caggggtgagc ttgaggctgg tcctgctggc
8101 gctgaagcgc tgcgggtctt cgccctgcgc gtcggccagg tagcatttga ccatggtgtc
8161 atagtccagc ccctccgcgg cgtggccctt ggccgcgagc ttgcccttgg aggaggcgcc
8221 gcacgagggg cagtgcagac ttttgagggc gtagagcttg ggccgcgaga ataccgattc
8281 cggggagtag gcatccgcgc cgcaggcccc gcagacggtc tcgcattcca cgagccaggt
8341 gagctctggc cgttcggggc caaaaaccag gtttccccca tgctttttga tgcgtttctt
8401 acctctgggt tccatgagcc ggtgtccacg ctccgtgacg aaaaggctgt ccgtgtcccc
8461 gtatacagac ttgagaggcc tgtcctcgag cgggtgttcc cggtcctcct cgtatagaaa
8521 ctccggaccac tctgagacaa aggtcgcgtt ccaggccagc acgaaggagg ctaagtggga
8581 ggggtagcgg tcgttgtcca ctagggggtc cactcgtctc aggggtgtga gacacatgtc
8641 gccctcttcg gcatcaagga aggtgattgg tttgtagggt taggccacgt gaccgggtgt
8701 tcctgaaggg gggctataaa aggggggtgg ggccggttcg tcctcactct ctccgcctc
8761 gctgtctgag agggccagct gttgggggtg gtactccctc tgaaaagcgg gcatgacttc
8821 tgcgctaaga ttgtcagttt ccaaaaacga ggaggatttg atattcacct ggcccgcggc
8881 gatgcctttg aggggtggcc catccatctg gtcagaaaag acaatctttt tgttgtcaag
8941 cttgggtggc aacgaccgct agagggcggt ggacagcaac ttggcgatgg agcgcagggt
9001 ttggtttttg tcgogatcgg cgcgctcctt ggccgcgatg tttagctgca cgtattcgcg
9061 cgcaacgcac cgccattcgg gaaagacggt ggtgcgctcg tcgggcacca ggtgcacgcg
9121 ccaaccgcgg ttgtgcaggg tgacaaggtc aacgctgggt gctacctctc cgcgtaggcg
9181 ctggttggtc cagcagaggc ggccgccctt gcgcgagcag aatggcggtg gggggtctag
9241 ctgctgtctc tccggggggc ctgctccac ggtaaagacc ccgggcagca ggccgcgctc
9301 gaagtagtct atcttgcctc cttgcaagtc tagcgcctgc tgccatgcgc gggcggaag
9361 cgccgcgtcg tatgggttga gtgggggacc ccatggcatg ggggtgggtg gcgcggaggc

```

FIG. 31A-3

82/126

9421 gtacatgccg caaatgtcgt aaacgtagag gggctctctg agtattccaa gatatgtagg
9481 gtagcatctt ccaccgcgga tgctggcgcg cacgtaatcg tatagttcgt gcgagggagc
9541 gaggaggtcg ggaccgaggt tgctacgggc gggctgctct gctcggaga ctatctgcct
9601 gaagatggca tgtgagttgg atgatatggg tggacgctgg aagacgttga agctggcgctc
9661 tgtgagacct accgcgtcac gcacgaagga ggcgtaggag tcgcgcagct tgttgaccag
9721 ctggcggtg acctgcacgt ctagggcgca gtagtccagg gtttccttga tgatgtcata
9781 cttatcctgt cccttttttt tccacagctc gcggttgagg acaaactctt cgcggtcttt
9841 ccagtactct tggatcggaa acccgtcggc ctccgaacgg taagagccta gcatgtagaa
9901 ctggttgacg gcctggtagg cgcagcatcc cttttctacg ggtagcgcgt atgcctgcgc
9961 ggccttcggg agcgaggtgt gggtagcgcg aaaggtgtcc ctgaccatga ctttgaggta
10021 ctggtatttg aagtcagtggt cgtcgcaccc gccctgctcc cagagcaaaa agtccgtgcg
10081 ctttttgga cgcggatttg gcagggcgaa ggtgacatcg ttgaagagta tctttcccg
10141 gcgaggcata aagttgcgtg tgatgcggaa ggggtcccgcc acctcggaac ggttggtaat
10201 tacctgggcg gcgagcacga tctcgtcaaa gccgttgatg ttgtggccca caatgtaaag
10261 ttccaagaag cgcgggatgc ccttgatgga aggcattttt ttaagttcct cgtaggtgag
10321 ctcttcaggg gagctgagcc cgtgctctga aagggcccag tctgcaagat gagggttgga
10381 agcgacgaat gagctccaca ggtcacgggc cattagcatt tgcaggtggt cgcgaaaggt
10441 cctaaactgg cgacctatgg ccattttttc tggggtgatg cagtagaagg taagcgggctc
10501 ttgttcccag cgggtccatc caaggttcgc ggctaggtct cgcgcggcag tcactagagg
10561 ctcactctcg ccgaacttca tgaccagcat gaagggcacg agctgcttcc caaaggcccc
10621 catccaagta taggtctcta catcgtaggt gacaaagaga cgctcgggtgc gaggatgcga
10681 gccgatcggg aagaactgga tctcccgcga ccaattggag gagtggctat tgatgtggtg
10741 aaagtagaag tccctgcgac gggccgaaca ctctgctggg cttttgtaaa aacgtgcgca
10801 gtactggcag cgggtgcacgg gctgtacatc ctgcacgagg ttgacctgac gaccgcgcac
10861 aaggaagcag agtgggaatt tgagcccctc gcctggcggg tttggctggt ggtcttctac
10921 ttcggctgct tgctcttgac cgtctggctg ctcgagggga gttacggtgg atcggaccac
10981 cagcgcgcgc gagcccaaag tccagatgct cgcgcgcggc ggtcggagct tgatgacaac
11041 atcgcgcaga tgggagctgt ccatggtctg gagctcccgc ggcgtcaggt caggcgggag
11101 ctctctcagg tttacctcgc atagacgggt cagggcgcgg gctagatcca ggtgatacct
11161 aatttccagg ggctgggttg tggcgcgctc gatggcttgc aagaggccgc atcccccgcg
11221 cgcgactacg gtaccgcgcg gcgggcggtg ggcgcggggg gtgtccttgg atgatgcac
11281 taaaagcggg gacgcgggag agcccccgga ggtagggggg gctccggacc cgcggggaga
11341 gggggcaggg gcacgtcggc gccgcgcgcg ggcaggagct ggtgctgcgc gcgtaggttg
11401 ctggcgaaac cgacgacgcg gcggttgatc tcctgaatct ggcgcctctg cgtgaagacg
11461 acgggcccgg tgagcttgaa cctgaaagag agttcgacag aatcaatttc ggtgtcgttg
11521 acggcggcct ggcgcaaaat ctctcgcag tctcctgagt tgtcttgata ggcgatctcg
11581 gccatgaact gctcgatctc ttctctctgg agatctccgc gtccggctcg ctccacgggtg
11641 gcggcgaggt cgttggaatg gcggggccat agctgcgaga aggcgttgag gcctccctcg
11701 ttccagacgc ggctgtagac cagccccctc tcggcatcgc gggcgcgcat gaccacctgc
11761 gcgagattga gctccacgtg ccgggcgaag acggcgtagt ttcgcaggcg ctgaaagagg
11821 tagttgaggg tgggtggcgg gtgttctgcc acgaagaagt acataaccga gcgtcgcaac
11881 gtggattcgt tgatatcccc caaggcctca aggcgtcca tggcctcgta gaagtccacg
11941 gcgaagttga aaaactggga gttgcgcgcc gacacggtta actcctcctc cagaagacgg
12001 atgagctcgg cgacagtgtc gcgcacctcg cgtcaaagg ctacaggggc ctcttcttct
12061 tcttcaatct cctcttccat aagggcctcc ccttcttctt cttctggcgg cgggtggggga
12121 ggggggacac ggcggcgacg acggcgacac gggaggcggt cgacaaagcg ctcgatcatc
12181 tccccgcggc gacggcgcat ggtctcgggt acggcgcggc cgttctcgcg ggggcgcagt
12241 tggaagacgc cgcccgatc gtcccgggta tgggttgggc gggggctgcc atgcggcagg
12301 gatacggcgc taacgatgca tctcaacaat tgttggttag gtactccgcc gccgagggac
12361 ctgagcgagt ccgcatcgac cggatcggaa aacctctcga gaaaggcgtc taaccagtca
12421 cagtcgcaag gtaggctgag caccgtggcg ggcggcagcg ggcggcggtc ggggttggtt
12481 ctggcgaggg tgctgctgat gatgtaatta aagtaggcgg tcttgagacg gcggatgggtc
12541 gacagaagca ccatgtcctt gggtcgggac tgctgaatgc gcaggcggtc ggccatgccc
12601 caggcttctg tttgacatcg gcgcaggtct ttgtagtagt cttgcatgag cctttctacc
12661 ggcacttctt cttctccttc ctcttgctct gcactctctg catctatcgc tgcggcgggc

FIG. 31A-4

83/126

12721 gcggagtttg gccgtaggtg gcgccctctt cctcccatgc gtgtgacccc gaagcccctc
12781 atcggctgaa gcagggctag gtcggcgaca acgcgctcgg ctaatatggc ctgctgcacc
12841 tgcgtgaggg tagactggaa gtcattccatg tccacaaagc ggtggtatgc gcccggttg
12901 atggtgtaag tgcagttggc cataacggac cagttaacgg tctggtgacc cggctgcgag
12961 agctcgggtg acctgagacg cgagtaagcc ctcgagtcaa atacgtagtc gttgcaagtc
13021 cgcaccaggt actggtatcc caccaaaaag tgcggcgggc gctggcggtg gaggggcccag
13081 cgtaggggtg ccggggctcc gggggcgaga tcttccaaca taaggcgatg atatccgtag
13141 atgtacctgg acatccaggt gatgccggcg gcggtggtgg aggcgcgcgg aaagtcgcgg
13201 acgcggttcc agatggtgcg cagcggcaaa aagtgctcca tggtcgggac gctctggccg
13261 gtcaggcgcg cgcaatcggt gacgctctag accgtgcaaa aggagagcct gtaagcgggc
13321 actcttccgt ggtctggtgg ataaattcgc aagggtatca tggcggacga ccggggttcg
13381 agccccgtat ccggccgtcc gccgtgatcc atgcggttac cgcccgctg tcgaaccag
13441 gtgtgcgacg tcagacaacg ggggagtgct ctttttggct tccttccagg cgcggcggt
13501 gctgcgctag cttttttggc cactggccgc gcgcagcgta agcgggttagg ctggaagcg
13561 aaagcattaa gtggctcgct ccctgtagcc ggaggggttat tttccaaggg ttgagtcgcg
13621 ggacccccgg ttcgagtctc ggaccggccg gactgcggcg aacgggggtt tgctccccg
13681 tcatgcaaga ccccgcttgc aaattcctcc ggaaacaggg acgagcccct tttttgctt
13741 tcccagatgc atccggtgct gcggcagatg cgcctccctc ctcagcagcg gcaagagcaa
13801 gagcagcggc agacatgcag ggcaccctcc cctcctccta ccgctcagg aggggcgaca
13861 tccgcggttg acgcggcagc agatggtgat tacgaacccc cgcggcgccg ggcccggcac
13921 tacctggact tggaggaggg cgagggcctg gcgcggctag gagcgcctc tcctgagcgg
13981 cacccaaggg tgcagctgaa gcgtgatacg cgtgaggcgt acgtgcccg gcagaacctg
14041 tttcgcgacc gcgagggaga ggagcccgag gagatgcggg atcgaaagtt ccacgcaggg
14101 cgcgagctgc ggcattggct gaatcgcgag cggttgctgc gcgaggagga ctttgagccc
14161 gacgcgcgaa ccgggattag tcccgcgcg gcacacgtgg cggccgcca cctggtaacc
14221 gcatacgagc agacgggtgaa ccaggagatt aactttcaaa aaagcttta caaccacgtg
14281 cgtacgcttg tggcgcgca ggaggtggct ataggactga tgcattctgt ggactttgta
14341 agcgcgctgg agcaaaaccc aaatagcaag ccgctcatgg cgcagctgtt ccttatagtg
14401 cagcacagca gggacaacga ggcattcagg gatgcgctgc taaacatagt agagcccag
14461 ggccgctggc tgctcgattt gataaacatc ctgcagagca tagtggtgca ggagcgcagc
14521 ttgagcctgg ctgacaaggt ggccgccatc aactattcca tgcttagcct gggcaagttt
14581 tacgcccga agatatacca tacccttac gttcccatag acaaggaggt aaagatcgag
14641 gggttctaca tgcgcatggc gctgaagggt cttacctga gcgacgacct gggcgtttat
14701 cgcaacgagc gcatccacaa ggccgtgagc gtgagccggc ggcgcgagct cagcgaccgc
14761 gagctgatgc acagcctgca aaggccctg gctggcacgg gcagcggcga tagagaggcc
14821 gagtccact ttgacgcggg cgctgacctg cgctgggccc caagccgacg cgccctggag
14881 gcagctgggg ccggacctgg gctggcggtg gcacccgcgc gcgctggcaa cgtcggcggc
14941 gtggaggaat atgacgagga cgatgagtac gagccagagg acggcgagta ctaagcgggtg
15001 atgtttctga tcagatgatg caagacgcaa cggacccggc ggtgcgggcg gcgctgcaga
15061 gccagccgtc cggccttaac tccacggacg actggcgcca ggtcatggac cgcattcatgt
15121 cgctgactgc gcgcaatcct gacgcgttcc ggcagcagcc gcaggccaac cggctctccg
15181 caattctgga agcgggtggc ccggcgcgcg caaaccacc gcacgagaag gtgctggcga
15241 tcgtaaacgc gctggccgaa aacagggcca tccggcccga cgaggccggc ctggtctacg
15301 acgcgctgct tcagcgcggt gctcgttaca acagcggcaa cgtgcagacc aacctggacc
15361 ggctggtggg ggatgtgcgc gaggcggtg cgagcgtga gcgcgcgag cagcagggca
15421 acctgggctc catggttgca ctaaacgcct tcctgagtac acagcccgcc aacgtgccgc
15481 ggggacagga ggactacacc aactttgtga gcgcactgcg gctaattggtg actgagacac
15541 cgcaaagtga ggtgtaccag tctgggcccag actatttttt ccagaccagt agacaaggcc
15601 tgcagaccgt aaacctgagc caggctttca aaaacttgca ggggctgtgg ggggtgcggg
15661 ctcccacagg cgaccgcgcg accgtgtcta gcttgctgac gcccaactcg cgcctgttgc
15721 tgctgctaat agcgccttcc acggacagt gcagcgtgtc ccgggacaca tacctaggtc
15781 acttgctgac actgtaccgc gaggccatag gtcaggcgca tgtggacgag catactttcc
15841 aggagattac aagtgtcagc cgcgcgctgg ggcaggagga cacgggcagc ctggaggcaa
15901 ccctaaacta cctgctgacc aaccggcggc agaagatccc ctcgttgac agtttaacaa
15961 gcgaggagga gcgcattttg cgctacgtgc agcagagcgt gagccttaac ctgatgcgcg

FIG. 31A-5

WO 2006/020480

PCT/US2005/027658

84/126

```

16021 acggggtaac gccagcgtg gcgctggaca tgaccgcgcg caacatggaa cggggcatgt
16081 atgcctcaaa ccggccggtt atcaaccgcc taatggacta cttgcatcgc gcggccgccg
16141 tgaaccccgga gtatttcacc aatgccatct tgaacccgca ctggctaccg ccccttggtt
16201 tctacaccgg gggattcgag gtgcccaggg gtaacgatgg attcctctgg gacgacatag
16261 acgacagcgt gttttccccc caaccgcaga ccctgctaga gttgcaacag cgcgagcagg
16321 cagaggcggc gctgcgaaag gaaagcttcc gcaggccaag cagcttgtcc gatctaggcg
16381 ctgcggcccc gcggtcagat gctagtagcc catttccaag cttgataggg tctcttacca
16441 gcactcgcac caccgcgccg cgcctgctgg gcgaggagga gtacctaaac aactcgctgc
16501 tgcagccgca gcgcgaaaaa aacctgcctc cggcatttcc caacaacggg atagagagcc
16561 tagtggacaa gatgagtaga tgggaagacgt acgcgcagga gcacagggac gtgccaggcc
16621 cgcgccgcc caccgctcgt caaaggcacg accgtcagcg ggtcttggtg tgggaggacg
16681 atgactcggc agacgacagc agcgtcctgg atttgggagg gaggggcaac ccgtttgcgc
16741 accttcgccc caggctgggg agaattgttt aaaaaaaaaa aaagcatgat gcaaaaataa
16801 aaactcacca aggccatggc accgagcgtt ggttttcttg tattccccctt agtatgcggc
16861 gcgcggcgat gtatgaggaa ggtcctctc cctctacga gagtgtggtg agcgcggcgc
16921 cagtggcggc ggcgctgggt tctcccttcg atgctccctt ggaccgcgcg tttgtgcctc
16981 cgcggtacct gcggcctacc ggggggagaa acagcatccg ttactctgag ttggcacccc
17041 tattcgacac caccgctgtg tacttggtgg acaacaagtc aacggatgtg gcatccctga
17101 actaccagaa cgaccacagc aactttctga ccacggtcat tcaaaacaat gactacagcc
17161 cgggggaggc aagcacacag accatcaatc ttgacgaccg gtcgactgg ggcggcgacc
17221 tgaaaacat cctgcatacc aacatgccaa atgtgaacga gttcatgttt accaataagt
17281 ttaaggcgcg ggtgatggtg tcgcgcttgc ctactaagga caatcagggtg gagctgaaat
17341 acgagtgggt ggagttcacg ctgcccaggg gcaactactc cgagaccatg accatagacc
17401 ttatgaacaa cgcgatcgtg gagcactact tgaaagtggg cagacagaac ggggttctgg
17461 aaagcgacat cggggtaaaag tttgacaccc gcaacttcag actgggggtt gaccccgta
17521 ctggtcttgt catgcctggg gtatatacaa acgaagcctt ccatccagac atcattttgc
17581 tgccaggatg cggggtggac ttcaccacac gccgcctgag caacttgttg ggcattccga
17641 agcggaacc cttccaggag ggctttagga tcacctacga tgatctggag ggtggttaac
17701 ttcccgact gttggatgtg gacgcctacc aggcgagctt gaaagatgac accgaacagg
17761 gcgggggtgg cgcaggcggc agcaacagca gtggcagcgg cgcggaagag aactccaacg
17821 cggcagccgc ggcaatgcag ccggtggagg acatgaacga tcatgccatt cgcggcgaca
17881 cctttgccac acgggctgag gagaagcgcg ctgaggccga agcagcggcc gaagctgccg
17941 cccccgctgc gcaaccgag gtgcgagaag ctcagaagaa accggtgatc aaaccctga
18001 cagaggacag caagaaacgc agttacaacc taataagcaa tgacagcacc ttcaccagt
18061 accgcagctg gtaccttgca tacaactacg gcgaccctca gaccggaatc cgctcatgga
18121 ccctgctttg cactcctgac gtaacctgcg gctcggagca ggtctactgg tcgttgccag
18181 acatgatgca agaccccggt acctccgct ccacgcgcca gatcagcaac tttccggtg
18241 tgggcgcca gctgttgccc gtgcactcca agagcttcta caacgaccag gccgtctact
18301 cccaactcat ccgccagttt acctctctga cccacgtgtt caatcgcttt cccgagaacc
18361 agattttggc gcgcccgcca gccccacca tcaccaccgt cagtgaatac gttcctgctc
18421 tcacagatca cgggacgcta ccgctgcgca acagcatcgg aggagtccag cgagtgaaca
18481 ttactgacgc cagacgccc acctgcccct acgtttacaa ggccctgggc atagtctcgc
18541 cgcgcgtcct atcgagccgc actttttgag caagcatgtc catccttata tcgcccagca
18601 ataacacagg ctggggcctg cgcttcccaa gcaagatgtt tggcggggcc aagaagcgt
18661 ccgaccaaca cccagtgcgc gtgcgcgggc actaccgcgc gccctggggc gcgcacaaac
18721 gcggccgcac tgggcgcacc accgtcgatg acgccatcga cgcggtggtg gaggaggcgc
18781 gcaactacac gccacgccc ccaccagtgt ccacagtggg cgcggccatt cagaccgtgg
18841 tgccgaggag ccggcgctat gctaaaatga agagacggcg gaggcgcgta gcacgtcgcc
18901 accgcccgcg acccggcact gccgcccaac gcgcggcggc ggccctgctt aaccgcgcac
18961 gtcgcaccgg ccgacgggg gccatgcggg ccgctcgaag gctggccgcg ggtattgtca
19021 ctgtgcccc caggtccagg cgacgagcgg ccgcccagc agccgcggcc attagtgtca
19081 tgactcaggg tcgcaggggc aacgtgtatt ggggtgcgca ctcggttagc ggcctgcgcg
19141 tgcccgtgcg caccgcccc ccgcgcaact agattgcaag aaaaaactac ttagactcgt
19201 actgttgtat gtatccagcg gcggcggcgc gcaacgaagc tatgtccaag cgcaaatca
19261 aagaagagat gctccaggtc atcgcgccgg agatctatgg ccccccgaag aaggagagc

```

FIG. 31A-6

85/126

19321 aggattacaa gccccgaaag ctaaagcggg tcaaaaagaa aaagaaagat gatgatgatg
19381 aacttgacga cgagggtggaa ctgctgcacg ctaccgcgcc caggcgacgg gtacagtgga
19441 aaggtcgacg cgtaaaacgt gttttgcgac ccggcaccac cgtagtcttt acgcccgggtg
19501 agcgctccac ccgcacctac aagcgcgtgt atgatgaggt gtacggcgac gaggacctgc
19561 ttgagcaggg caacgagcgc ctcggggagt ttgcctacgg aaagcggcat aaggacatgc
19621 tggcgttgcc gctggacgag ggcaacccaa cacctagcct aaagcccgtg acactgcagc
19681 aggtgctgcc cgcgcttgca ccgtccgaag aaaagcgcgg cctaaagcgc gagtctggtg
19741 acttggcacc caccgtgcag ctgatggtac ccaagcgcca gcgactggaa gatgtcttgg
19801 aaaaaatgac cgtggaacct gggctggagc ccgagggtccg cgtgcggcca atcaagcagg
19861 tggcgccggg actgggcgtg cagaccgtgg acgttcagat acccactacc agtagcacca
19921 gtattgccac cgccacagag ggcattggaga cacaacgtc cccggttgcc tcagcgggtg
19981 cggatgccgc ggtgcaggcg gtcgctgcgg ccgcgtccaa gacctctacg gagggtgcaa
20041 cggacccgtg gatgtttcgc gtttcagccc cccggcgccc gcgcccgttc aggaagtacg
20101 gcgcccgcag cgcgctactg cccgaatatg ccctacatcc ttccattgcg cctacccccg
20161 gctatcgtgg ctacacctac cgccccagaa gacgagcaac taccgacgc cgaaccacca
20221 ctggaacccg ccgcccgcgt cgccgtcgcc agcccggtgt ggccccgatt tccgtgcgca
20281 ggggtggctcg cgaaggaggc aggaccctgg tgctgccaac agcgcgctac caccacagca
20341 tcgtttaaaa gccggtcttt gtggttcttg cagatatggc cctcacctgc cgcctccgtt
20401 tcccgggtgcc gggattccga ggaagaatgc accgtaggag gggcatggcc ggccacggcc
20461 tgacgggcgg catgcgtcgt gcgcaccacc ggccggcgcg cgcgtcgac cgtcgcatgc
20521 gcggcggtat cctgcccctc cttattccac tgatcgccgc ggcgattggc gccgtgcccg
20581 gaattgcatc cgtggccttg caggcgacga gacactgatt aaaaacaagt tgcatgtgga
20641 aaaatcaaaa taaaaagtct ggactctcac gctcgcttgg tcctgtaact attttgtaga
20701 atggaagaca tcaactttgc gtctctggcc ccgcgacacg gctcgcgccc gttcatggga
20761 aactggcaag atatcggcac cagcaatatg agcgggtggc ccttcagctg gggctcgctg
20821 tggagcggca ttaaaaattt cggttccacc gttaagaact atggcagcaa ggcctggaac
20881 agcagcacag gccagatgct gagggataag ttgaaagagc aaaatttcca acaaaagggtg
20941 gtagatggcc tggcctctgg cattagcggg gtggtggacc tggccaacca ggcagtgcaa
21001 aataagatta acagtaagct tgatccccgc cctcccgtag aggagcctcc accggccgtg
21061 gagacagtgt ctccagaggg gcgtggcgaa aagcgtccgc gccccgacag ggaagaaact
21121 ctggtgacgc aaatagacga gcctccctcg tacgaggagg cactaaagca aggcctgccc
21181 accacccgtc ccategcgcc catggctacc ggagtgtggt gccagcacac acccgtaacg
21241 ctggacctgc ctccccccgc cgacaccag cagaaacctg tgctgccagg cccgaccgcc
21301 gttgttgtaa cccgtcctag ccgcgcgtcc ctgcgcgcgc ccgccagcgg tccgcgatcg
21361 ttgcggcccc tagccagtgg caactggcaa agcacactga acagcatcgt gggctctggg
21421 gtgcaatccc tgaagcgccg acgatgcttc tgatagctaa cgtgtcgtat gtgtgtcatg
21481 tatgcgtcca tgtcgcccgc agaggagctg ctgagccgcc gcgcgcccgc tttccaagat
21541 ggctacccct tcgatgatgc cgcagtggtc ttacatgcac atctcgggccc aggacgcctc
21601 ggagtacctg agccccgggc tgggtgcagt tgcccgcgcc accgagacgt acttcagcct
21661 gaataacaag tttagaaacc ccacggtggc gcctacgcac gacgtgacca cagaccggtc
21721 ccagcgtttg acgctgcggt tcacccctgt ggaccgtgag gatactgcgt actcgtacaa
21781 ggcgcggttc accctagctg tgggtgataa ccgtgtgctg gacatggctt ccacgtactt
21841 tgacatccgc ggcgtgctgg acaggggccc tacttttaag ccctactctg gcactgccta
21901 caacgccctg gctcccaagg gtgccccaaa tccttgcgaa tgggatgaag ctgctactgc
21961 tcttgaaata aacctagaag aagaggacga tgacaacgaa gacgaagtag acgagcaagc
22021 tgagcagcaa aaaactcacg tatttgggca ggccgcttat tctggtataa atattacaaa
22081 ggagggtatt caaatagggt tcgaagggtc aacacctaaa tatgccgata aaacatttca
22141 acctgaacct caaataggag aatctcagtg gtacgaaaca gaaattaatc atgcagctgg
22201 gagagtccta aaaaagacta ccccaatgaa accatgttac ggttcatatg caaaaccac
22261 aatgaaaat ggagggcaag gcattcttgt aaagcaacaa aatggaaagc tagaaagtca
22321 agtggaaatg caatttttct caactactga ggcagccgca ggcaatgggtg ataacttgac
22381 tcctaaagtg gtattgtaca gtgaagatgt agatatagaa accccagaca ctcatatttc
22441 ttacatgccc actattaagg aaggtaactc acgagaacta atgggccaac aatctatgcc
22501 caacaggcct aattacattg cttttaggga caattttatt ggtctaattg attacaacag
22561 cacgggtaat atgggtgttc tggcgggcca agcatcgacg ttgaatgctg ttgtagatth

FIG. 31A-7

86/126

22621 gcaagacaga aacacagagc tttcatacca gcttttgctt gattccattg gtgatagaac
 22681 cagggtacttt tctatgtgga atcagggtgt tgacagctat gatccagatg ttagaattat
 22741 tgaaaatcat ggaactgaag atgaacttcc aaattactgc tttccactgg gaggtgtgat
 22801 taatacagag actcttacca aggtaaaacc taaaacaggt caggaaaatg gatgggaaaa
 22861 agatgctaca gaattttcag ataaaaatga aataagagtt ggaaataatt ttgccatgga
 22921 aatcaatcta aatgcccaacc tgtggagaaa tttcctgtac tccaacatag cgctgtattt
 22981 gcccagacaag ctaaagtaca gtccttccaa cgtaaaaatt tctgataacc caaacaccta
 23041 cgactacatg aacaagcgag tgggtggctcc cgggctagtg gactgctaca ttaaccttgg
 23101 agcacgctgg tcccttgact atatggacaa cgtcaaccca ttttaaccacc accgcaatgc
 23161 tggcctgcgc taccgctcaa tgttgcgtgg caatggctgc tatgtgccct tccacatcca
 23221 ggtgcctcag aagttctttg ccattaaaaa cctccttctc ctgccgggct catacaccta
 23281 cgagtggaaac ttcaggaagg atgttaacat gggtctgcag agctccctag gaaatgacct
 23341 aagggttgac ggagccagca ttaagtttga tagcatttgc ctttacgcca ccttcttccc
 23401 catggccccc aacaccgcct ccacgcttga ggccatgctt agaaacgaca ccaacgacca
 23461 gtcctttaac gactatctct ccgccgcaa catgctctac cctatacccg ccaacgctac
 23521 caacgtgccc atatccatcc cctcccgcaa ctgggcgggt ttccgcggtt gggccttcac
 23581 gcgccttaag actaaggaaa ccccatcact gggctcgggc tacgaccctt attacaccta
 23641 ctctggctct ataccctacc tagatggaaac cttttacctc aaccacacct ttaagaaggt
 23701 ggccattacc tttgactctt ctgtcagctg gcctggcaat gaccgcctgc ttaccccca
 23761 cgagtttgaa attaagcgct cagttgacgg ggagggttac aacgttgccc agtgtaacat
 23821 gaccaaagac tggttcctgg tacaatgct agctaactat aacattggct accagggtt
 23881 ctatatccca gagagctaca aggaccgcat gtactccttc tttagaaact tccagcccat
 23941 gagccgtcag gtggtggatg atactaaata caaggactac caacagggtg gcatectaca
 24001 ccaacacaa aactctggat ttgttggtta ccttgccccc accatgcgcg aaggacaggc
 24061 ctaccctgct aacttcccct atccgcttat aggcaagacc gcagttgaca gcattaccca
 24121 gaaaaagttt ctttgcgac gcaccctttg gcgcaccca ttctccagta actttatgtc
 24181 catgggcgca ctcacagacc tgggccaata ccttctctac gccaaactccg cccacgcgt
 24241 agacatgact tttgaggtgg atcccattga cgagcccacc cttctttatg ttttgtttga
 24301 agtctttgac gtggtccgtg tgcaccagcc gcaccgcggc gtcacgaaa ccgtgtacct
 24361 gcgcacgccc ttctcggccg gcaacgccac aacataaaga agcaagcaac atcaacaaca
 24421 gctgccgcca tgggctccag tgagcaggaa ctgaaagcca ttgtcaaaga tcttggttgt
 24481 gggccatatt ttttgggcac ctatgacaag cgctttccag gctttgtttc tccacacaag
 24541 ctgcctgctg ccatagtcaa tacggccggc cgcgagactg ggggcgtaca ctggatggcc
 24601 tttgcctgga acccgcactc aaaaacatgc tacctctttg agccctttgg cttttctgac
 24661 cagcgactca agcaggttta ccagtttgag tacgagtcac tctgcgccg tagcgccatt
 24721 gcttcttccc ccgaccgctg tataacgctg gaaaagtcca ccaaagcgt acaggggccc
 24781 aactcggccg cctgtggact attctgctgc atgtttctcc acgcctttgc caactggccc
 24841 caaactccca tggatcaca cccaccatg aaccttatta ccggggtacc caactccatg
 24901 ctcaacagtc cccaggtaca gccaccctg cgtcgcaacc aggaacagct ctacagcttc
 24961 ctggagcgcc actcgcccta cttccgcagc cacagtgcgc agattaggag cgccacttct
 25021 ttttgtcact tgaaaaacat gtaaaaataa tgtactagag acactttcaa taaaggcaaa
 25081 tgcttttatt tgtacactct cgggtgatta tttaccccca cccttgccgt ctgcgccgtt
 25141 taaaaatcaa aggggttctg ccgcgcacgc ctatgcgcca ctggcaggga cacgttgcca
 25201 tactggtgtt tagtgctcca cttaaactca ggcacaacca tccgcggcag ctcggtgaag
 25261 ttttactccc acaggctgcg caccatcacc aacgcgttta gcaggtcggg cgccgatatc
 25321 ttgaagtcgc agttggggcc tccgccctgc gcgcgcaggt tgcgatacac aggggtgcag
 25381 cactggaaca ctatcagcgc cgggtggtgc acgctggcca gcacgctctt gtcggagatc
 25441 agatccgctg ccaggtcctc cgcgttgctc agggcgcaac gagtcaactt tggtagctgc
 25501 cttcccaaaa agggcgcgctg cccaggcttt gagttgact cgcaccgtag tggcatcaaa
 25561 aggtgaccgt gcccggtctg ggcgttagga tacagcgcct gcataaaagc cttgatctgc
 25621 ttaaaagcca cctgagcctt tgcgccttca gagaagaaca tgccgcaaga cttgccggaa
 25681 aactgattgg ccggacaggc cgcgtcgtgc acgcagcacc ttgcgtcggg gttggagatc
 25741 tgcaccacat ttcggcccca ccggttcttc acgatcttgg ccttgctaga ctgctccttc
 25801 agcgcgcgct gcccgtttct gctcgtcaca tccatttcaa tcacgtgctc cttatttate
 25861 ataagtcttc cgtgtagaca cttaaagctc cttcgtatct cagcgcagcg gtgcagccac

FIG. 31A-8

WO 2006/020480

PCT/US2005/027658

87/126

```

25921 aacgcgcagc ccgtgggctc gtgatgcttg taggtcacct ctgcaaacga ctgcagggtac
25981 gcctgcagga atcgccccc atcgctcaca aaggctcttg tgctgggtgaa gggtcagctgc
26041 aaccgcggt gctcctcgtt cagccaggtc ttgcatacgg ccgccagagc ttccacttgg
26101 tcaggcagta gtttgaagtt cgcctttaga tcgttatcca cgtgggtactt gtccatcagc
26161 gcgcgcgcag cctccatgcc cttctcccac gcagacacga tcggcacact cagcgggttc
26221 atcacgtaa tttcactttc cgcttcgctg ggctcttcct cttcctcttg cgtccgcata
26281 ccacgcgcca ctgggtcgtc ttcattcagc cgccgactg tgcgcttacc tcctttgcca
26341 tgcttgatta gcaccggtgg gttgctgaaa ccaccattt gtagcgccac atcttctctt
26401 tcttcctcgc tgtccacgat tacctctggt gatggcgggc gctcgggctt gggagaaggg
26461 cgcttctttt tcttcttggg cgcaatggcc aaatccgccc ccgaggtcga tggccgcggg
26521 ctgggtgtgc gcggcaccag cgcgtcttgt gatgagctt cctcgtcctc ggactcgata
26581 cgccgcctca tccgcttttt tgggggcgcc cggggaggcg gcggcgacgg ggacggggac
26641 gacacgtcct ccatggttgg gggacgtcgc gccgcaccgc gtccgcgctc ggggggtggt
26701 tcgcgctgct cctcttcccg actggccatt tccttctcct ataggcagaa aaagatcatg
26761 gagtcagtcg agaagaagga cagcctaacc gcccctcttg agttcgccac caccgcctcc
26821 accgatgccg ccaacgcgcc taccacctc ccgctcgagg caccctcgct tgaggaggag
26881 gaagtgatta tcgagcagga ccaggtttt gtaagcgaag acgacgagga ccgctcagta
26941 ccaacagagg ataaaaagca agaccaggac aacgcagagg caaacgagga acaagtccgg
27001 cgggggggac aaaggcatgg cgactaccta gatgtgggag acgacgtgct gttgaagcat
27061 ctgcagcgcc agtgcccat tatctgcgac gcgttgcaag agcgacgca tgtgcccctc
27121 gccatagcgg atgtcagcct tgcctacgaa cgccacctat tctacccgc cgtaccccc
27181 aaacgccaag aaaacggcac atgcgagccc aaccgcgcc tcaacttcta ccccgatatt
27241 gccgtgccag aggtgcttgc cacctatcac atctttttcc aaaactgcaa gataccccta
27301 tcctgccgtg ccaaccgcag ccgagcggac aagcagctgg ccttgccgca gggcgctgtc
27361 atacctgata tcgcctcgtc caacgaagtg ccaaaaatct ttgagggtct tggacgcgac
27421 gagaagcgcg cggcaaacgc tctgcaacag gaaaacagcg aaaatgaaag tactctgga
27481 gtgttggtgg aactcgaggg tgacaacgcg cgcttagccg tactaaaacg cagcatcgag
27541 gtcaccact ttgcctacct ggcacttaac ctacccccca aggtcatgag cacagtcatg
27601 agtgagctga tcgtgcgccg tgcgcagccc ctggagaggg atgcaaattt gcaagaacaa
27661 acagaggagg gcctaccgc agttggcgac gagcagctag cgcgctggct tcaaacgcgc
27721 gagcctgccg acttgaggga gcgacgcaaa ctaatgatgg ccgcagtgct cgttacccgtg
27781 gagcttgagt gcatgcagcg gttctttgct gaccgggaga tgcagcgcaa gctagaggaa
27841 acattgcact acacctttcg acagggctac gtacgccagg cctgcaagat ctccaacgtg
27901 gagctctgca acctggtctc ctaccttggg attttgcacg aaaaccgcct tgggcaaaac
27961 gtgcttcatt ccacgtcaca gggcgaggcg cgccgcgact acgtccgcga ctgcgtttac
28021 ttatttctat gctacacctg gcagacggcc atgggcgttt ggcagcagtg cttggaggag
28081 tgcaacctca aggagctgca gaaactgcta aagcaaaact tgaaggacct atggacggcc
28141 ttcaacgagc gctccgtggc cgcgcacctg gcggacatca ttttccccga acgcctgctt
28201 aaaaccctgc aacagggtct gccagacttc accagtcaaa gcatgttgca gaactttagg
28261 aactttatcc tagagegctc aggaatcttg cccgccacct gctgtgcact tcctagcgac
28321 tttgtgcca ttaagtaccg cgaatgccct ccgcccgttt ggggccactg ctacctctg
28381 cagctagcca actaccttgc ctaccactct gacataatgg aagacgtgag cggtagcgg
28441 ctactggagt gtcactgtcg ctgcaacctg tgcaccocgc accgtccctt ggtttgcaat
28501 tcgcagctgc ttaacgaaag tcaaattatc ggtacctttg agctgcaggg tccctcgcct
28561 gacgaaaagt ccgcggctcc ggggttgaaa ctactccgg ggctgtggac gtcggcttac
28621 cttcgcaaat ttgtacctga ggactaccac gccacgaga ttaggttcta cgaagaccaa
28681 tcccgcgcgc ctaatgcgga gcttaccgcc tgcgtcatta ccaggggcca cattcttggc
28741 caattgcaag ccatcaacaa agcccgcgca gagtttctgc tacgaaaggg acgggggggtt
28801 tacttggaac ccagtcagg cgaggagctc aaccaatcc cccgcgccgc gcagccctat
28861 cagcagcagc cgcgggccct tgcttcccag gatggcacc aaaaagaagc tgcagctgcc
28921 gccgccacc acggacgagg aggaatactg ggacagtcag gcagaggagg ttttggaaga
28981 ggaggaggag gacatgatgg aagactggga gagcctagac gaggaagctt ccgaggtcga
29041 agaggtgtca gacgaaacac cgtcacctc ggctgcattc cctcgcggc cgcccagaa
29101 atcggcaacc ggttccagca tggctacaac ctccgctcct caggcgccgc cggcactgcc
29161 cgttcgccga cccaaccgta gatgggacac cactggaacc agggccggta agtccaagca

```

FIG. 31A-9

WO 2006/020480

PCT/US2005/027658

88/126

```

29221 gccgcgcgcg ttagcccaag agcaacaaca gcgccaaggc taccgctcat ggcgcgggca
29281 caagaacgcc atagttgctt gcttgcaaga ctgtgggggc aacatctcct tcgcccggcg
29341 ctttcttctc taccatcacg gcgtggcctt ccccgtaac atcctgcatt actaccgtca
29401 tctctacagc ccatactgca ccggcggcag cggcagcaac agcagcggcc acacagaagc
29461 aaaggcgacc ggatagcaag actctgacaa agcccaagaa atccacagcg gcggcagcag
29521 caggaggagg agcgtgcgt ctggcgccca acgaaccgt atcgaccgcg gagcttagaa
29581 acaggathtt tcccactctg tatgctatat ttcaacagag caggggcca gaacaagagc
29641 tgaaaataaa aaacaggtct ctgcgatccc tcaccgcgag ctgcctgtat cacaaaagcg
29701 aagatcagct tcggcgcacg ctggaagacg cggaggctct cttcagtaaa tactgcgcgc
29761 tgactcttaa ggactagttt cgcgcccttt ctcaaattta agcgcgaaaa ctacgtcatc
29821 tccagcggcc acaccggcg ccagcacctg ttgtcagcgc cattatgagc aaggaaattc
29881 ccacgcccta catgtggagt taccagccac aaatgggact tgcggctgga gctgcccagg
29941 actactcaac ccgaataaac tacatgagcg cgggacccca catgatatcc cgggtcaacg
30001 gaatacgcgc ccaccgaaac cgaattctcc tggaacaggc ggctattacc accacacctc
30061 gtaataacct taatccccgt agttggcccg ctgccctggt gtaccaggaa agtcccgcctc
30121 ccaccactgt ggtacttccc agagacgccc aggcggaagt tcagatgact aactcagggg
30181 cgcagcttgc gggcggcttt cgtcacaggg tgcggtcgcc cgggcagggt ataactcacc
30241 tgacaatcag agggcgagggt attcagctca acgacgagtc ggtgagctcc tcgcttggtc
30301 tccgtccgga cgggacattt cagatcggcg gcgcgggccc ctcttcattc acgcctcgctc
30361 aggcaatcct aactctgcag acctcgtcct ctgagccgcg ctctggaggc attggaactc
30421 tgcaatttat tgaggagttt gtgccatcgg tctactttaa ccccttctcg ggacctcccg
30481 gccactatcc ggatcaattt attcctaact ttgacgcggt aaaggactcg gcggacggct
30541 acgactgaat gttaagtgga gaggcagagc aactgcgcct gaaacacctg gtccactgtc
30601 gccgccacaa gtgctttgcc cgcgactccg gtgagttttg ctactttgaa ttgcccggag
30661 atcatatcga gggcccggcg cagggcgctc ggcttaccgc ccagggagag cttgcccgta
30721 gcctgattcg ggagtttacc cagcgcccc tgctagttga gcgggacagg ggacctgtg
30781 ttctcactgt gatttgcaac tgtcctaacc ctggattaca tcaagatcct ctagttataa
30841 ctagagtacc cggggatcct attcccttta actaataaaa aaaaataata aagcatcact
30901 tacttaaaat cagttagcaa atttctgtcc agtttattca gcagcacctc cttgccctcc
30961 tcccagctct ggtattgcag cttcctcctg gctgcaaact ttctccacaa tctaaatgga
31021 atgtcagttt cctcctgttc ctgtccatcc gcacccacta tcttcatgtt gttgcagatg
31081 aagcgcgcaa gaccgtctga agataccttc aaccctgtgt atccatatga cacggaaacc
31141 ggtcctccaa ctgtgccttt tcttactcct cctttgtat cccccaatgg gtttcaagag
31201 agtccccctg gggtagctct tttgcgccta tccgaacctc tagttacctc caatggcatg
31261 cttgcgctca aaatgggcaa cggcctctct ctggacgagg ccggcaacct tacctcccaa
31321 aatgtaacca ctgtgagccc acctctcaaa aaaaccaagt caaacataaa cctggaaata
31381 tctgcacccc tcacagttac ctcagaagcc ctaactgtgg ctgccgcgcg acctctaattg
31441 gtcgcgggca acacactcac catgcaatca caggccccgc taaccgtgca cgactccaaa
31501 cttagcattg ccaccaagg acccctcaca gtgtcagaag gaaagctagc cctgcaaaca
31561 tcaggccccc tcaccaccac cgatagcagt acccttacta tcaactgcctc acccccttta
31621 actactgcca ctggtagctt gggcattgac ttgaaagagc ccatttatac acaaaatgga
31681 aaactaggac taaagtacgg ggctcctttg catgtaacag acgacctaaa cactttgacc
31741 gtagcaactg gtccagggtg gactattaat aatacttctt tgcaaactaa agttactgga
31801 gccttgggtt ttgattcaca aggcaatatg caacttaatg tagcaggagg actaaggatt
31861 gattctcaaa acagacgcct tatacttgat gttagttatc cgtttgatgc tcaaaaccaa
31921 ctaaatctaa gactaggaca gggccctctt ttataaact cagcccacaa cttggatatt
31981 aactacaaca aaggccttta cttgtttaca gcttcaaaca attccaaaaa gcttgagggtt
32041 aacctaagca ctgccaaggg gttgatgttt gacgctacag ccatagccat taatgcagga
32101 gatgggcttg aatttggttc acctaatgca ccaaacacaa atcccctcaa aacaaaaatt
32161 ggccatggcc tagaatttga ttcaaacaag gctatggttc ctaaactagg aactggcctt
32221 agttttgaca gcacaggtgc cattacagta ggaaacaaaa ataataataa gctaactttg
32281 tggaccacac cagctccatc tcctaactgt agactaaatg cagagaaaga tgctaaactc
32341 actttgggtc taacaaaatg tggcagtcac atacttgcta cagtttcagt tttggctgtt
32401 aaaggcagtt tggctccaat atctggaaca gttcaaagtg ctcatcttat tataagattt
32461 gacgaaaatg gagtgctact aaacaattcc ttcctggacc cagaatattg gaactttaga

```

FIG. 31A-10

89/126

```

32521 aatggagatc ttactgaagg cacagcctat acaaacgctg ttggatttat gcctaaccta
32581 tcagcttata caaaatctca cggtaaaact gccaaaagta acattgtcag tcaagtttac
32641 ttaaacggag acaaaactaa acctgtaaca ctaaccatta cactaaacgg tacacaggaa
32701 acaggagaca caactccaag tgcatactct atgtcatttt catgggactg gtctggccac
32761 aactacatta atgaaatatt tgccacatcc tcttacactt tttcatacat tgcccaagaa
32821 taaagaatcg tttgtgttat gtttcaacgt gtttattttt caattgcaga aaatttcaag
32881 tcatttttca ttcagtagta tagccccacc accacatagc ttatacagat caccgtacct
32941 taatcaaact cacagaaccc tagtattcaa cctgccacct cctcccaac acacagagta
33001 cacagtcctt tctccccggc tggccttaaa aagcatcata tcatgggtaa cagacatatt
33061 cttaggtgtt atattccaca cggtttcctg tcgagccaaa cgctcatcag tgatattaat
33121 aaactccccg ggcagctcac ttaagttcat gtcgctgtcc agctgctgag ccacaggctg
33181 ctgtccaact tgcggttgct taacgggcgg cgaaggagaa gtccacgcct acatgggggt
33241 agagtcataa tcgtgcatca ggatagggcg gtggtgctgc agcagcgcgc gaataaactg
33301 ctgccgccgc cgctccgtcc tgcaggaata caacatggca gtggtctcct cagcgatgat
33361 tcgcaccgcc cgcagcataa ggcgccttgt cctccgggca cagcagcgca ccctgatctc
33421 acttaaatca gcacagtaac tgcagcacag caccacaata ttgttcaaaa tcccacagtg
33481 caaggcgctg tatccaaagc tcatggcggg gaccacagaa cccacgtggc catcatacca
33541 caagcgcagg tagattaagt ggcgaccctt cataaacacg ctggacataa acattacctc
33601 ttttggcatg ttgtaattca ccacctcccg gtaccatata aacctctgat taaacatggc
33661 gccatccacc accatcctaa accagctggc caaaacctgc ccgccggcta tacactgcag
33721 ggaaccggga ctggaacaat gacagtggag agcccaggac tcgtaaccat ggatcatcat
33781 gctcgtcatg atatcaatgt tggcacaaca caggcacacg tgcatacact tctcaggat
33841 tacaagctcc tcccgcgtta gaaccatata ccagggaaca acccattcct gaatcagcgt
33901 aaatcccaca ctgcaggga gacctgcac gtaactcacg ttgtgcattg tcaaagtgtt
33961 acattcgggc agcagcggat gatcctccag tatggtagcg cgggtttctg tctcaaaagg
34021 aggtagacga tccctactgt acggagtgcg ccgagacaac cgagatcgtg ttggtcgtag
34081 tgtcatgcca aatggaacgc cggacgtagt catatttcct gaagcaaaac caggtgcggg
34141 cgtgacaaac agatctgctt ctcgggtctc gccgcttaga tcgctctgtg tagtagttgt
34201 agtatatcca ctctctcaaa gcatccaggc gccccctggc ttcgggttct atgtaaactc
34261 cttcatgcgc cgctgccctg ataacatcca ccaccgcaga ataagccaca cccagccaac
34321 ctacacattc gttctgcgag tcacacacgg gaggagcggg aagagctgga agaaccatgt
34381 tttttttttt attccaaaag attatccaaa acctcaaaat gaagatctat taagtgaacg
34441 cgctcccctc cgggtggcgtg gtcaaactct acagccaaag aacagataat ggcatttgta
34501 agatgttgca caatggcttc caaaaggcaa acggccctca cgtccaagtg gacgtaaagg
34561 ctaaaccctt caggggtgaat ctctctata aacattccag caccttcaac catgccccaa
34621 taattctcat ctgcgccact tctcaatata tctctaagca aatcccgaat attaagtccg
34681 gccattgtaa aaatctgctc cagagcggcc tccaccttca gcctcaagca gcgaatcatg
34741 attgcaaaaa ttcagggttc tcacagacct gtataagatt caaaagcggg acattaacaa
34801 aaataaccgc atcccgtagg tcccttcgca gggccagctg aacataatcg tgcaggctctg
34861 cacggaccag cgcggccact tccccgccag gaaccatgac aaaagaacct acactgatta
34921 tgacacgcat actcggagct atgctaacca gcgtagcccc gatgtaagct tgttgcatgg
34981 gcggcgatat aaaatgcaag gtgctgctca aaaaatcagg caaagcctcg cgcaaaaaag
35041 aaagcacatc gtagtcatgc tcatgcagat aaaggcagggt aagctccgga accaccacag
35101 aaaaagacac cattttttct tcaaacatgt ctgcgggttt ctgcataaac acaaaataaa
35161 ataacaaaaa aacattttaa cattagaagc ctgtcttaca acaggaaaaa caacccttat
35221 aagcataaga cggactacgg ccatgccggc gtgaccgtaa aaaaactggt caccgtgatt
35281 aaaaagcacc accgacagct cctcgggtcat gtccggagtc ataatgtaag actcggtaaa
35341 cacatcagggt tgattcacat cggtcagtgc taaaaagcga ccgaaatagc ccgggggaat
35401 acatacccgc aggcgtagag acaacattac agcccccata ggaggtataa caaaattaat
35461 aggagagaaa aacacataaa cacctgaaaa accctcctgc ctaggcaaaa tagcaccctc
35521 ccgctccaga acaacataca gcgcttccac agcggcagcc ataacagtca gccttaccag
35581 taaaaaagaa aacctattaa aaaaacacca ctgcacacgg caccagctca atcagtcaca
35641 gtgtaaaaaa gggccaagtg cagagcgagt atatatagga ctaaaaaatg acgtaacggg
35701 taaagtccac aaaaacacc cagaaaaccg cagcgaacc tacgccaga aacgaaagcc
35761 aaaaaccca caacttctc aaatcgtcac ttccgttttc ccacgttacg tcaactccca

```

FIG. 31A-11

WO 2006/020480

PCT/US2005/027658

90/126

35821 ttttaagaaa actacaattc ccaacacata caagttactc cgccctaaaa cctacgtcac
35881 ccgccccggtt cccacgcccc gcgccacgtc acaaactcca cccctcatt atcatattgg
35941 cttcaatcca aaataaggta tattattgat gatg (SEQ ID NO: 20)

FIG. 31A-12

91/126

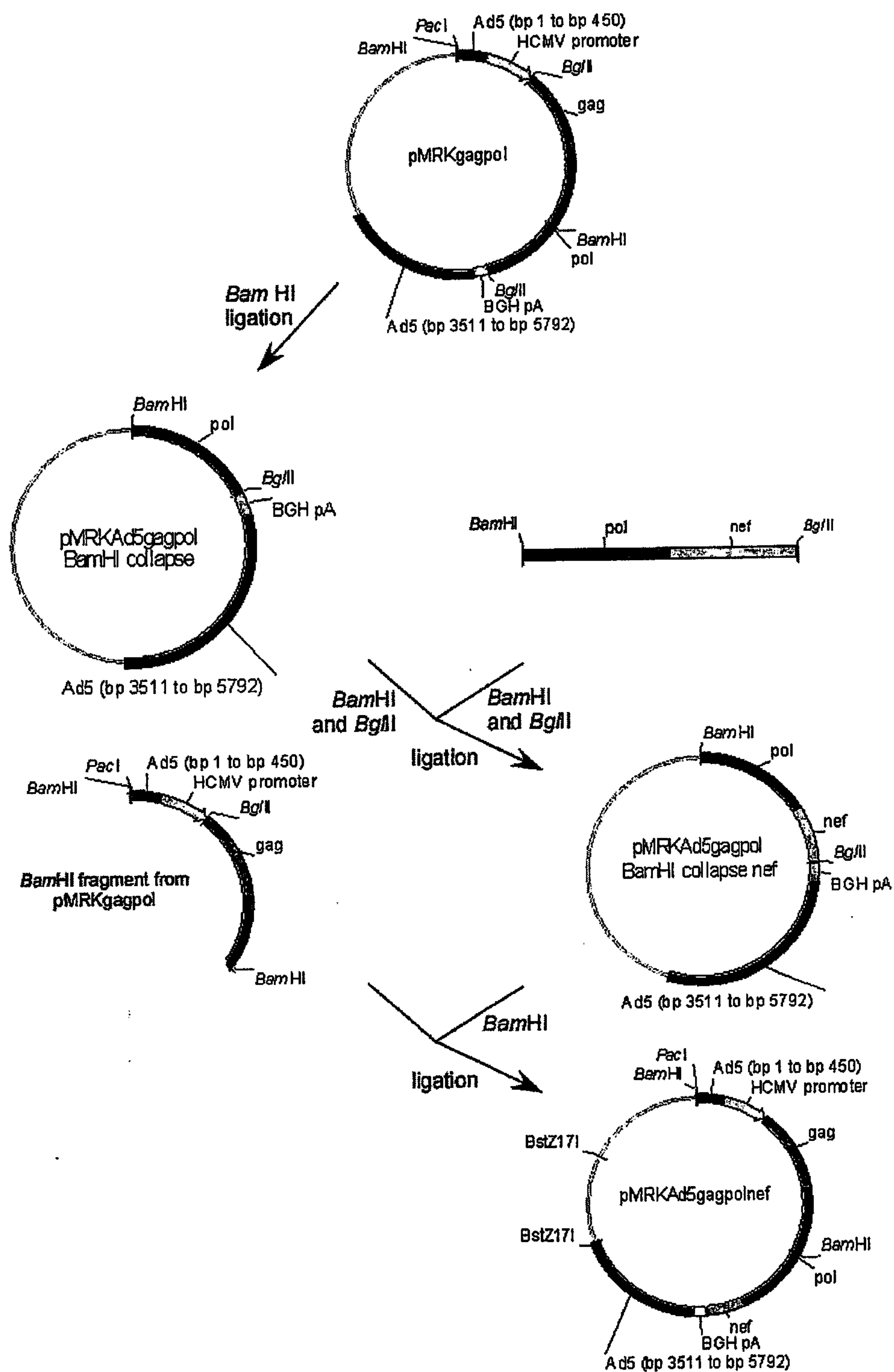


FIG. 32

92/126

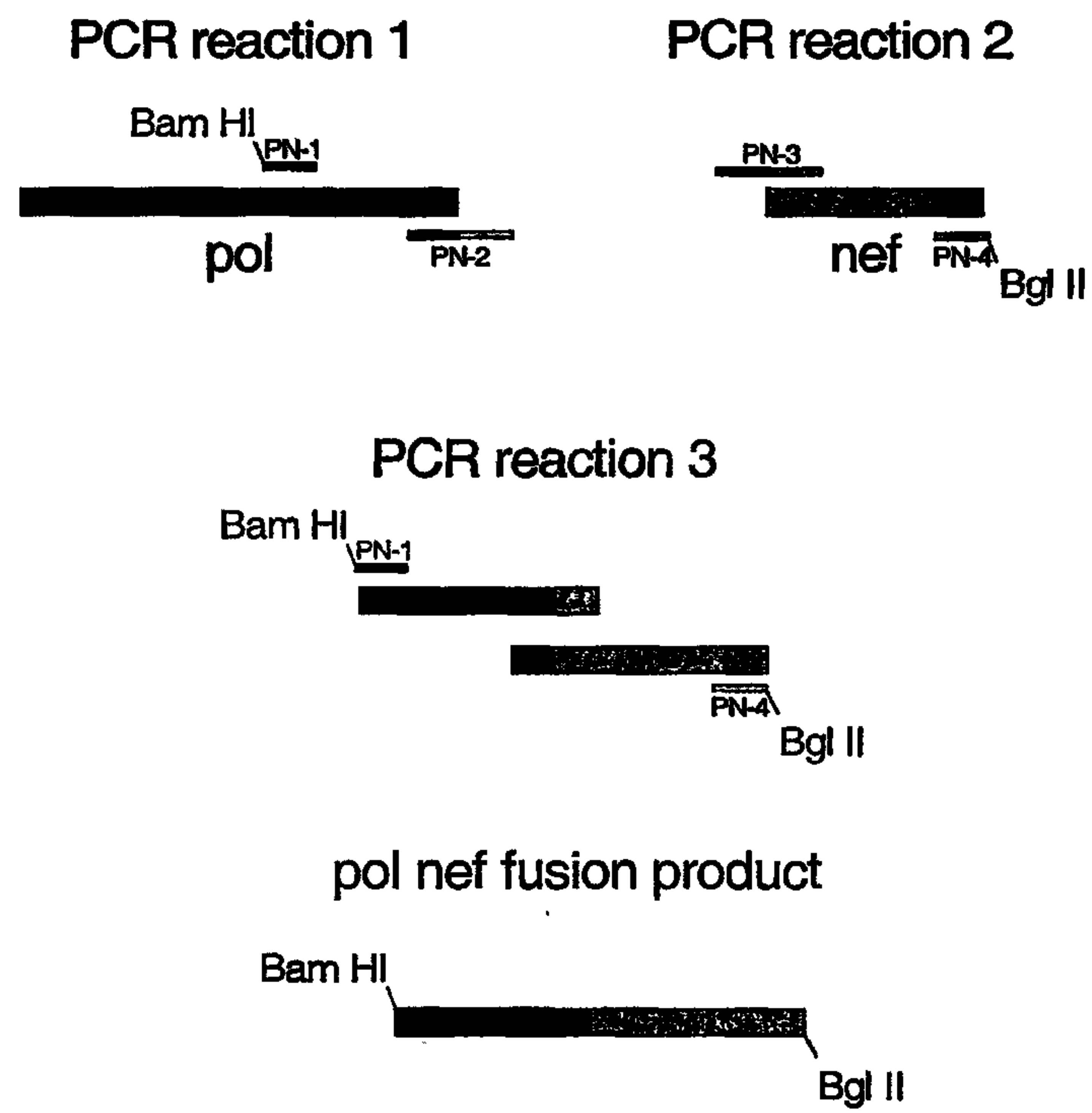


FIG. 33

93/126

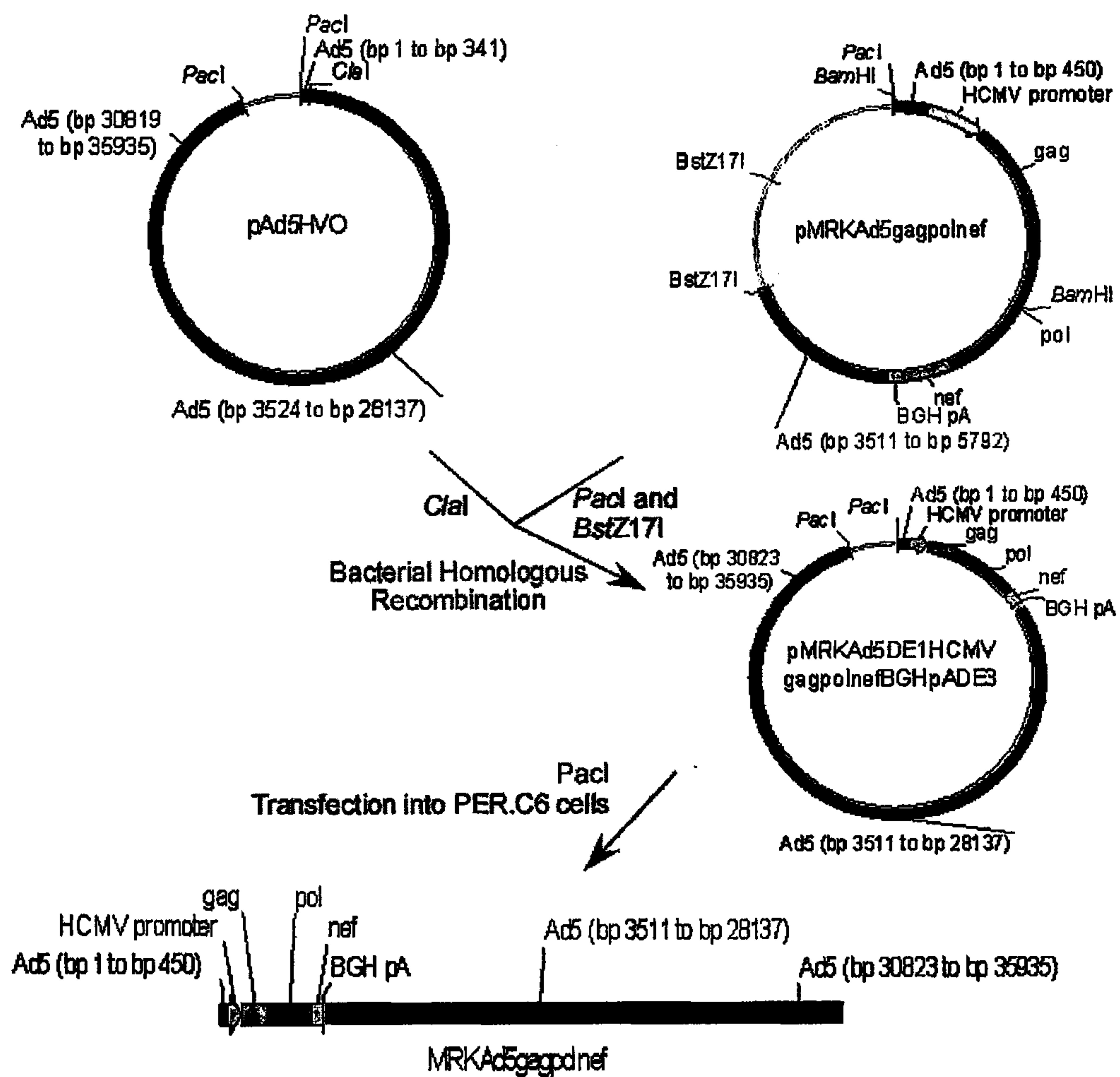
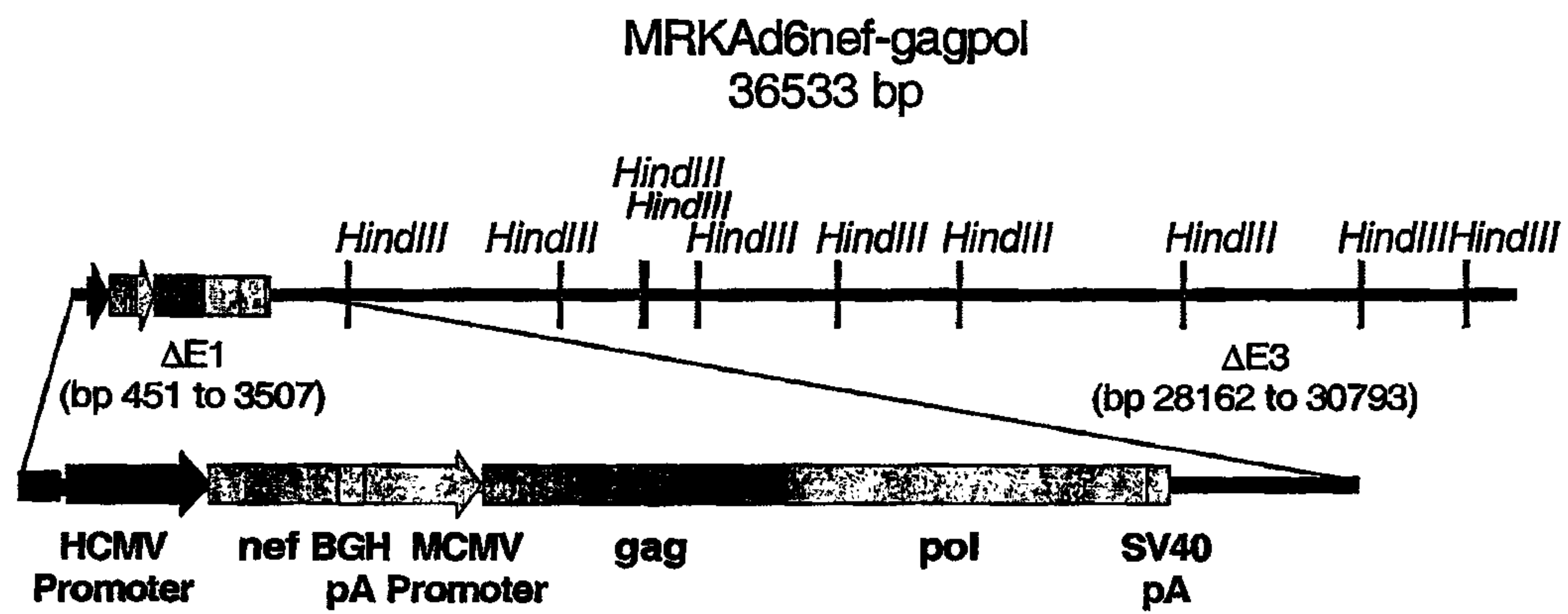


FIG. 34

94/126

**FIG. 35**

WO 2006/020480

PCT/US2005/027658

95/126

MRKAd6nef-gagpol

KEY: ____ HCMV promoter ____ Nef ____ BGH pA MCMV promoter ____ Gag ____ Pol SV40 pA

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgtaa gtgtggcggg acacatgtaa gcgccggatg tggtaaaagt gacgtttttg
181 gtgtgcgcgg gtgtacacgg gaagtgacaa ttttcgcgcg gttttaggcg gatgtttag
241 taaatttggg cgtaaccaag taatatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataattct gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcggttt attattatag cgccgcgat ccattgcata cgttgtatcc
481 atatcataat atgtacattt atattggctc atgtccaaca ttaccgcat gttgacattg
541 attattgact agttattaat agtaatcaat tacgggggtca ttagttcata gcccatatat
601 ggagttccgc gttacataac ttacggtaaa tggccgcct ggctgaccgc ccaacgacc
661 ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag ggactttcca
721 ttgacgtcaa tgggtggagt atttacggt aactgccac ttggcagtac atcaagtgt
781 tcatatgcca agtacgccc ctattgacgt caatgacggt aaatggccc cctggcatta
841 tgcccagtac atgacctat gggactttcc tacttggcag tacatctacg tattagtcat
901 cgctattacc atggtgatgc ggttttggca gtacatcaat gggcgtggat agcgtttga
961 ctcacgggga tttccaagtc tccaccccat tgacgtcaat gggagtttgt tttggacca
1021 aaatcaacgg gactttccaa aatgtcgtaa caactccgc ccattgacgc aaatggcgg
1081 taggcgtgta cgggtggagg tctatataag cagagctcgt ttagtgaacc gtcagatcgc
1141 ctggagacgc catccacgct gttttgacct ccatagaaga caccgggacc gatccagcct
1201 ccgcccggcg gaacggtgca ttggaacgcg gattccccgt gccaaagagt agatctgcca
1261 ccattggccg caagtgttc aagaggtccg tgcccgcctg gtccaccgtg agggagagga
1321 tgaggagggc cgagcccgcg gccgacaggg tgaggaggac cgagcccgcg gcagtggggc
1381 tgggcgcctg gtccagggac ctggagaagc acggcgccat caccctctcc aacaccggcg
1441 ccaccaacgc cgactgcgc tggtggagg ccaggaagg cgaggaggtg ggttccccc
1501 tgaggcccca ggtgccctg aggcccatga cctacaagg cccgtggac ctgtccact
1561 tcctgaagga gaaggcggc ctggagggc tgatccact ccagaagag caggacatcc
1621 tggacctgtg ggtgtaccac acccagggct acttccccga ctggcagaac tacaccccc
1681 gccccggcat caggttcccc ctgaccttcg gctggtgctt caagctggtg cccgtggagc
1741 ccgagaaggt ggaggaggg aacgagggc agaacaactg cctgctgcac cccatgtccc
1801 agcacggcat cgaggacccc gagaaggagg tgctggagtg gaggttcgac tccaagctgg
1861 ccttccacca cgtggccagg gagctgcacc ccgagtacta caaggactgc taaagcccg
1921 gcagatctgc tgtgccttct agttgccagc catctgttgt ttgcccctcc cccgtgcctt
1981 ccttgaccct ggaaggtgcc actccactg tcctttccta ataaatgag gaaattgcat
2041 cgcattgtct ggtaggtgt cattctattc tggggggtgg ggtggggcag gacagcaagg
2101 gggaggattg ggaagacaat agcaggcatg ctggggatgc ggtgggctct atggccgatc
2161 ggcgcggcat atactgagtc attagggact ttccaatggg ttttggcccag tacataaggt
2221 caataggggt gaatcaacag gaaagtccca ttggagccaa gtacactgag tcaataggg
2281 ctttccattg ggttttggcc agtacaagg gtcaatagg ggtgagtc aaatgggtttt
2341 ccattattgg caggtacata aggtcaatag ggtgagtc aaatgggtttt ccagccaatt
2401 tataaacgc catgtacttt cccaccattg acgtcaatgg gctattgaaa ctaatgcaac
2461 gtgaccttta aacggtactt tcccatagct gattaatggg aaagtaccgt tctcgagcca
2521 atacacgtca atgggaagt aaagggcagc caaacgtaa caccgccccg gttttccct
2581 ggaattcca tattggcacg cattctattg gctgagctgc gttctacgtg ggtataagag
2641 gcgcgaccag cgtcggtacc gtgcagctct tgggtctgac caccgtagaa cgcagatcga
2701 gatctaccat ggtgctagg gcttctgtgc tgtctggtgg tgagctggac aagtgggaga
2761 agatcaggt gaggcctgt ggcaagaaga agtacaagct aaagcacatt gtgtggcct
2821 ccaggagct ggagaggttt gctgtgaacc ctggcctgct ggagacctct gagggtgca

```

FIG. 36A-1

WO 2006/020480

PCT/US2005/027658

96/126

2881 ggcagatcct gggccagctc cagccctccc tgcaaacagg ctctgaggag ctgagggtccc
2941 tgtacaacac agtggctacc ctgtactgtg tgcaccagaa gattgatgtg aaggacacca
3001 aggaggccct ggagaagatt gaggaggagc agaacaagtc caagaagaag gccagcagg
3061 ctgctgctgg cacaggcaac tccagccagg tgtcccagaa ctacccatt gtgcagaacc
3121 tccagggcca gatggtgcac caggccatct ccccccggac cctgaatgcc tgggtgaagg
3181 tgggtgagga gaaggccttc tcccctgagg tgatcccat gttctctgcc ctgtctgagg
3241 gtgccacccc ccaggacctg aacaccatgc tgaacacagt ggggggcat caggctacca
3301 tgcagatgct gaaggagacc atcaatgagg aggtctgtga gtgggacagg ctgcattctg
3361 tgcagctgg cccattgcc cccggccaga tgagggagcc caggggctct gacattgctg
3421 gcaccacctc caccctccag gaggagattg gctggatgac caacaacccc cccatccctg
3481 tgggggaaat ctacaagagg tggatcatcc tgggctgaa caagattgtg aggatgtact
3541 cccccacctc catcctggac atcaggcagg gccccaagga gcccttcagg gactatgtgg
3601 acaggttcta caagaccctg agggctgagc aggcctccca ggaggtgaag aactggatga
3661 cagagaccct gctggtgcag aatggcaacc ctgactgcaa gaccatcctg aaggccctgg
3721 gccctgctgc caccctggag gagatgatga caggctacca gggggtgggg ggccttgctc
3781 acaaggccag ggtgctggct gaggccatgt cccaggtgac caactccgcc accatcatga
3841 tgcagagggg caacttcagg aaccagagga agacagtga gtgcttcaac tgtggcaagg
3901 tgggccacat tgccaagaac ttagggccc ccaggaagaa gggctgctgg aagtgtggca
3961 aggaggcca ccagatgaag gactgcaatg agaggcagg caacttcctg ggcaaatct
4021 ggcctccca caaggcagg cctggcaact tctccagtc caggcctgag cccacagccc
4081 ctcccagga gtccttcagg tttggggagg agaagaccac ccccaagcag aagcaggagc
4141 ccattgacaa ggagctgtac cccctggcct cctgagggtc cctgtttggc aacgaccct
4201 cctcccagcc catctcccc attgagactg tgcctgtgaa gctgaagcct ggcattggatg
4261 gcccgaaggt gaagcagtgg cccctgactg aggagaagat caaggccctg gtggaatct
4321 gcactgagat ggagaaggag ggcaaatct ccaagattgg ccccagaaac ccctacaaca
4381 cccctgtgtt tgccatcaag aagaaggact ccaccaagtg gaggaagctg gtgacttca
4441 gggagctgaa caagaggacc caggacttct gggagggtga gctgggcatc ccccacccc
4501 ctggcctgaa gaagaagaag tctgtgactg tgctggctgt gggggatgcc tacttctctg
4561 tgcccctgga tgaggacttc aggaagtaca ctgccttcac catcccctcc atcaacaatg
4621 agacccttg catcaggtag cagtacaatg tgctgcccc gggctggaag ggtccccc
4681 ccattctcca gtctccatg accaagatcc tggagccctt caggaagcag aaccctgaca
4741 ttgtgatcta ccagtacatg gctgccctgt atgtgggctc tgacctggag attgggcagg
4801 acaggacca gattgaggag ctgaggcagc acctgctgag gtggggcctg accaccctg
4861 acaagaagca ccagaaggag cccccccttc tgtggatggg ctatgagctg caccgccaca
4921 agtggactgt gcagccatt gtgctgctg agaaggactc ctggactgtg aatgacatcc
4981 agaagctggt gggcaagctg aactgggct cccaaatcta cctggcatc aaggtgaggg
5041 agctgtgcaa gctgctgagg ggcaccaagg cctgactga ggtgatcccc ctgactgagg
5101 aggtgagct ggagctggct gagaacagg agatcctgaa ggagcctgtg catggggtgt
5161 actatgacc ctccaaggac ctgattgctg agatccagaa gcagggccag ggcagtgga
5221 cctaccaaat ctaccaggag ccttcaaga acctgaagac tggcaagtat gccaggatga
5281 ggggggcca caccaatgat gtgaagcagc tgactgaggc tgtgcagaag atcaccactg
5341 agtccattgt gatctggggc aagaccacca agttcaagct gccatccag aagagacct
5401 gggagacctg gtgactgag tactggcagg ccacctggat cctgagtg ggtttgtga
5461 acaccccc cctggtgaag ctgtgtacc agctggagaa ggagccatt gtggggctg
5521 agaccttcta tgtgctggg gctgccaaca gggagacca gctgggcaag gctggtatg
5581 tgaccaacag gggcaggcag aaggtggtga cctgactga caccaccaac cagaagactg
5641 cctccaggc catctacctg gccctccagg actctggcct ggaggtgaac attgtgactg
5701 cctcccagta tgcctgggc atcatccag cccagcctga tcagtctgag tctgagctg
5761 tgaaccagat cattgagcag ctgatcaaga aggagaaggt gtacctggc tgggtgctg
5821 cccacaagg cattgggggc aatgagcag tggacaagct ggtgtctgct ggcattcaga
5881 aagtgctgtt cctggatggc attgacaagg cccaggtatg gcatgagaag taccactcca
5941 actggaggc tatggcctct gacttcaacc tccccctgt ggtggctaag gagattgtg
6001 cctcctgtga caagtccag ctgaagggg aggcctatga tggcaggtg gactgctccc
6061 ctggcatctg gcagctggcc tgcaccacc tggagggcaa ggtgatcctg gtggctgtg
6121 atgtggctc cggctacatt gaagctgagg tgatccctgc tgagacaggc caggagactg

FIG. 36A-2

WO 2006/020480

PCT/US2005/027658

97/126

6181 cctacttccct gctgaagctg gctggcaggt ggcctgtgaa gaccatccac actgccaatg
 6241 gctccaactt cactggggcc acagtgaggg ctgctgtctg gtgggctggc atcaagcagg
 6301 agtttggcat cccctacaac cccagtcce aggggggtggg ggcctccatg aacaaggagc
 6361 tgaagaagat cattgggcag gtgagggacc aggctgagca cctgaagaca gctgtgcaga
 6421 tggctgtgtt catccacaac ttcaagagga aggggggcat cgggggctac tccgctgggg
 6481 agaggattgt ggacatcatt gccacagaca tccagaccac ggagctccag aagcagatca
 6541 ccaagatcca gaacttcagg gtgtactaca gggactccag gaacccctg tgggaaggcc
 6601 ctgccaaagt gctgtggaag ggggaggggg ctgtggtgat ccaggacaac tctgacatca
 6661 aggtggtgcc caagggaag gccaaagatca tcagggacta tggcaagcag atggctgggg
 6721 atgactgtgt ggcctccagg caggatgagg actaaagccc gggcagatct aacttggtta
 6781 ttgcagctta taatgggtac aaataaagca atagcatcac aaatttcaca aataaagcat
 6841 ttttttact gcattctagt tgtgggttgt ccaactcat caatgtatct tatcatgtct
 6901 ggatcggcgc gccgtactga aatgtgtggg cgtggcttaa ggggtggaaa gaatatataa
 6961 ggtgggggtc tcatgtagtt ttgtatctgt ttgacagcag ccgcccgcct gagcgccaac
 7021 tcgtttgatg gaagcattgt gagctcatat ttgacaacgc gcacgcccc atggggccggg
 7081 gtgcgtcaga atgtgatggg ctccagcatt gatggtcgcc ccgtcctgcc cgcaaactct
 7141 actaccttga cctacgagac cgtgtctgga acgcccgttg agactgcagc ctccgcccgc
 7201 gcttcagccg ctgcagccac cggccgaggg attgtgactg actttgcttt cctgagcccg
 7261 cttgcaagca gtgcagcttc ccgttcaccc gccgcgatg acaagttgac ggctcttttg
 7321 gcacaattgg attctttgac ccgggaactt aatgtcgttt ctacagcagc gtggatctg
 7381 cgccagcagg tttctgccct gaaggcttc tcccctcca atgcggttta aaacataaat
 7441 aaaaaccaga ctctgtttgg atttgatca agcaagtgtc ttgctgtctt tatttagggg
 7501 ttttgccgcg gcggtaggcc cgggaccagc ggtctcggtc gttgagggtc ctgtgtattt
 7561 tttccaggac gtggtaaagg tgactctgga ttttcagata catgggcata agcccgtctc
 7621 tgggggtggag gtagcaccac tgcagagctt catgctgcgg ggtgggtgtg tagatgatcc
 7681 agtcgtagca ggagcgtgg gcgtgggtgcc taaaaatgtc tttcagtagc aagctgattg
 7741 ccaggggcag gcccttgggt taagtgttta caagcgggt aagctgggat ggggtgcatac
 7801 gtggggatat gagatgcac ttggactgta tttttagggt ggctatgttc ccagccatat
 7861 ccctccgggg attcatgttg tgcagaacca ccagcacagt gtatccggtg cacttgggaa
 7921 atttgtcatg tagcttagaa ggaaatgcgt ggaagaactt ggagacgccc ttgtgacctc
 7981 caagattttc catgcattcg tccataatga tggcaatggg cccacggggc gcggcctggg
 8041 cgaagatatt tctgggatca ctaacgtcat agttgtgttc caggatgaga tcgtcatagg
 8101 ccattttttac aaagcgcggg cggaggggtgc cagactgcgg tataatgggt ccatccggcc
 8161 caggggctga gttaccctca cagatttgca tttcccacgc tttgagttca gatgggggga
 8221 tcatgtctac ctgcggggcg atgaagaaa ccgtttccgg ggtaggggag atcagctggg
 8281 aagaaagcag gttcctaagc agctgcgact taccgcagcc ggtggggccc taaatcacac
 8341 ctattaccgg ctgcaactgg tagttaagag agctgcagct gccgtcatcc ctgagcaggg
 8401 gggccacttc gttaagcatg tccctgactt gcattgtttt cctgaccaa tccgccagaa
 8461 ggcgctcgcc gccagcgat agcagttctt gcaaggaagc aaagtttttc aacggtttga
 8521 ggccgtccgc cgtaggcatg cttttgagcg tttgaccaag cagttccagg cgggtccaca
 8581 gctcggtcac gtgctctacg gcactctcat ccagcatatc tctcgtttc gcgggttggg
 8641 gcggctttcg ctgtacggca gtagtcgggt ctcgtccaga cgggccaggg tcatgtcttt
 8701 ccacgggcgc agggctctcg tcagcgtagt ctgggtcacg gtgaaggggt gcgctccggg
 8761 ttgcgcgtg gccaggggtc gcttgaggct ggtcctgctg gtgctgaagc gctgcccgtc
 8821 ttgcacctgc gcgtcggcca ggtagcattt gaccatgggt tcatagtcca gccctccgc
 8881 ggcgtggccc ttggcgcgca gcttgccctt ggaggaggcg ccgcacgagg ggcagtgcag
 8941 acttttaagg gcgtagagct tgggcgcgag aaataccgat tccggggagt aggcattccg
 9001 gccgcaggcc ccgcagacgg tctcgcattc cacgagccag gtgagctctg gccgttcggg
 9061 gtcaaaaacc aggtttcccc catgcttttt gatgcgtttc ttacctctgg tttccatgag
 9121 ccggtgtcca cgctcgggtg cgaagaggct gtccgtgtcc ccgtatacag acttgagagg
 9181 cctgtcctcg agcgggtgtc cgcggctctc ctcttataga aactcggacc actctgagac
 9241 gaaggctcgc gtccaggcca gcacgaagga ggctaagtgg gaggggtagc ggtcgttgtc
 9301 cactaggggg tccactcgtc ccagggtgtg aagacacatg tcgccctctt cggcatcaag
 9361 gaagggtgatt ggtttatagg ttagggccac gtgaccgggt gttcctgaag gggggctata
 9421 aaagggggtg ggggcgcggt cgtcctcact ctcttcgca tcgctgtctg cgagggccag

FIG. 36A-3

WO 2006/020480

PCT/US2005/027658

98/126

9481 ctgttggggt gagtactccc tctcaaaagc gggcatgact tctgcgctaa gattgtcagt
9541 ttccaaaaac gaggaggatt tgatattcac ctggcccgcg gtgatgcctt tgagggtggc
9601 cgcgtccatc tggtcagaaa agacaatcct tttgttgtca agcttgggtg caaacgaccc
9661 gtagagggcg ttggacagca acttggcgat ggagcgcagg gtttggtttt tgcgcgatc
9721 ggcgcgctcc ttggccgcga tgtttagctg cacgtattcg cgcgcaacgc accgccattc
9781 gggaaagacg gtggtgcgct cgtcgggcac taggtgcacg cgccaaccgc ggttgtgcag
9841 ggtgacaagg tcaacgctgg tggctacctc tccgcgtagg cgctcgttgg tccagcagag
9901 gcggccgccc ttgcgcgagc agaatggcgg tagtgggtct agctgcgtct cgtccggggg
9961 gtctgcgtcc acggtaaaga ccccgggcag caggcgcgcg tcgaagtagt ctatcttgca
10021 tccttgcaag tctagcgctt gctgccatgc gcgggaggca agcgcgcgct cgtatgggtt
10081 gagtggggga ccccatggca tggggtgggt gagcgcggag gcgtacatgc cgcaaatgtc
10141 gtaaacgtag aggggctctc tgagtattcc aagatatgta gggtagcatc tccaccgcg
10201 gatgctggcg cgcacgtaat cgtatagtcc gtgcgagggg gcgaggaggt cgggaccgag
10261 gttgctacgg gcgggctgct ctgctcggaa gactatctgc ctgaagatgg catgtgagtt
10321 ggatgatatg gttggacgct ggaagacggt gaagctggcg tctgtgagac ctaccgcgtc
10381 acgcacgaag gaggcgtagg agtcgcgcag cttgttgacc agctcggcgg tgacctgcac
10441 gtctagggcg cagtagtcca gggtttcctt gatgatgtca tacttatcct gtcccttttt
10501 tttccacagc tcgcggttga ggacaaactc ttcgcggtct tccagtagt cttggatcgg
10561 aaaccgctcg gcctccgaac ggtaagagcc tagcatgtag aactgggttga cggcctggta
10621 ggcgcagcat cccttttcta cgggtagcgc gtatgcctgc gcggccttcc ggagcgaggt
10681 gtgggtgagc gcaaagggtg ccctaaccat gactttgagg tactggtatt tgaagtcagt
10741 gtcgtcgcac ccgccctgct cccagagcaa aaagtccgtg cgcttttttg aacgcgggtt
10801 tggcagggcg aaggtgacat cgttgaagag tatctttccc gcgcgaggca taaagttgcg
10861 tgtgatgcgg aaggtcccg gcacctcgga acggttggtt attacctggg cggcgagcac
10921 gatctcgtca aagccgttga tgttgtggcc cacaatgtaa agttccaaga agcgcgggat
10981 gcccttgatg gaaggcaatt ttttaagtcc ctctaggtg agctcttcag gggagctgag
11041 cccgtgctct gaaagggccc agtctgcaag atgaggggtg gaagcgacga atgagctcca
11101 caggtcacgg gccattagca tttgcagggt gtcgcgaaag gtcctaaact ggcgacctat
11161 ggccattttt tctggggtga tgcagtagaa ggtaagcggg tcttgttccc agcgggtcca
11221 tccaaggtec gcggctaggt ctgcgcggcg ggtcactaga ggctcatctc cgccgaactt
11281 catgaccagc atgaagggca cgagctgctt cccaaaggcc cccatccaag tataggtctc
11341 tacatcgtag gtgacaaaga gacgctcggg gcgaggatgc gagccgatcg ggaagaactg
11401 gatctcccgc caccagttgg aggagtggct gttgatgtgg tgaaagtaga agtccctgcg
11461 acgggcccga cactcgtgct ggcttttgta aaaacgtgcg cagtactggc agcgggtcac
11521 gggctgtaca tctgcacga ggttgacctg acgaccgcgc acaaggaagc agagtgggaa
11581 tttgagcccc tcgcctggcg ggtttggctg gtggtcttct acttcggctg cttgtccttg
11641 accgtctggc tgctcgaggg gagttacggt ggatcggacc accacgccgc gcgagcccaa
11701 agtccagatg tccgcgcgcg gcggtcggag cttgatgaca acatcgcgca gatgggagct
11761 gtccatggtc tggagctccc gcggcgtcag gtcaggcggg agctcctgca ggtttacctc
11821 gcatagccgg gtcagggcgc gggctaggtc cagggtgatac ctgattttcca ggggctggtt
11881 ggtggcggcg tcgatggctt gcaagaggcc gcatccccgc ggcgcgacta cggtagccgc
11941 cggcggggcg tgggcccgcg ggggtgtcct ggatgatgca tctaaaagcg gtgacgcggg
12001 cgggcccccg gaggtagggg gggctcggga cccgccggga gagggggcag gggcacgtcg
12061 gcgccgcgcg cgggcaggag ctggtgctgc gcgcggaggt tgctggcgaa cgcgacgacg
12121 cggcgggtga tctcctgaat ctggcgcttc tgcgtgaaga cgacgggccc ggtgagcttg
12181 aacctgaaag agagttcgac agaataaatt tcggtgtcgt tgacggcggc ctggcgcaaa
12241 atctcctgca cgtctcctga gttgtcttga taggcgatct cggccatgaa ctgctcgatc
12301 tcttcctcct ggagatctcc gcgtccggct cgctccacgg tggcggcgag gtcgttggag
12361 atgcgggcca tgagctgcga gaaggcgttg aggcctccct cgttccagac gcggtgtag
12421 accacgcccc cttcggcatc gcgggcgcgc atgaccacct gcgcgagatt gagctccacg
12481 tgccgggcga agacggcgta gtttcgcagg cgctgaaaga ggtagttgag ggtggtggcg
12541 gtgtgttctg ccacgaagaa gtacataacc cagcgcgcga acgtggattc gttgatatcc
12601 cccaaggcct caaggcgctc catggcctcg tagaagtcca cggcgaagtt gaaaaactgg
12661 gagttgcgcg ccgacacggt taactcctcc tccagaagac ggatgagctc ggcgacagtg
12721 tcgcgcacct cgcgctcaaa ggctacaggg gcctcttctt cttcttcaat ctcctcttcc

FIG. 36A-4

WO 2006/020480

PCT/US2005/027658

99/126

12781 ataagggcct ccccttcttc ttcttctggc ggcggtgggg gaggggggac acggcggcga
12841 cgacggcgca ccgggaggcg gtcgacaaag cgctcgatca tctccccgcg gcgacggcgc
12901 atggtctcgg tgacggcgcg gccgttctcg cggggggcgca gttggaagac gccgcccgtc
12961 atgtcccggg tatgggttgg cggggggctg ccgtgcggca gggatacggc gctaacgatg
13021 catctcaaca attgttgtgt aggtactccg ccaccgaggg acctgagcga gtccgcatcg
13081 accggatcgg aaaacctctc gagaaaggcg tctaaccagt cacagtcgca aggtaggctg
13141 agcaccgagg cgggcggcag cgggcggcgg tcggggttgt ttctggcgga ggtgctgctg
13201 atgatgtaat taaagtaggc ggtcttgaga cggcggatgg tcgacagaag caccatgtcc
13261 ttgggtccgg cctgctgaat gcgcaggcgg tcggccatgc cccaggcttc gttttgacat
13321 cggcgcaggg cttttagtag gtcttgcatg agcctttcta ccggcacttc ttcttctcct
13381 tcctcttgct ctgcatctct tgcatctatc gctgcggcgg cggcggaggt tggccgtagg
13441 tggcgccctc ttcttcccat gcgtgtgacc ccgaagcccc tcatcggtcg aagcagggcc
13501 aggtcggcga caacgcgctc ggctaataat gcctgctgca cctgcgtgag ggtagactgg
13561 aagtcgtcca tgtccacaaa gcggtgggtat gcgcccgtgt tgatggtgta agtgagttg
13621 gccataacgg accagttaac ggtctgggtg cccggctgcg agagctcggg gtacctgaga
13681 cgcgagtaag cccttgagtc aaagacgtag tcgttgcaag tccgcaccag gtactggtat
13741 cccacaaaaa agtgcgggcg cggctggcgg tagaggggcc agcgtagggt ggccggggct
13801 ccggggggcg ggtcttccaa cataaggcga tgatatccgt agatgtacct ggacatccag
13861 gtgatgccgg cggcgggtgt ggaggcgcg gcgaaagtcac ggacgcgggt ccagatggtg
13921 cgcagcggca aaaagtgtct catggtcggg acgctctggc cggtcaggcg cgcgcagtcg
13981 ttgacgctct agaccgtgca aaaggagagc ctgtaagcgg gcaactcttc gtggtctggt
14041 ggataaattc gcaagggtat catggcggac gaccgggggt cgaacccccg atccggccgt
14101 ccgccgtgat ccatgcgggt accgcccgcg tgtcgaacct aggtgtgcga cgtcagacaa
14161 cgggggagcg ctctttttgg cttccttcca ggcgcggcgg atgctgcgct agcttttttg
14221 gccactggcc gcgcgcggcg taagcgggta ggctggaaag cgaaagcatt aagtggctcg
14281 ctccctgtag ccggagggtt attttccaag ggttgagtcg cgggaccccc ggttcgagtc
14341 tcgggcccgc cggactgcgg cgaacggggg tttgcctccc cgtcatgcaa gacccccgtt
14401 gcaaattcct ccggaaacag ggacgagccc cttttttgct tttcccagat gcacccggtg
14461 ctgcggcaga tgcgcccccc tcctcagcag cggcaagagc aagagcagcg gcagacatgc
14521 agggcacccct ccccttctcc taccgcgtca ggagggggcaa catccgcggc tgacgcggcg
14581 gcagatggtg attacgaacc cccgcggcgc cggacccggc actacttggg cttggaggag
14641 ggcgagggcc tggcgcggct aggagcgcgc tctcctgagc gacacccaag ggtgcagctg
14701 aagcgtgaca cgcgcgaggg gtacgtgccg cggcagaacc tgtttcgcga ccgcgagggg
14761 gaggagcccg aggagatgcg ggatcgaaag ttccatgcag ggcgcgaggt gccgcatggc
14821 ctgaaccgcg agcgggtgct gcgcgaggag gactttgagc ccgacgcgcg gaccgggatt
14881 agtcccgcgc gcgcacacgt ggcggccgcc gacctggtta ccgcgtacga gcagacgggtg
14941 aaccaggaga ttaactttca aaaaagcttt aacaaccacg tgcgcacgct tgtggcgcgc
15001 gaggaggtgg ctataggact gatgcatctg tgggactttg taagcgcgct ggagcaaaac
15061 ccaaatagca agccgctcat ggcgcagctg ttccttatag tgcagcacag cagggacaac
15121 gaggcattca gggatgcgct gctaaacata gtagagcccg agggccgctg gctgctcgat
15181 ttgataaaca ttctgcagag catagtgggt caggagcgca gcttgagcct ggctgacaag
15241 gtggccgccca ttaactattc catgctcagt ctgggcaagt tttacgcccg caagatatac
15301 catacccctt acgttcccat agacaaggag gtaaagatcg aggggttcta catgcgcatg
15361 gcgctgaagg tgcttacctt gagcgacgac ctgggcgttt atcgcaacga gcgcatccac
15421 aaggccgtga gcgtgagccg gcggcgcgag ctcagcgacc gcgagctgat gcacagcctg
15481 caaaggggcc tggctggcac gggcagcggc gatagagagg ccgagtccta ctttgacgcg
15541 ggcgctgacc tgcgctgggc cccaagccga cgcgccctgg aggcagctgg ggccggacct
15601 gggctggcgg tggcacccgc gcgcgctggc aacgtcggcg gcgtggagga atatgacgag
15661 gacgatgagt acgagccaga ggacggcgag tactaagcgg tgatgtttct gatcagatga
15721 tgcaagacgc aacggacccg gcggtgcggg cggcgtgca gagccagccg tccggcctta
15781 actccacgga cgactggcgc caggtcatgg accgcatcat gtcgctgact gcgcgcaacc
15841 ctgacgcgtt ccggcagcag ccgcaggcca accggctctc cgcaattctg gaagcgggtg
15901 tcccggcgcg cgcaaccccc acgcacgaga aggtgctggc gatcgtaaac gcgctggccg
15961 aaaacagggc catccggccc gatgaggccg gcctggtcta cgacgcgctg cttcagcgcg
16021 tggctcgtta caacagcagc aacgtgcaga ccaacctgga ccggctgggtg ggggatgtgc

FIG. 36A-5

WO 2006/020480

PCT/US2005/027658

100/126

16081 gcgaggccgt ggcgcagcgt gagcgcgcgc agcagcaggg caacctgggc tccatgggtg
16141 cactaaacgc cttcctgagt acacagcccg ccaacgtgcc gcggggacag gaggactaca
16201 ccaactttgt gagcgactg cggctaattg tgactgagac accgcaaagt gaggtgtatc
16261 agtccggggc agactatttt ttccagacca gtagacaagg cctgcagacc gtaaacctga
16321 gccaggcttt caagaacttg caggggctgt ggggggtgcg ggctcccaca ggcgaccgcg
16381 cgaccgtgtc tagcttgctg acgcccact cgcgccctgtt gctgctgcta atagcgccct
16441 tcacggacag tggcagcgtg tcccgggaca catacctagg tcacttgctg acactgtacc
16501 gcgaggccat aggtcaggcg catgtggacg agcatacttt ccaggagatt acaagtgtta
16561 gccgcgcgct ggggcaggag gacacgggca gcctggaggc aacctgaac tacctgctga
16621 ccaaccggcg gcaaaaaatc ccctcgttgc acagtttaaa cagcgaggag gagcgcattt
16681 tgcgctatgt gcagcagagc gtgagcctta acctgatgcg cgacggggta acgcccagcg
16741 tggcgctgga catgaccgcg cgcaacatgg aaccgggcat gtatgcctca aaccggccgt
16801 ttatcaatcg cctaattggac tacttgcatc gcgcggccgc cgtgaacccc gagtatttca
16861 ccaatgccat cttgaacccg cactggctac cgccccctgg tttctacacc gggggattcg
16921 aggtgcccga gggtaacgat ggattcctct gggacgacat agacgacagc gtgttttccc
16981 cgcaaccgca gaccctgcta gagttgcaac aacgcgagca ggcagaggcg gcgctgcgaa
17041 aggaaagctt ccgcaggcca agcagcttgt ccgatctagg cgctgcggcc ccgcggtcag
17101 atgctagtag ccattttcca agcttgatag ggtctcttac cagcactcgc accaccgcgc
17161 cgcgcctgct gggcgaggag gagtacctaa acaactcgcg gctgcagccg cagcgcgaaa
17221 agaacctgcc tccggcgttt cccaacaacg ggatagagag cctagtggac aagatgagta
17281 gatggaagac gtatgcgcag gagcacaggg atgtgcccgg ccgcgcgccg cccaccgcgc
17341 gtcaaaggca cgaccgtcag cgggggtctg tgtgggagga cgatgactcg gcagacgaca
17401 gcagcgtctt ggatttggga gggagtggca acccgtttgc acaccttcgc cccaggctgg
17461 ggagaatgtt ttaaaaaaag catgatgcaa aataaaaaac tcaccaaggc catggcaccg
17521 agcgttgggt ttcttgtatt ccccttagta tgcggcgcgc ggcgatgtat gaggaaggct
17581 ctccctccct ctacgagagc gtggtgagcg cggcgccagt ggcggcgcg cggtgttcac
17641 ccttcgatgc tccctggac ccgcggttcg tgcctccgcg gtacctgcgg cctaccgggg
17701 ggagaaacag catccgttac tctgagttgg caccctatt cgacaccacc cgtgtgtacc
17761 ttgtggacaa caagtcaacg gatgtggcat ccctgaacta ccagaacgac cacagcaact
17821 ttctaaccac ggtcattcaa aacaatgact acagcccggg ggaggcaagc acacagacca
17881 tcaatcttga cgaccggtcg cactggggcg gcgacctgaa aaccatcctg cataccaaca
17941 tgccaaatgt gaacgagttc atgtttacca ataagtttaa ggcgcgggtg atggtgtcgc
18001 gctcgcttac taaggacaaa caggtggagc tgaaatacga gtgggtggag ttcacgctgc
18061 ccgagggcaa ctactccgag accatgacca tagaccttat gaacaacgcg atcgtggagc
18121 actacttgaa agtgggcagg cagaacgggg ttctggaaag cgacatcggg gtaaagtttg
18181 acaccgcaa cttcagactg gggtttgacc cagtactgg tcttgatcag cctgggggtat
18241 atacaaacga agccttccat ccagacatca ttttgctgcc aggatgcggg gtggacttca
18301 cccacagccg cctgagcaac ttgttgggca tccgcaagcg gcaacccttc caggagggct
18361 ttaggatcac ctacgatgac ctggagggtg gtaacattcc cgcactgttg gatgtggacg
18421 cctaccaggc aagcttgaaa gatgacaccg aacaggcgcg ggggtggcgca ggcggcgca
18481 acaacagtgg cagcggcgcg gaagagaact ccaacgcggc agctgcggca atgcagccg
18541 tggaggacat gaacgatcat gccattcgcg gcgacacctt tgccacacgg gcggaggaga
18601 agcgcgctga ggccgaggca gcggccgaag ctgccgcccc cgctgcggag gctgcacaac
18661 ccgaggtcga gaagcctcag aagaaaccgg tgattaaacc cctgacagag gacagcaaga
18721 aacgcagtta caacctata agcaatgaca gcaccttcac ccagtaccgc agctggtacc
18781 ttgcatacaa ctacggcgac cctcaggccg ggatccgctc atggaccctg ctttgcactc
18841 ctgacgtaac ctgcggtcgc gagcaggtat actggtcgtt gcccgacatg atgcaagacc
18901 ccgtgacctt ccgctccacg cgccagatca gcaactttcc ggtggtgggc gccgagctgt
18961 tgcccgtgca ctccaagagc ttctacaacg accaggccgt ctactcccag ctcatccgc
19021 agtttacctc tetgaccac gtgttcaatc gctttcccgga gaaccagatt ttggcgcgcc
19081 cgccagcccc caccatcacc accgtcagtg aaaacgttcc tgccttcaca gatcacggga
19141 cgctaccgct gcgcaacagc atcggaggag tccagcgagt gaccattact gacgccagac
19201 gccgcacctg cccctacgtt tacaaggccc tgggcatagt ctgcgcgcg gtccatcga
19261 gccgcacttt ttgagcaagc atgtccatcc ttatatcgcc cagcaataac acaggctggg
19321 gcctgcgctt cccaagcaag atgtttggcg gggccaagaa gcgctccgac caacaccag

FIG. 36A-6

WO 2006/020480

PCT/US2005/027658

1000 20 4000 6000 8000

101/126

```

19381 tgcgcgtgcg cgggcactac cgcgcgccct ggggcgcgca caaacgcggc cgcactgggc
19441 gcaccaccgt cgatgacgcc atcgacgcgg tggaggagga ggcgcgcaac tacacgcca
19501 cgccgccgcc agtgtccacc gtggacgcgg ccattcagac cgtggtgcmc ggagcccgcc
19561 gctacgctaa aatgaagaga cggcggaggg gcgtagcacg tcgccaccgc cgccgaccgc
19621 gactgccgc ccaacgcgcg gcggcgcccc tgcttaaccg cgcacgtcmc accggccgac
19681 gggcgcccat gcgagccgct cgaaggctgg ccgcggttat tgtcactgtg ccccccaggt
19741 ccaggcgacg agcggccgcc gcagcagccg cggccattag tgctatgact cagggtcgca
19801 ggggcaacgt gtactgggtg cgcgactcgg ttagcgccct gcgctgccc gtgcgcaccc
19861 gccccccgcg caactagatt gcaataaaaa actacttaga ctcgtactgt tgtatgtatc
19921 cagcggcgcc ggcgcgcatc gaagctatgt ccaagcgcaa aatcaaagaa gagatgctcc
19981 aggtcatcmc gccggagatc tatggccccc cgaagaagga agagcaggat tacaagcccc
20041 gaaagctaaa gcgggtcaaa aagaaaaaga aagatgatga tgatgatgaa cttgacgacg
20101 aggtggaact gttgcacgcg accgcgcccc ggcgacgggt acagtggaaa ggtcgacgcg
20161 taagacgtgt tttgcgaccc ggcaccaccg tagtctttac gcccggtgag cgctccaccc
20221 gcacctacaa gcgctgttat gatgaggtgt acggcgacga ggacctgctt gagcaggcca
20281 acgagcgcct cggggagttt gcctacggaa agcggcataa ggacatgctg gcgttgccgc
20341 tggacgaggg caaccaaca cctagcctaa agcccgtagc actgcagcag gtgctgcccg
20401 cgcttgaccc gtccgaagaa aagcgcgccc taaagcgca gtctggtgac ttggcaccca
20461 ccgtgcagct gatggtaccc aagcgtcagc gactggaaga tgtcttgaa aaaatgaccg
20521 tggagcctgg gctggagccc gaggtccgcg tcgggccaat caagcagggtg gcaccgggac
20581 tgggcgtgca gaccgtggac gttcagatac ccaccaccag tagcactagt attgccactg
20641 ccacagaggg catggagaca caaacgtccc cggttgcctc ggcggtggca gatgccgcgg
20701 tgcaggcgcc cgctgcggcc gcgtccaaga cctctacgga ggtgcaaacg gaccctgga
20761 tgtttcgtgt ttcagccccc cgcgctccgc gccgttcaag gaagtacggc gccgccagcg
20821 cgctactgcc cgaatatgcc ctacatcctt ccacgcgcgc tacccecgcc tatcgtggct
20881 acacctaccg cccagaaga cgagcaacta cccgacgcgc aaccaccact ggaaccgcgc
20941 gccgcgctcg ccgtcgccag ccgctgctgg ccccgatttc cgtgcgcagg gtggctcgcg
21001 aaggaggcag gaccctggtg ctgccaacag cgcgctacca cccagcatc gtttaaaagc
21061 cggctctttgt ggttcttgca gatatggccc tcacctgccg cctccgtttc ccggtgccgg
21121 gattccgagg agaattgcac cgtaggaggg gcatggccgg ccacggcctg acgggcggca
21181 tgcgtcgtgc gcaccaccgg cggcgccgcg cgtcgacacc tcgcatgcmc ggcggtatcc
21241 tgccctcct tattccactg atcgccgcgg cgattggcmc cgtgcccgga attgcatccg
21301 tggccttgca ggcgagaga cactgattaa aaacaagtta catgtggaaa aatcaaaaata
21361 aaagtctgga ctctcacgct cgcttggtcc tgtaactatt ttgtagaatg gaagacatca
21421 actttgcgtc actggccccg cgacacggct cgcgcccgtt catgggaaac tggcaagata
21481 tcggcaccag caatatgagc ggtggcgcc ttagctgggg ctcgctgtgg agcggcatta
21541 aaaatttcgg ttccgccgtt aagaactatg gcagcaaagc ctggaacagc agcacaggcc
21601 agatgctgag ggacaagttg aaagagcaaa atttccaaca aaaggtggta gatggcctgg
21661 cctctggcat tagcgggggtg gtggacctgg ccaaccaggc agtgcaaaat aagattaaca
21721 gtaagcttga tccccgccct ccgtagaggg agcctccacc ggccgtggag acagtgtctc
21781 cagagggggcg tggcgaaaag cgtccgcgac ccgacaggga agaaactctg gtgacgcaaa
21841 tagacgagcc tccctcgtag gaggaggcac taaagcaagg cctgcccacc acccgtccca
21901 tcgcgcccac ggctaccgga gtgctgggac agcacacacc cgtaacgctg gacctgcctc
21961 cccccgccga caccagcag aaacctgtgc tgccaggccc gtccgccgtt gttgtaaccc
22021 gtcctagccg cgctccctg cgccgcgcgc ccagcggtcc gcgacggtt cgccccgtag
22081 ccagtggcaa ctggcaaagc aactgaaca gcacgtggg tttgggggtg caatccctga
22141 agcgcgcgac atgcttctga tagctaactg gtcgtatgtg tgtcatgtat gcgtccatgt
22201 cgccgccaga ggagctgctg agccgcgcgc cgcgcgtttt ccaagatggc tacccttcg
22261 atgatgccgc agtggcttta catgcacatc tcgggcccag acgcctcgga gtacctgagc
22321 cccgggctgg tgcagttcmc ccgcgccacc gagacgtact tcagcctgaa taacaagttt
22381 agaaacccca cggtggcgac tacgcacgac gtgaccacag accggtctca gcgtttgacg
22441 ctgcggttca tccccgtgga ccgcgaggat actgcgtact cgtacaaggc gcggttcacc
22501 ctagctgtgg gtgataaccg tgtgctagac atggcttcca cgtactttga catccgcggc
22561 gtgctggaca ggggccctac ttttaagccc tactctggca ctgcctacaa cgcactggcc
22621 cccaagggtg ccccaactc gtgcgagtgga gaacaaaatg aaactgcaca agtggatgct

```

FIG. 36A-7

WO 2006/020480

PCT/US2005/027658

102/126

```

22681 caagaacttg acgaagagga gaatgaagcc aatgaagctc aggcgcgaga acaggaacaa
22741 gctaagaaaa cccatgtata tgcccaggct ccactgtccg gaataaaaaat aactaaagaa
22801 ggtctacaaa taggaactgc cgacgccaca gtagcagggtg ccggcaaaga aattttcgca
22861 gacaaaactt ttcaacctga accacaagta ggagaatctc aatggaacga agcggatgcc
22921 acagcagctg gtggaagggg tcttaaaaag acaactccca tgaaaccctg ctatggctca
22981 tacgctagac ccaccaattc caacggcgga cagggcggtta tggttgaaca aaatggtaaa
23041 ttggaaagtc aagtcgaaat gcaatttttt tccacatcca caaatgccac aaatgaagtt
23101 aacaatatac aaccaacagt tgtattgtac agcgaagatg taaacatgga aactccagat
23161 actcatcttt cttataaacc taaaatgggg gataaaaatg ccaaagtcac gcttggacaa
23221 caagcaatgc caaacagacc aaattacatt gcttttagag acaattttat tggctctcatg
23281 tattacaaca gcacaggtaa catgggtgtc cttgctgggtc aggcacgcga gttgaacgct
23341 gttgtagatt tgcaagacag aaacacagag ctgtcctacc agcttttgct tgattcaatt
23401 ggcgacagaa caagatactt ttcaatgtgg aatcaagctg ttgacagcta tgatccagat
23461 gtcagaatta ttgagaacca tggaaactgag gatgagttgc caaattattg ctttctctct
23521 ggtggaattg ggattactga cacttttcaa gctgttaaaa caactgctgc taacggggac
23581 caaggcaata ctacctggca aaaagattca acatttgtag aacgcaatga aataggggtg
23641 ggaaataact ttgccatgga aattaacctg aatgccaacc tatggagaaa tttcctttac
23701 tccaatattg cgctgtacct gccagacaag ctaaaataca accccacca tgtggaaata
23761 tctgacaacc ccaacaccta cgactacatg aacaagcgag tgggtggctcc tgggcttgta
23821 gactgtaca ttaaccttgg ggcgcgctgg tctctggact acatggacaa cgttaatccc
23881 tttaaccacc accgcaatgc gggcctgctg taccgctcca tgttgttggg aaacggccgc
23941 tacgtgccct ttcacattca ggtgccccaa aagttttttg ccattaaaaa cctcctctc
24001 ctgccaggct catcacata tgaatggaac ttcaggaagg atgttaacat ggttctgcag
24061 agctctctgg gaaacgacct tagagttgac ggggctagca ttaagtttga cagcatttgt
24121 ctttacgcca ccttcttccc catggcccac aacacggcct ccacgctgga agccatgctc
24181 agaaatgaca ccaacgacca gtcctttaat gactaccttt ccgccgcaa catgctatat
24241 cccatacccg ccaacgccac caacgtgccc atctccatcc catcgcgcaa ctgggcagca
24301 tttcgcggtt gggccttcac acgcttgaag acaaaggaaa ccccttccct gggatcaggg
24361 tacgacctt actacaccta ctctggctcc ataccatacc ttgacggaac cttctatctt
24421 aatcacacct ttaagaaggt ggccattact tttgactctt ctgttagctg gccgggcaac
24481 gaccgcctgc ttactcccaa tgagtttgag attaagcgct cagttgacgg ggagggctat
24541 aacgtagctc agtgcaacat gacaaaggac tgggttcctag tgcagatgtt ggccaactac
24601 aatattggct accagggctt ctacattcca gaaagctaca aagaccgcat gtactcgttc
24661 ttcagaaact tccagcccat gagccggcaa gtgggtggacg atactaaata caaagattat
24721 cagcagggtg gaattatcca ccagcataac aactcaggct tcgtaggcta cctcgctccc
24781 accatgcgcg agggacaagc ttaccccgct aatgttccct acccactaat aggcaaaacc
24841 gcggttgata gtattacca gaaaaagttt ctttgcgacc gcaccctgtg gcgcatcccc
24901 ttctccagta actttatgtc catgggtgcg ctacacagacc tgggcaaaaa ccttctctac
24961 gcaaactccg cccacgcgct agacatgacc tttgaggtgg atcccatgga cgagcccacc
25021 cttcttttatg ttttgtttga agtctttgac gtggtccgtg tgcaccagcc gcaccgccc
25081 gtcacgcaga ccgtgtacct gcgcacgccc ttctcgcccg gcaacgccac aacataaaga
25141 agcaagcaac atcaacaaca gctgccgcca tgggctccag tgagcaggaa ctgaaagcca
25201 ttgtcaaaga tcttggttgt gggccatatt ttttgggcac ctatgacaag cgcttcccag
25261 gctttgtttc cccacacaag ctgcctgctg ccatagttaa cacggccggt cgcgagactg
25321 ggggcgtaca ctggatggcc tttgcctgga acccgcgctc aaaaacatgc tacctctttg
25381 agcccttttg cttttctgac caacgtctca agcaggttta ccagtttgag tacgagtcac
25441 tcctgcgcg tagcgccatt gcctcttccc ccgaccgctg tataacgctg gaaaagtcca
25501 cccaaagcgt gcaggggccc aactcggccg cctgtggcct attctgctgc atgtttctcc
25561 acgcctttgc caactggccc caaactccca tggatcacia cccaccatg aaccttatta
25621 ccgggggtacc caactccatg cttaacagtc cccaggtaca gccaccctg cgccgcaacc
25681 aggaacagct ctacagcttc ctggagcgcc actcgcccta cttccgcagc cacagtgcgc
25741 aaattaggag cgccacttct ttttgtcact tgaaaaacat gtaaaaataa tgtactagga
25801 gacactttca ataaaggcaa atgtttttat ttgtacactc tcgggtgatt atttaccccc
25861 acccttgccg tctgcgcgct ttaaaaatca aaggggttct gccgcgcac gctatgcgcc
25921 actggcaggg acacgttgcg atactggtgt ttagtgctcc acttaaaactc aggcacaacc

```

FIG. 36A-8

WO 2006/020480

PCT/US2005/027658

103/126

25981 atccgcggca gctcgggtgaa gttttcactc cacaggctgc gcaccatcac caacgcgttt
26041 agcaggtcgg gcgccgatat cttgaagtcg cagttggggc ctccgccctg cgcgcgcgag
26101 ttgcgataca caggggttaca gcactggaac actatcagcg ccgggtggtg cacgctggcc
26161 agcacgctct tgtcggagat cagatccgcg tccaggctct ccgcgttgct cagggcgaac
26221 ggagtcaact ttggtagctg ctttcccaa aagggtgcat gccaggctt tgagttgcac
26281 tcgcaccgta gtggcatcag aaggtagccg tgcccagctt gggcgttagg atacagcgcc
26341 tgcataaaag cttgatctg cttaaaagcc acctgagcct ttgcgccttc agagaagaac
26401 atgccgcaag acttgccgga aaactgattg gccggacagg ccgcgtcatg cagcgagcac
26461 cttgcgtcgg tgttgagat ctgcaccaca ttccggcccc accggttctt cagcatcttg
26521 gccttgctag actgctcctt cagcgcgcgc tgcccgtttt cgctcgtcac atccatttca
26581 atcacgtgct cttattttat cataatgctc ccgtgtagac acttaagctc gccttcgatc
26641 tcagcgcagc ggtgcagcca caacgcgcag ccggtgggct cgtggtgctt gtaggttacc
26701 tctgcaaacg actgcaggta cgcctgcagg aatcgcccc tcatcgtcac aaaggtcttg
26761 ttgctggtga aggtcagctg caaccgcgg tgctcctcgt ttagccaggt cttgcatacg
26821 gccgccagag cttccacttg gtcaggcagt agcttgaagt ttgcctttag atcgttatcc
26881 acgtggtact tgtccatcaa cgcgcgcgca gcctccatgc ctttctccca cgcagacacg
26941 atcggcaggg tcagcgggtt tatcaccgtg ctttccactt ccgcttccact ggactcttcc
27001 ttttctctt gcacccgcac acccgcgcgc actgggtcgt cttcattcag ccgcgcacc
27061 gtgcgcttac ctcccttgcc gtgcttgatt agcaccggtg ggttgctgaa acccaccatt
27121 tgtagcgcca catcttctct ttcttctctg ctgtccacga tcacctctgg ggatggcggg
27181 cgctcgggct tgggagaggg gcgcttcttt ttctttttgg acgcaatggc caaatccgcc
27241 gtcgaggtcg atggccgcgg gctgggtgtg cgcggcacca gcgcatcttg tgacgagctt
27301 tcttcgtcct cggactcgag acgcccctc agccgctttt ttgggggcgc gcggggaggc
27361 ggcggcgacg gcgacgggga cgagacgtcc tccatggttg gtggacgtcg cgccgcaccg
27421 cgtccgcgct cgggggtggt ttcgcgctgc tctcttccc gactggccat ttccttctcc
27481 tataggcaga aaaagatcat ggagtcagtc gagaaggagg acagcctaac cgccccctt
27541 gagttcgcca ccaccgcctc caccgatgcc gccaacgcgc ctaccacctt ccccgctcag
27601 gcacccccgc ttgaggagga ggaagtgatt atcgagcagg acccaggttt tgtaagcgaa
27661 gacgacgaag atcgctcagt accaacagag gataaaaagc aagaccagga cgacgcagag
27721 gcaaacgagg aacaagtgcg gcggggggac caaaggcatg gcgactacct agatgtggga
27781 gacgacgtgc tgttgaagca tctgcagcgc cagtgcgcca ttatctgcga cgcgttgcaa
27841 gagcgcagcg atgtgcccct cgccatagcg gatgtcagcc ttgcctacga acgccacctg
27901 ttctcaccgc gcgtaccccc caaacgcca gaaaacggca catgcgagcc caaccgcgc
27961 ctcaacttct acccgtatt tgccgtgcca gaggtgcttg ccacctatca catcttttct
28021 caaaactgca agataccctt atcctgccgt gccaacgcga gccgagcgga caagcagctg
28081 gccttgcggc agggcgctgt catacctgat atcgccctgc tcgacgaagt gccaaaaatc
28141 tttgagggtc ttggacgcga cgagaagcgc gcggcaaacg ctctgcaaca agaaaacagc
28201 gaaaatgaaa gtcactgtgg agtgctggtg gaacttgagg gtgacaacgc gcgcctagcc
28261 gtgctgaaac gcagcatcga ggtcaccac tttgcctacc cggcacttaa cctaccccc
28321 aaggttatga gcacagtcac gagcagctg atcgtgcgcc gtgcacgacc cctggagagg
28381 gatgcaaact tgcaagaaca aaccgaggag ggcctaccgg cagttggcga tgagcagctg
28441 gcgcgctggc ttgagacgcg cgagcctgcc gacttgagg agcgacgcaa gctaattgat
28501 gccgcagtcg ttgttaccgt ggagcttgag tgcatgcagc ggttctttgc tgaccggag
28561 atgcagcgca agctagagga aacgttgac tacaccttcc gccagggcta cgtgcgccag
28621 gcctgcaaaa tttccaacgt ggagctctgc aacctggtct cctaccttgg aattttgcac
28681 gaaaaccgcc ttgggcaaaa cgtgcttcat tccacgctca agggcgaggc gcgccgcgac
28741 tacgtccgcg actgcgttta cttatttctg tgctacacct ggcaaacggc catgggcgtg
28801 tggcagcagt gcctggagga gcgcaacctg aaggagctgc agaagctgct aaagcaaac
28861 ttgaaggacc tatggacggc cttcaacgag cgctccgtgg ccgcgcacct ggccgacatt
28921 atcttccccg aacgcctgct taaaacctg caacagggtc tgccagactt caccagtcaa
28981 agcatgttgc aaaactttag gaactttatc ctagagcgtt caggaattct gcccgccacc
29041 tgctgtgcgc ttcctagcga ctttgtgccc attaatgacc gtgaatgccc tccgcgctt
29101 tgggggtcact gctaccttct gcagctagcc aactaccttg cctaccactc cgacatcatg
29161 gaagacgtga gcggtgacgg cctactggag tgtcactgtc gctgcaacct atgcaccccg
29221 caccgctccc tggctctgcaa ttcacaactg cttagcgaaa gtcaaattat cggctacctt

FIG. 36A-9

WO 2006/020480

PCT/US2005/027658

104/126

29281 gagctgcagg gtccctcgcc tgacgaaaag tccgcggctc cgggggttgaa actcactccg
29341 gggctgtgga cgtcggctta ccttcgcaaa tttgtacctg aggactacca cgcccacgag
29401 attaggttct acgaagacca atcccgccc ccaaatgcgg agcttaccgc ctgctgcatt
29461 acccagggcc acatccttgg ccaattgcaa gccattaaca aagcccgcca agagtttctg
29521 ctacgaaagg gacgggggggt ttacttggac ccccgatccg gcgaggagct caaccaatc
29581 cccccgccc cgcagcccta tcagcagccg cggggccctg cttcccagga tggcacccaa
29641 aaagaagctg cagctgccgc cgccgccacc cacggacgag gaggaatact gggacagtca
29701 ggcagaggag gttttggacg aggaggagga gatgatggaa gactgggaca gcctagacga
29761 ggaagcttcc gagggcgaag aggtgtcaga cgaaacaccg tcaccctcgg tcgcattccc
29821 ctgcgcggcg cccagaaat cggcaaccgt tcccagcatt gctacaacct ccgctcctca
29881 ggcgcgcgg gcactgcccg ttgcgcgacc caaccgtaga tgggacacca ctggaaccag
29941 ggcgggtaag tctaagcagc cgccgcccgt agcccagag caacaacagc gccaaaggcta
30001 ccgctcgtgg cgcgtgcaca agaacgccat agttgcttgc ttgcaagact gtgggggcaa
30061 catctccttc gcccgccgct ttcttctcta ccatcacggc gtggccttcc cccgtaacat
30121 cctgcattac taccgtcatc tctacagccc ctactgcacc ggcggcagcg gcagcaacag
30181 cagcggccac gcagaagcaa aggcgaccgg atagcaagac tctgacaaag cccaagaaat
30241 ccacagcggc ggcagcagca ggaggaggag cactgcgtct ggcgcccac gaaccgctat
30301 cgacccgcga gcttagaaac aggttttttc ccactctgta tgctatatatt caacagagca
30361 gggggccaaga acaagagctg aaaataaaaa acaggtctct gcgctccctc acccgagct
30421 gcctgtatca caaaagcgaa gatcagcttc ggcgcacgct ggaagacgcg gaggctctct
30481 tcagcaaata ctgcgcgctg actcttaagg actagtttcg cgccctttct caaatttaag
30541 cgcgaaaact acgtcatctc cagcggccac acccggcgcc agcacctgtc gtcagcgcca
30601 ttatgagcaa ggaaattccc acgccctaca tgtggagtta ccagccacaa atgggacttg
30661 cggctggagc tgcccaagac tactcaacct gaataaacta catgagcgcg ggaccccaca
30721 tgatatcccg ggtcaacgga atccgcgcc accgaaaccg aattctctct gaacaggcgg
30781 ctattaccac cacacctcgt aataacctta atccccgtag ttggcccgct gccctggtgt
30841 accaggaaag tcccgtctcc accactgtgg tacttcccag agacgcccag gccgaagttc
30901 agatgactaa ctcaggggcg cagcttgccg ggggctttcg tcacagggtg cggctgcccg
30961 ggcagggtat aactcacctg aaaatcagag ggcgaggtat tcagctcaac gacgagtcgg
31021 tgagctctct tcttgggtct cgtccggacg ggacatttca gatcggcggc gctggccgct
31081 cttcatttac gcccgctcag gcgatcctaa ctctgcagac ctctcctcgt gagccgcgct
31141 ccggaggcat tggaactcta caatttattg aggagtctgt gccttcgggt tacttcaacc
31201 ccttttctgg acctcccggc cactaccgag accagtttat tcccaacttt gacgcggtaa
31261 aagactcggc ggacggctac gactgaatga ccagtggaga ggcagagcaa ctgctcctga
31321 cacacctcga ccactgccgc cgccacaagt gctttgcccg cggctccggt gagttttgtt
31381 actttgaatt gcccgaagag catatcgagg gcccggcgca cggcgctccg ctcaccaccc
31441 aggtagagct tacacgtagc ctgattcggg agtttaccac gcgccccctg ctagtggagc
31501 gggagcgggg tccctgtgtt ctgaccgtgg tttgcaactg tcccaacctt ggattacatc
31561 aagatcttat tccattcaac taacaataaa cacacaataa attacttact taaaatcagt
31621 cagcaaactt ttgtccagct tattcagcat cacctccttt ccctcctccc aactctggta
31681 tttcagcagc cttttagctg cgaactttct ccaaagtcta aatgggatgt caaatctctc
31741 atgttcttgt ccctccgcac ccactatctt catattgttg cagatgaaac gcgccagacc
31801 gtctgaagac accttcaacc ctgtgtaccc atatgacacg gaaaccggcc ctccaactgt
31861 gcctttcctt acccctccct ttgtgtcgcc aaatgggttc caagaaagtc ccccgaggat
31921 gctttctttg cgtctttcag aacctttggt tacctcacac ggcattgctt cgctaaaaat
31981 gggcagcggc ctgtccctgg atcaggcagg caaccttaca tcaaatacaa tcaactgttc
32041 tcaaccgcta aaaaaaacia agtccaatat aactttggaa acatccgccc cccttacagt
32101 cagctcaggc gccctaacca tggccacaac ttgccttttg gtggtctctg acaacactct
32161 taccatgcaa tcacaagcac cgctaaccgt gcaagactca aaacttagca ttgctaccaa
32221 agagccactt acagtgttag atggaaaact ggccttcgag acatcagccc ccctctctgc
32281 cactgataac aacgccctca ctatcactgc ctcacctcct cttactactg caaatggtag
32341 tctggctgtt accatggaaa acccacttta caacaacaat ggaaaacttg ggctcaaaat
32401 tggcggctct ttgcaagtgg ccaccgactc acatgcacta acactaggta ctggtcaggg
32461 ggttgagctt cataacaatt tgctacatac aaaagttaca ggcgcaatag ggtttgatac
32521 atctggcaac atggaactta aaactggaga tggcctctat gtggatagcg ccggtcctaa

FIG. 36A-10

WO 2006/020480

PCT/US2005/027658

105/126

32581 ccaaaaacta catattaatc taaataccac aaaaggcctt gcttttgaca acaccgcaat
32641 aacaattaac gctggaaaag ggttggaatt tgaacacagac tcctcaaacg gaaatcccat
32701 aaaaacaaaa attggatcag gcatacaata taataccaat ggagctatgg ttgcaaaact
32761 tggaacaggg ctcagttttg acagctccgg agccataaca atgggcagca taaacaatga
32821 cagacttact ctttggacaa caccagaccc atccccaaat tgcagaattg cttcagataa
32881 agactgcaag ctaactctgg cgctaacaaa atgtggcagt caaattttgg gcactgtttc
32941 agctttggca gtatcaggta atatggcctc catcaatgga actctaagca gtgtaaactt
33001 ggttcttaga tttgatgaca acggagtgtc tatgtcaaat tcactactgg acaaacagta
33061 ttggaacttt agaaacgggg actccactaa cggteaacca tacacttatg ctgttggtt
33121 tatgccaaac ctaaaagctt acccaaaaac tcaaagtaaa actgcaaaaa gtaatatgt
33181 tagccagggtg tatcttaatg gtgacaagtc taaaccattg cattttacta ttacgctaaa
33241 tggaacagat gaaaccaacc aagtaagcaa atactcaata tcattcagtt ggtcctggaa
33301 cagtggacaa tacactaatg acaaatttgc caccaattcc tataccttct cctacattgc
33361 ccaggaataa agaatcgtga acctgttgca tgttatgttt caacgtgttt atttttcaat
33421 tgcagaaaat ttcaagtcac ttttcattca gtagtatagc cccaccacca catagcttat
33481 actaatcacc gtaccttaac caaactcaca gaaccctagt attcaacctg ccacctccct
33541 cccaacacac agagtacaca gtcctttctc cccggctggc cttaaacagc atcatatcat
33601 gggtaacaga catattctta ggtgttatat tccacacggc ctctgtcga gccaaacgct
33661 catcagtgat gttaataaac tccccgggca gctcgcttaa gttcatgtcg ctgtccagct
33721 gctgagccac aggctgctgt ccaacttgcg gttgctcaac gggcgccgaa ggagaagtcc
33781 acgcctacat gggggtagag tcataatcgt gcacagcat agggcggtgg tgctgcagca
33841 gcgcgcgaat aaactgctgc cgccgcgct ccgtcctgca ggaatacaac atggcagtgg
33901 tctcctcagc gatgatctgc accgcccgc gcataaggcg ccttgtctc cgggcacagc
33961 agcgcaccct gatctcactt aagtcagcac agtaactgca gcacagtacc acaatatgt
34021 ttaaaatccc acagtgaag gcgctgtatc caaagctcat ggcggggacc acagaaccca
34081 cgtggccatc ataccacaag cgcaggtaga ttaagtggcg accctcata aacacgtgg
34141 acataaacat tacctctttt ggcagtgtgt aattcaccac ctcccggtag catataaacc
34201 tctgattaaa catggcgcca tccaccacca tcctaaacca gctggccaaa acctgcccgc
34261 cggctatgca ctgcaggga cgggactgg aacaatgaca gtggagagcc caggactcgt
34321 aaccatggat catcatgtc gtcatgatc caatgttggc acaacacagg cacacgtgca
34381 tacacttctt caggattaca agctcctccc gcgtcagaac catatcccag ggaacaaccc
34441 attcctgaat cagcgtaaat cccacactgc aggggaagacc tcgcacgtaa ctcacgttgt
34501 gcattgtcaa agtggtacat tcgggcagca gcgcatgatc ctccagtatg gtagcgcgtg
34561 tctctgtctc aaaaggaggt aggcgatccc tactgtacgg agtgcccgga gacaaccgag
34621 atcgtgttgg tcgtagtgtc atgccaaatg gaacgccgga cgtagtcata tttcctgaag
34681 caaaaccagg tcggggcggtg acaaacagat ctgcgtctcc ggtctcgtcg cttagctcgc
34741 tctgtgtagt agttgtagta tatccactct ctcaaagcat ccaggcgccc cctggcttcg
34801 ggttctatgt aaactccttc atgcgcgct gccctgataa catccaccac cgcagaataa
34861 gccacacca gccaacctac acattcgttc tgcgagtcac acacgggagg agcgggaaga
34921 gctggaagaa ccatgttttt tttttttatt ccaaagatt atccaaaacc tcaaatgaa
34981 gatctattaa gtgaacgcgc tcccctccgg tggcgtggtc aaactctaca gccaaagaac
35041 agataatggc atttgtaaga tggtgcacaa tggcttccaa aaggcaaact gccctcacgt
35101 ccaagtggac gtaaaggcta aacccttcag ggtgaatctc ctctataaac attccagcac
35161 cttcaaccat gcccaaataa ttttctctc gccaccttat caatatgtct ctaagcaaat
35221 cccgaatatt aagtccggcc attgtaaaaa tctgtctcag agcgccctcc accttcagcc
35281 tcaagcagcg aatcatgatt gcaaaaattc aggttctctc dagacctgta taagattcaa
35341 aagcgggaaca ttaacaaaaa taccgcgatc ccgtaggctc cttcgcaggg ccagctgaac
35401 ataatcgtgc aggtctgcac ggaccagcgc ggccacttcc ccgccaggaa ccatgacaaa
35461 agaaccacac ctgattatga cagcactact cggagctatg ctaaccagcg tagccccgat
35521 gtaagcttgt tgcatgggcg gcgatataaa atgcaaggta ctgctcaaaa aatcaggcaa
35581 agcctcgcgc aaaaaagcaa gcacatcgta gtcatgtctc tgcagataaa ggcaggtaag
35641 ttccggaacc accacagaaa aagacaccat ttttctctca aacatgtctg cgggttctctg
35701 cataaacaca aaataaaaata acaaaaaaaa aaaaacattt aaacattaga agcctgtctt
35761 acaacaggaa aaacaaccct tataagcata agacggacta cggccatgcc ggcgtgaccg
35821 taaaaaaact ggtcaccgtg attaaaaagc accaccgaca gttcctcggc catgtccgga

FIG. 36A-11

WO 2006/020480

PCT/US2005/027658

106/126

35881 gtcataatgt aagactcggg aaacacatca gggtgggttaa catcgggtcag tgctaaaaag
35941 cgaccgaaat agcccggggg aatacatacc cgcaggcgta gagacaacat tacagccccc
36001 ataggaggta taacaaaatt aataggagag aaaaacacat aaacacctga aaaaccctcc
36061 tgcctaggca aaatagcacc ctcccgtcc agaacaacat acagcgcttc cacagcggca
36121 gccataacag tcagccttac cagtaaaaaa acctattaaa aaacaccact cgacacggca
36181 ccagctcaat cagtcacagt gtaaaaagg ccaagtacag agcgagtata tataggacta
36241 aaaaatgacg taacgggttaa agtccacaaa aaccacccag aaaaccgcac gcgaacctac
36301 gccagaaac gaaagccaaa aaaccacaaa cttcctcaaa tcttcaacttc cgttttccca
36361 cgatacgtca cttcccatTT taaaaaaaaa ctacaattcc caatacatgc aagttactcc
36421 gccctaaaac ctacgtcacc cgccccgttc ccacgccccg cgccacgtca caaactccac
36481 cccctcatta tcatattggc ttcaatccaa aataaggat attattgatg atg

(SEQ ID NO: 21)

FIG. 36A-12

107/126

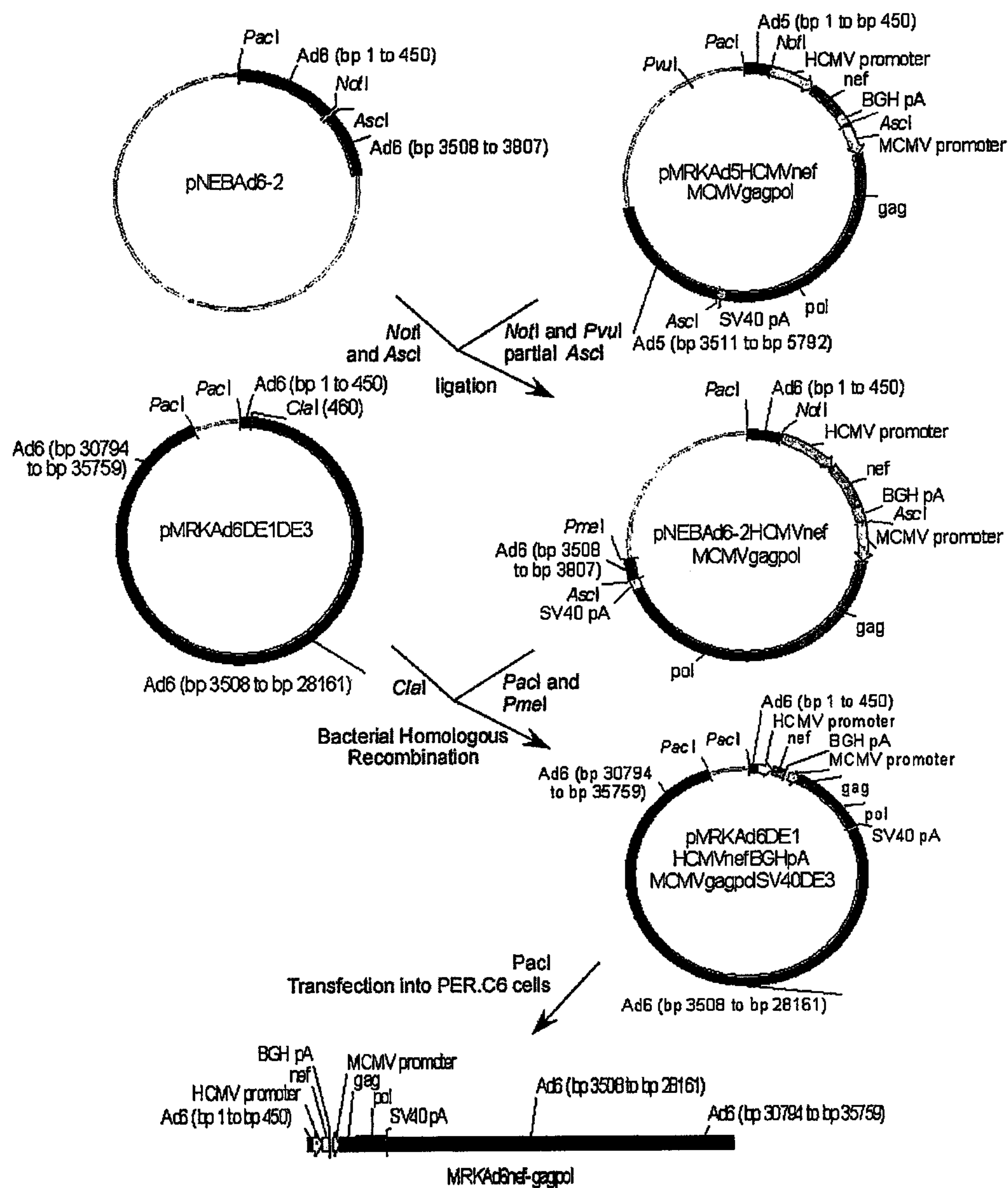


FIG. 37

108/126

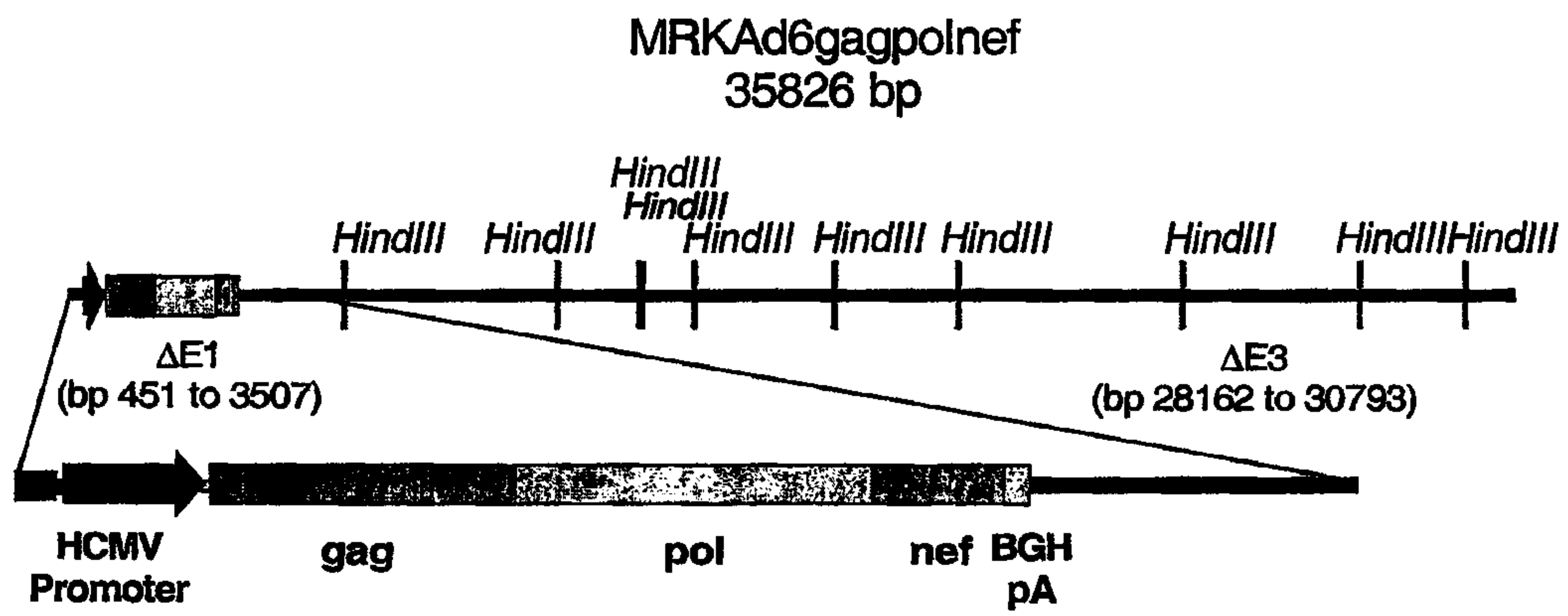


FIG. 38

109/126

MRKAd6gagpolnef

KEY: ____HCMV promoter ____Gag ____Pol ____Nef ____BGH pA

```

1 catcatcaat aatatacctt attttggatt gaagccaata tgataatgag ggggtggagt
61 ttgtgacgtg gcgcggggcg tgggaacggg gcgggtgacg tagtagtgtg gcggaagtgt
121 gatgttgtaa gtgtggcgga acacatgtaa gcgcgggatg tggtaaaagt gacgtttttg
181 gtgtgcgcgg gtgtacacgg gaagtgacaa ttttcgcgcg gttttaggcg gatgttgtag
241 taaatttggg cgtaaccaag taatatttgg ccattttcgc gggaaaactg aataagagga
301 agtgaaatct gaataattct gtgttactca tagcgcgtaa tatttgtcta gggccgcggg
361 gactttgacc gtttacgtgg agactcgccc aggtgttttt ctcaggtgtt ttccgcgttc
421 cgggtcaaag ttggcggttt attattatag cggccgcgat ccattgcata cgttgatcc
481 atatcataat atgtacattt atattggctc atgtccaaca ttaccgcat gttgacattg
541 attattgact agttattaat agtaatcaat tacgggggtc ttagttcata gcccatatat
601 ggagttccgc gttacataac ttacggtaaa tggcccgctt ggctgaccgc ccaacgacct
661 ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag ggactttcca
721 ttgacgtcaa tgggtggagt atttacggtt aactgcccac ttggcagtac atcaagtgtt
781 tcatatgcca agtacgccc ctattgacgt caatgacggt aaatggcccg cctggcatta
841 tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg tattagtcac
901 cgctattacc atggtgatgc ggttttggca gtacatcaat gggcgtggat agcggtttga
961 ctcacgggga tttccaagtc tccaccccat tgacgtcaat gggagtttgt tttggcacca
1021 aaatcaacgg gactttccaa aatgtcgtaa caactccgcc ccattgacgc aaatgggcgg
1081 taggcgtgta cgggtggagg tctatataag cagagctcgt ttagtgaacc gtcagatcgc
1141 ctggagacgc catccacgct gttttgacct ccatagaaga caccgggacc gatccagcct
1201 ccgcgcccg gaaacggtgca ttggaacgcg gattccccgt gccaaagagt agatctacca
1261 tgggtgctag ggcttctgtg ctgtctggtg gtgagctgga caagtgggag aagatcagcc
1321 tgaggcctgg tggcaagaag aagtacaagc taaaggacat tgtgtgggcc tccagggagg
1381 tggagaggtt tgctgtgaac cctggcctgc tgagacctc tgaggggtgc aggcagatcc
1441 tgggcccagct ccagccctcc ctgcaaacag gctctgagga gctgaggtcc ctgtacaaca
1501 cagtggctac cctgtactgt gtgcaccaga agattgatgt gaaggacacc aaggaggccc
1561 tggagaagat tgaggaggag cagaacaagt ccaagaagaa ggcccagcag gctgctgctg
1621 gcacaggcaa ctccagccag gtgtcccaga actaccccat tgtgcagaac ctccagggcc
1681 agatggtgca ccagggcatc tcccccgga cctgaatgc ctgggtgaag gtggtggagg
1741 agaaggcctt ctcccctgag gtgatcccca tgttctctgc cctgtctgag ggtgccaccc
1801 cccaggacct gaacaccatg ctgaacacag tggggggcca tcaggctgcc atgcagatgc
1861 tgaaggagac catcaatgag gaggtgctg agtgggacag gctgcaccc ctgcacgctg
1921 gcccattgc cccggccag atgaggagc ccagggctc tgacattgct ggcaccacct
1981 ccaccctcca ggagcagatt ggctggatga ccaacaacc cccatccct gtgggggaaa
2041 tctacaagag gtggatcatc ctgggcctga acaagattgt gaggatgtac tccccacct
2101 ccacccctga catcaggcag gcccacaagg agcccttcag ggactatgtg gacaggttct
2161 acaagaccct gagggctgag caggcctccc aggaggtgaa gaactggatg acagagaccc
2221 tgctggtgca gaatggcaac cctgactgca agaccatcct gaaggccctg ggcctgctg
2281 ccaccctgga ggagatgatg acagcctgcc agggggtggg gggccctggt cacaaggcca
2341 ggtgctgctg tgaggccatg tcccaggtga ccaactccgc caccatcatg atgcagaggg
2401 gcaacttcag gaaccagagg aagacagtga agtgcctcaa ctgtggcaag gtggccaca
2461 ttgccaagaa ctgtagggcc ccaggaaga agggctgctg gaagtgtgac aaggagggcc
2521 accagatgaa gactgcaat gagaggcagg ccaacttcct gggcaaaatc tggccctccc
2581 acaaggccag gcctggcaac ttcctccagt ccagggctga gcccacagcc cctcccaggg
2641 agtccttcag gtttggggag gagaagacca ccccagcca gaagcaggag cccattgaca
2701 aggagctgta cccctgggcc tccctgaggt cctgttttgg caacgacccc tccctccagg
2761 ccactcctcc cattgagact gtgcctgtga agctgaagcc tggcatggat ggcaccaagg
2821 tgaagcagtg gccctgact gaggagaaga tcaaggccct ggtggaaatc tgcactgaga
2881 tggagaagga gggcaaaatc tccaagattg gcccagaga cccctacaac acccctgtgt

```

FIG. 39A-1

110/126

2941 ttgccatcaa gaagaaggac tccaccaagt ggaggaagct ggtggacttc agggagctga
3001 acaagaggac ccaggacttc tgggaggtgc agctgggcat cccccacccc gctggcctga
3061 agaagaagaa gtctgtgact gtgctggctg tgggggatgc ctactttctct gtgcccctgg
3121 atgaggactt caggaagtac actgccttca ccatcccttc catcaacaat gagaccctg
3181 gcatcaggta ccagtacaat gtgctgcccc agggctggaa gggctcccct gccatcttcc
3241 agtcctccat gaccaagatc ctggaggcct tcaggaagca gaaccctgac attgtgatct
3301 accagtacat ggctgccctg tatgtgggct ctgacctga gattgggcag cacaggacca
3361 agattgagga gctgaggcag cacctgctga ggtggggcct gaccaccctt gacaagaagc
3421 accagaagga gcccccttc ctgtggatgg gctatgagct gcaccccgac aagtggactg
3481 tgcagcccat tgtgctgcct gagaaggact cctggactgt gaatgacatc cagaagctgg
3541 tgggcaagct gaactgggcc tcccaaatct accctggcat caaggtaggg cagctgtgca
3601 agctgctgag gggcaccaag gccctgactg aggtgatccc cctgactgag gaggctgagc
3661 tggagctggc tgagaacagg gagatcctga aggagcctgt gcctggggtg tactatgacc
3721 cctccaagga cctgattgct gagatccaga agcagggcca gggccagtgg acctaccaaa
3781 tctaccagga gcccttcaag aacctgaaga ctggcaagta tggcaggatg aggggggccc
3841 acaccaatga tgtgaagcag ctgactgagg ctgtgcagaa gatcaccact gagtccattg
3901 tgatctgggg caagaccccc aagttcaagc tgcccatcca gaaggagacc tgggagacct
3961 ggtggactga gtactggcag gccacctga tccctgagtg ggagttttgt aacacccccc
4021 ccttggtgaa gctgtggtac cagctggaga aggagcccat tgtgggggct gagaccttct
4081 atgtggctgg ggctgccaac agggagacca agctgggcaa ggctggctat gtgaccaaca
4141 ggggcaggca gaaggtagtg accctgactg acaccaccaa ccagaagact gccctccagg
4201 ccatctacct ggcctccag gactctggcc tggaggtgaa cattgtgact gcctcccagt
4261 atgccctggg catcatccag gccagcctg atcagtctga gtctgagctg gtgaaccaga
4321 tcattgagca gctgatcaag aaggagaagg totacctggc ctgggtgcct gccacaagg
4381 gcattggggg caatgagcag gtggacaagc tgggtgtctg tggcatcagg aaggtgctgt
4441 tcctggatgg cattgacaag gcccaggatg agcatgagaa gtaccactcc aactggaggg
4501 ctatggcctc tgacttcaac ctgccccctg tgggtggctaa ggagattgtg gcctcctgtg
4561 acaagtcca gctgaagggg gaagccatgc atgggcaagt ggaactgctcc cctggcatct
4621 ggcagctggc ctgcaccac ctggagggca aggtgatcct ggtggctgtg catgtggcct
4681 ccggctacat tgaggctgag gtgatccctg ctgagacagg ccaggagact gcctacttcc
4741 tgctgaagct ggctggcagg tggcctgtga agaccatcca cactgccaat ggctccaact
4801 tcactggggc cacagtgagg gctgcctgct ggtgggctgg catcaaggag gagtttggca
4861 tcccctacaa ccccgatcc cagggggtgg tggcctccat gaacaaggag ctgaagaaga
4921 tcattgggca ggtgaggggc caggctgagc acctgaagac agctgtgcag atggtgtgt
4981 tcattccaaa cttcaagagg aaggggggca tggggggcta ctccgctggg gagaggattg
5041 tggacatcat tggcacagac atccagacca aggagctcca gaagcagatc accaagatcc
5101 agaacttcag ggtgtactac agggactcca ggaacccct gtggaagggc cctgccaagg
5161 tgctgtgaa gggggagggg gctgtggtga tccaggacaa ctctgacatc aaggtgggtg
5221 ccaggaggaa ggccaagatc atcagggact atggcaagca gatggctggg gatgactgtg
5281 tggcctccag gcaggatgag gacggcggca agtggtccaa gaggtccgtg cccggctggt
5341 ccaccgtgag ggagaggatg aggaggggcg agcccgccgc cgacagggtg aggaggaccg
5401 agcccgccgc agtgggctg ggcggcgtgt ccaggagcct ggagaagcac ggcgccatca
5461 cctcctcaa caccggcgc accaagcgc actgcgctg gctggaggcc caggaggagc
5521 aggaggtggg cttccccgtg agggcccagg tggcctgag gccatgacc tacaaggggc
5581 ccgtggacct gtcccacttc ctgaaggaga agggcgccct ggagggctg atccactccc
5641 agaagaggca ggacatcctg gacctgtggg tgtaccacac ccagggctac tccccgact
5701 ggcagaacta cccccggc cccggcatca ggttccccct gaccttcggc tgggtcttca
5761 agctgggtgc cgtggagccc gagaagggtg aggagggcaa cgaggggcag aacaactgcc
5821 tgctgcaccc catgtccag caggcatcg aggaccccg gaaggagggtg ctggagtggg
5881 ggttcgactc caagctggcc tccaccacg tggccaggga gctgcacccc gagtactaca
5941 aggactgcta aagccggggc agatctgctg tgcttctag ttgccagcca tctgttttt
6001 gccctcccc cgtgccttcc ttgacctgg aaggtggcac tcccactgtc ctttctaat
6061 aaaatgagga aattgcatcg cattgtctga gtagggtgca ttctattctg gggggtggg
6121 tggggcagga cagcaagggg gaggattggg aagacaatag caggcatgct ggggatgagg
6181 tgggctctat ggcgatcgg cgcgccgtac tgaaatgtgt gggcgtggct taagggtggg
6241 aaagaatata taagggtggg gtctcatgta gttttgtatc tgttttgag cagccggcgc

FIG. 39A-2

111/126

6301 catgagcgcc aactcgtttg atggaagcat tgtgagctca tatttgacaa cgcgcatgcc
6361 cccatggggc ggggtgctgc agaattgat gggctccagc attgatggtc gccccgtcct
6421 gcccgcacaa tctactacct tgacctacga gaccgtgtct ggaacgccgt tggagactgc
6481 agcctccgcc gccgcttcag ccgctgcagc caccgcccgc gggatttgtga ctgactttgc
6541 tttcctgagc ccgcttgcaa gcagtgcagc ttcccgttca tccgcccgcg atgacaagtt
6601 gacggctctt ttggcacaat tggattcttt gaccgggaa cttaatgtcg tttctcagca
6661 gctgttggat ctgcgccagc aggtttctgc cctgaaggct tctctccctc ccaatgcggt
6721 ttaaaacata aataaaaacc agactctgtt tggatttggg tcaagcaagt gtcttgctgt
6781 ctttatattag gggttttgct gcgcggttag gcccgggacc agcggctctg gtcttgagg
6841 gtcctgtgta tttttccag gacgtggtta aggtgactct ggatgttcag atacatgggc
6901 ataagcccgt ctctggggtg gaggtagcac cactgcagag cttcatgctg cggggtggtg
6961 ttgtagatga tccagtcgta gcaggagcgc tgggcgtggt gcctaaaaat gtctttcagt
7021 agcaagctga ttgccagggg caggcccttg gtgtaagtgt ttacaaagcg gtttaagctg
7081 gatgggtgca tacgtgggga tatgagatgc atcttggact gtatttttag gttggctatg
7141 tttccagcca tatccctccg gggattcatg ttgtgcagaa ccaccagcac agtgtatccg
7201 gtgcacttgg gaaatttgtc atgtagctta gaaggaaatg cgtggaagaa cttggagacg
7261 cccttgtgac ctccaagatt ttccatgcat tegtccataa tgatggcaat gggcccacgg
7321 gcggcgccct gggcgaagat atttctggga tcaactaact catagtgtgt ttcaggatg
7381 agatcgctcat aggccatttt taaaaagcgc gggcgagggg tggcagactg cgggtataatg
7441 gttccatccg gcccaggggc gtagttacct tcacagattt gcatttccca cgctttgagt
7501 tcagatgggg ggatcatgtc tacctgcggg gcgatgaaga aaaccgtttc cggggtaggg
7561 gagatcagct gggaagaaag caggttccca agcagctgcg acttaccgca gccggtgggc
7621 ccgtaaatca cacctattac cggctgcaac tggtagttta gagagctgca gctgccgtca
7681 tccctgagca gggggggccac ttctgtaagc atgtccctga cttgcatgtt ttcctgacc
7741 aaatccgcca gaaggcgtc gccgcccagc gatagcagtt cttgcaagga agcaaagttt
7801 ttcaacggtt tgaggcgtc gccgtaggc atgcttttga gcgtttgacc aagcagttcc
7861 aggcggtccc acagctcggg cagctgctct acggcatctc gatccagcat atctcctcgt
7921 ttgcggtgtt ggggcgggtt tgcgtgtacg gcagtagtcg gtgctcgtcc agacgggcca
7981 gggcatgtc tttccacggg cgcagggtcc tgcgcagcgt agtctgggtc acggtgaagg
8041 ggtgcgtccc ggggtgcgcg ctggccaggg tgcgcttgag gctggtcctg ctggtgctga
8101 agcgtgccc gtcttcgccc tgcgcgtcgg ccaggtagca tttgaccatg gtgtcatagt
8161 ccagccctc cgcggtgtg cccttggcgc gcagcttgcc cttggaggag gcgcccacg
8221 aggggcagtg cagactttta agggcgtaga gcttgggcgc gagaaatacc gattccgggg
8281 agtaggcata cgcgccgcag gccccgcaga cggctctgca ttccacgagc caggtgagct
8341 ctggccgttc ggggtcaaaa accaggtttc ccccatgctt tttgatgctt ttcttacctc
8401 tggtttccat gagccggtgt ccacgctcgg tgacgaaaag gctgtccgtg tccccgtata
8461 cagacttgag aggcctgtcc tgcagcgtg ttccgcggtc ctctcgtat agaaactcgg
8521 accactctga gacgaaggct cgcgtccagg ccagcacgaa ggaggctaag tgggaggggt
8581 agcgtcgtt gtccactagg ggtccactc gctccagggg gtgaagacac atgtcgcctc
8641 cttcggcatac aaggaagggt attggtttat aggtgtaggc cacgtgaccg ggtgttccgt
8701 aaggggggct aaaaagggg gtggggggcgc gttcgtcctc actctcttcc gcacgtctgt
8761 ctgcgagggc cagctgttgg ggtgagtact cctctcaaaa agcgggcatg acttctgcgc
8821 taagattgtc agtttccaaa aacgaggagg atttgatatt cacctggccc gcggtgatgc
8881 ctttgagggt ggccgcgtcc atctggtcag aaaagacaat ctttttgttg tcaagcttgg
8941 tggcaaacga cccgtagagg gcgttggaac gcaacttggc gatggagcgc agggtttggg
9001 ttttgtcgcg atcggcgcgc tcttggccg cgatgtttag ctgcacgtat tcgcgcgcaa
9061 cgcaccgcca ttcgggaaag acggtggtgc gctcgtcggg cactaggtgc acgcgccaac
9121 cgcggttgtg cagggtgaca aggtcaacgc tgggtggctac ctctccgctg aggcgtcgt
9181 tgggtccagca gaggcggccg cccttgcgcg agcagaatgg cggtagtggg tctagctgcg
9241 tctcgtccgg ggggtctgcg tccacggtta agacccggg cagcaggcgc gcgtcgaagt
9301 agtctatctt gcaccttgc aagtctagcg cctgctgcca tgcgcgggcg gcaagcgcgc
9361 gctcgtatgg gttgagtggg ggaccccatg gcattgggtg ggtgagcgcg gaggcgtaca
9421 tgccgcaaat gtcgtaaacg tagaggggct ctctgagtat tccaagatat gtagggtagc
9481 atcttccacc gcggatgctg gcgcgcacgt aatcgtatag ttcgtgcgag ggagcgagga
9541 ggtcgggacc gaggttgcta cgggcgggct gctctgctcg gaagactatc tgccgtaaga
9601 tggcatgtga gttggatgat atggttggac gctggaagac gttgaagctg gcgtctgtga

FIG. 39A-3

WO 2006/020480

PCT/US2005/027658

112/126

```

9661 gacctaccgc gtcacgcacg aaggaggcgt aggagtcgcg cagcttggtg accagctcgg
9721 cggtgacctg cacgtctagg gcgcagtagt ccagggtttc cttgatgatg tcatacttat
9781 cctgtccctt ttttttccac agctcgcggt tgaggacaaa ctcttcgcgg tctttccagt
9841 actcttgat cggaaccccg tcggcctccg aacggtaaga gcctagcatg tagaactggt
9901 tgacggcctg gtaggcgcag catccctttt ctacgggtag cgcgtatgcc tgcgcggcct
9961 tccggagcga ggtgtgggtg agcgcaaagg tgtccctaac catgactttg aggtactggt
10021 atttgaagtc agtgtcgtcg catccgccct gctcccagag caaaaagtcc gtgcgctttt
10081 tggaacgcgg gtttggcagg gcgaagggtg catcgttgaa gagtatcttt cccgcgcgag
10141 gcataaagtt gcgtgtgatg cggaagggtc ccggcacctc ggaacgggtg ttaattacct
10201 gggcggcgag cacgatctcg tcaaagccgt tgatgttggt gccacaatg taaagttcca
10261 agaagcgcgg gatgcccttg atggaaggca attttttaag ttcctcgtag gtgagctctt
10321 caggggagct gagcccgtgc tctgaaaggg ccagtcctgc aagatgaggg ttggaagcga
10381 cgaatgagct ccacaggtca cgggccatta gcatttgcag gtggtcgcga aaggtcctaa
10441 actggcgacc tatggccatt ttttctgggg tgatgcagta gaaggtaagc gggctctggt
10501 cccagcggtc ccatccaagg tccgcggcta ggtctcgcgc ggcggtcact agaggctcat
10561 ctccgccgaa cttcatgacc agcatgaagg gcacgagctg cttcccaaag gccccatcc
10621 aagtataggt ctctacatcg taggtgacaa agagacgctc ggtgcgagga tgcgagccga
10681 tcgggaagaa ctggatctcc cgccaccagt tggaggagtg gctgttgatg tggtgaaagt
10741 agaagtcctt gcgacgggcc gaacactcgt gctggctttt gtaaaaacgt gcgcagtact
10801 ggcagcggtg cacgggctgt acatcctgca cgaggttgac ctgacgaccg cgcacaagga
10861 agcagagtgg gaatttgagc cctcgcctg gcgggtttgg ctggtggtct tctacttcgg
10921 ctgcttgctc ttgaccgtct ggctgctcga ggggagttac ggtggatcgg accaccacgc
10981 cgcgcgagcc caaagtccag atgtccgcgc gcggcggtcg gagcttgatg acaacatcgc
11041 gcagatggga gctgtccatg gtctggagct cccgcggcgt caggtcaggc gggagctcct
11101 gcaggtttac ctgcgatagc cgggtcaggg cgcgggctag gtccagggtg tacctgattt
11161 ccaggggctg gttggtggcg gcgtcgatgg cttgcaagag gccgcacccc cgcggcgaga
11221 ctacggtacc gcgcggcggg cgggtgggccg cgggggtgtc cttggatgat gcatctaaaa
11281 gcggtgacgc gggcggggccc ccggaggtag ggggggctcg ggaccgcgcg ggagaggggg
11341 caggggcacg tcggcgccgc gcgcgggcag gagctggtgc tgcgcgcgga ggttgctggc
11401 gaacgcgacg acgcggcggt tgatctcctg aatctggcgc ctctgcgtga agacgacggg
11461 cccggtgagc ttgaacctga aagagagttc gacagaatca atttcgggtg cgttgacggc
11521 ggcctggcgc aaaatctcct gcacgtctcc tgagttgtct tgataggcga tctcggccat
11581 gaactgctcg atctcttctt cctggagatc tccgcgtccg gctcgtcca cgggtggcggc
11641 gaggtcgttg gagatgcggg ccatgagctg cgagaaggcg ttgaggcctc cctcgttcca
11701 gacgcggctg tagaccacgc ccccttcggc atcgcggggc cgcacgacca cctgcgcgag
11761 attgagctcc acgtgccggg cgaagacggc gtagtttcgc aggcgctgaa agaggtagtt
11821 gaggggtggt gcggtgtgtt ctgccacgaa gaagtacata acccagcgcc gcaacgtgga
11881 ttggttgata tcccccaagg cctcaaggcg ctccatggcc tcgtagaagt ccacggcgaa
11941 gttgaaaaac tgggagttgc gcgccgacac ggttaactcc tcctccagaa gacggatgag
12001 ctcggcgaca gtgtcgcgca cctcgcgctc aaaggctaca ggggcctctt cttcttcttc
12061 aatctcctct tccataaggg cctccccttc ttcttcttct ggcggcggtg ggggaggggg
12121 gacacggcgg cgacgacggc gcaccgggag gcggtcgaca aagcgtcga tcatctcccc
12181 gcggcgacgg cgcacgtgtc cggtgacggc gcggcgttc tcgcgggggc gcagttggaa
12241 gacgcggccc gtcacgtccc ggttatgggt tggcgggggg ctgccgtgcg gcagggatac
12301 ggcgctaacg atgcatctca acaattgttg ttaggttact ccgccaccga gggacctgag
12361 cgagtccgca tcgaccggat cggaaaacct ctcgagaaag gcgtctaacc agtcacagtc
12421 gcaaggtagg ctgagcacgg tggcggggcg cagcgggcgg cggtcggggg tgtttctggc
12481 ggaggtgctg ctgatgatgt aattaaagta ggcggtcttg agacggcgga tggtcgacag
12541 aagcaccatg tccttgggtc cggcctgctg aatgcgcagg cggtcggcca tgccccaggg
12601 ttggttttga catcggcgca ggtcttttga gtagtcttgc atgagccttt ctaccggcac
12661 ttcttcttct ccttctctct gtctgcac tccttgcact atcgtgcgg cggcggcgga
12721 gtttggcgt aggtggcgcc ctcttctct catgcgtgtg acccgaagc ccctcatcgg
12781 ctgaagcagg gccaggtcgg cgacaacgcg ctcggctaata atggcctgct gcacctgcgt
12841 gagggtagac tggaaagtcgt ccatgtccac aaagcgggtg tatgcggccg tgttgatggt
12901 gtaagtgcag ttggccataa cggaccagtt aacggtctgg tgaccgggct gcgagagctc
12961 ggtgtacctg agacgcgagt aagcccttga gtcaaagacg tagtcgttgc aagtccgcac

```

FIG. 39A-4

WO 2006/020480

PCT/US2005/027658

113/126

```

13021 caggtactgg tatcccacca aaaagtgcgg cggcgggctgg cggtagaggg gccagcgtag
13081 ggtggccggg gctccggggg cgaggtcttc caacataagg cgatgatatc cgtagatgta
13141 cctggacatc caggtgatgc cggcggcggg ggtggaggcg cgcggaaagt cacggacgcg
13201 gttccagatg ttgcgcagcg gcaaaaagtg ctccatggtc gggacgctct ggccggtcag
13261 gcgcgcgcag tcgttgacgc tctagaccgt gcaaaaggag agcctgtaag cgggcactct
13321 tccgtggtct ggtggataaa ttgcgaaggg tatcatggcg gacgaccggg gttcgaaccc
13381 cggatccggc cgtccgccgt gatccatgcg gttaccgccc gctgtgcgaa cccaggtgtg
13441 cgacgtcaga caacggggga gcgctccttt tggcttcctt ccaggcgcgg cggatgctgc
13501 gctagctttt ttggccactg gccgcgcgcg gcgtaagcgg ttaggctgga aagcgaagc
13561 attaagtggc tcgctccctg tagccggagg gttattttcc aagggttgag tcgcgggacc
13621 cccggttcga gtctcggggc ggccggactg cggcgaacgg gggtttgctt ccccgatcatg
13681 caagaccccg cttgcaaatt cctccggaaa cagggacgag cccctttttt gcttttccca
13741 gatgcatccg gtgctgcggc agatgcgccc ccctcctcag cagcggcaag agcaagagca
13801 gcggcagaca tgcagggcac cctccccttc tcctaccgcg tcaggagggg caacatccgc
13861 ggctgacgcg gcggcagatg gtgattacga acccccgcg cgcgggacc ggactactt
13921 ggacttgag gagggcgagg gcctggcgcg gctaggagcg ccctctcctg agcgacaccc
13981 aagggtgcag ctgaagcgtg acacgcgcga ggcgtagctg ccgcggcaga acctgtttcg
14041 cgaccgcgag ggagaggagc ccgaggagat gcgggatcga aagtcccatg cagggcgcga
14101 gttgcggcat ggcctgaacc gcgagcgggt gctgcgcgag gaggactttg agcccgacgc
14161 gcggaccggg attagtcccc cgcgcgcaca cgtggcgggc gccgacctg taaccgcgta
14221 cgagcagacg gtgaaccagg agattaactt tcaaaaaagc ttaacaacc acgtgcgcac
14281 gcttgtggcg cgcgaggagg tggctatagg actgatgcat ctgtgggact ttgtaagcgc
14341 gctggagcaa aacccaaata gcaagccgct catggcgag ctgttcctta tagtgacga
14401 cagcagggac aacgaggcat tcagggatgc gctgctaaac atagtagagc ccgagggccg
14461 ctggctgctc gatttgataa acattctgca gagcatagtg gtgcaggagc gcagcttgag
14521 cctggctgac aaggtggcgc ccattaacta ttccatgctc agtctgggca agttttacgc
14581 ccgcaagata taccataccc cttacgttcc catagacaag gaggtaaaga tcgaggggtt
14641 ctacatgcgc atggcgctga aggtgcttac cttgagcgac gacctgggcg tttatcgcaa
14701 cgagcgcac cacaaggccg tgagcgtgag ccggcgggcg gagctcagcg acccgcgagct
14761 gatgcacagc ctgcaaaggg ccctgggctg cacgggcagc ggcgatagag aggccgagtc
14821 ctactttgac gcgggcgctg acctgcgctg ggccccaagc cgacgcgccc tggaggcagc
14881 tggggccgga cctgggctgg cgggtggcacc cgcgcgcgct ggcaacgtcg gcggcgtgga
14941 ggaatatgac gaggacgatg agtacgagcc agaggacggc gagtactaag cggtgatgtt
15001 tctgatcaga tgatgcaaga cgcaacggac ccggcgggtg gggcgggcgt gcagagccag
15061 ccgtccggcc ttaactccac ggacgactgg cgccagggtc tggaccgcat catgtcgctg
15121 actgcgcgca acctgacgc gttccggcag cagccgcagg ccaaccggct ctccgcaatt
15181 ctggaagcgg tggteccggc gcgcgcaaac cccacgcacg agaaggtgct ggcgatcgta
15241 aacgcgctgg ccgaaaacag ggccatccgg cccgatgagg ccggcctggt ctacgacgcg
15301 ctgcttcagc gcgtggctcg ttacaacagc agcaacgtgc agaccaacct ggaccggctg
15361 gtgggggatg tgcgcgaggc cgtggcgagc cgtgagcgcg cgcagcagca gggcaacctg
15421 ggctccatgg ttgactaaa cgccttcctg agtacacagc ccgccaacgt gccgcgggga
15481 caggaggact acaccaactt tgtgagcgca ctgcggctaa tggtgactga gacaccgcaa
15541 agtgaggtgt atcagtccgg gccagactat tttttccaga ccagtagaca aggcctgcag
15601 accgtaaacc tgagccaggc tttcaagaac ttgcaggggc tgtgggggtt gcgggctccc
15661 acaggcgacc gcgcgacctg gtctagcttg ctgacgccc aactcgccct gttgctgctg
15721 ctaatagcgc ccttcacgga cagtggcagc gtgtcccggg acacatacct aggtcacttg
15781 ctgacactgt accgcgaggc catagggtcag gcgcatgtgg acgagcatac tttccaggag
15841 attacaagtg ttagccgcgc gctggggcag gaggacacgg gcagcctgga ggcaacctg
15901 aactacctgc tgaccaaccg gcggcaaaaa atcccctcgt tgcacagttt aaacagcgag
15961 gaggagcgca ttttgcgcta tgtgcagcag agcgtgagcc ttaacctgat gcgcgacggg
16021 gtaacgccc a gcgtggcgct ggacatgacc gcgcgcaaca tggaaaccgg catgtatgcc
16081 tcaaaccggc cgtttatcaa tcgcctaata gactacttgc atcgcgcggc cgccgtgaac
16141 cccgagtatt tcaccaatgc catcttgaa cgcactggc taccgcccc tggtttctac
16201 accgggggat tcgaggtgcc cgagggtaac gatggattcc tctgggacga catagacgac
16261 agcgtgtttt ccccgcaacc gcagaccctg ctagagttgc aacaacgcga gcaggcagag
16321 gcggcgctgc gaaaggaaag cttccgcagg ccaagcagct tgtccgatct aggcgctgcg

```

FIG. 39A-5

WO 2006/020480

PCT/US2005/027658

114/126

```

16381 gccccgcggt cagatgctag tagcccatth ccaagcttga tagggtctct taccagcact
16441 cgcaccaccc gcccgcgctt gctgggagag gaggagtacc taaacaactc gctgctgcag
16501 ccgcagcgcg aaaagaacct gcctccggcg tttcccaaca acgggataga gagcctagtg
16561 gacaagatga gtagatggaa gacgtatgag caggagcaca gggatgtgcc cggcccgcg
16621 ccgcccaccc gtcgtcaaag gcacgaccgt cagcgggggtc tgggtgtggga ggacgatgac
16681 tcggcagacg acagcagcgt cttggatttg ggagggagtg gcaacccgtt tgcacacctt
16741 cgccccaggg tggggagaaat gttttaaaaa aagcatgatg caaaataaaa aactcaccaa
16801 ggccatggca ccgagcggtg gttttcttgt attccctta gtatgcggcg cgcggcgatg
16861 tatgaggaag gtcctcctcc ctctacgag agcgtggtga gcgcggcgcc agtggcgcg
16921 gcgctgggtt cacccttcga tgctccctg gaccgcctg tcgtgcctcc gcggtacctg
16981 cggcctaccg gggggagaaa cagcatccgt tactctgagt tggcaccctt attcgacacc
17041 acccgtgtgt accttggtga caacaagtca acggatgtgg catccctgaa ctaccagaac
17101 gaccacagca actttctaac cacggtcatt caaaacaatg actacagccc gggggaggca
17161 agcacacaga ccatcaatct tgacgaccgg tcgcaactgg gcggcgacct gaaaaccatc
17221 ctgcatacca acatgcaaaa tgtgaacgag ttcatgttta ccaataagtt taaggcgagg
17281 gtgatgggtg cgcgctcgct tactaaggac aaacagggtg agctgaaata cgagtgggtg
17341 gagttcacgc tgcccgaggg caactactcc gagaccatga ccatagacct tatgaacaac
17401 gcgatcgtgg agcactactt gaaagtgggc aggcagaacg gggttctgga aagcgacatc
17461 ggggtaaagt ttgacacccg caacttcaga ctgggggttg acccagtcac tggctctgtc
17521 atgcctgggg tatatacaaa cgaagccttc catccagaca tcattttgct gccaggatgc
17581 ggggtggact tcacccacag ccgcttgagc aacttggttg gcatccgcaa gcggcaacct
17641 ttccaggagg gctttaggat cacctacgat gacctggagg gtggtaacat tcccgcactg
17701 ttggatgtgg acgcctacca ggcaagcttg aaagatgaca ccgaacaggg cgggggtggc
17761 gcaggcgagg gcaacaacag tggcagcggc gcggaagaga actccaacgc ggcagctgcg
17821 gcaatgcagc cgggtggagga catgaacgat catgccattc gcggcgacac ctttgccaca
17881 cgggcggagg agaagcgcg ctaggcggag gcagcgggcg aagctgccgc ccccgctgcg
17941 gaggtgacac aaccgaggt cgagaagcct cagaagaaac cggtgattaa acccctgaca
18001 gaggacagca agaaacgcag ttacaacctt ataagcaatg acagcacctt caccagtagc
18061 cgcagctggt accttgcata caactacggc gacctcagg ccgggatccg ctcatggacc
18121 ctgctttgca ctcttgacgt aacctgcggc tcggagcagg tatactgggtc gttgcccagc
18181 atgatgcaag acccgtgac ctcccgctcc acgcgccaga tcagcaactt tccggtgggtg
18241 ggcgcggagc tgttgccgt gcactccaag agcttctaca acgaccaggc cgtctactcc
18301 cagctcatcc gccagtttac ctctctgacc cagtggttca atcgctttcc cgagaaccag
18361 attttggcgc gcccgccagc cccaccatc accaccgtca gtgaaaacgt tcctgctctc
18421 acagatcacg ggacgctacc gctgcgcaac agcatcgag gagtccagcg agtgaccatt
18481 actgacgcca gacgcgcac ctgcccctac gtttacaagg ccctgggcat agtctcgccg
18541 cgcgtcctat cgagccgcac tttttgagca agcatgtcca tccttatatc gccagcaat
18601 aacacaggct ggggcctgcg ctcccaagc aagatgtttg gcggggccaa gaagcgctcc
18661 gaccaacacc cagtgcgct gcgcgggcac taccgcgcgc cctggggcg ccaaaaacgc
18721 ggccgcactg ggcgccacc cgtcgatgac gccatcgag cggtggtgga ggaggcgcg
18781 aactacacgc ccacgcgcgc gccagtgtcc accgtggagc cggccattca gaccgtgggtg
18841 cgcggagccc ggcgctacgc taaaatgaag agacggcgga ggcgcgtagc acgtcgccac
18901 cgccgcgac ccggcactgc cgcccaacgc gcggcgggcg ccctgcttaa ccgcgcacgt
18961 cgcaaccggc gacggggcg catgcgagcc gctcgaaggc tggccgcggg tattgtcact
19021 gtgcccccca ggtccaggcg acgagcgggc gccgcagcag ccgcggccat tagtgctatg
19081 actcagggtc gcaggggcaa cgtgtactgg gtgcgcgact cggttagcgg cctgcgcgtg
19141 cccgtgcgca cccgcccccc gcgcaactag attgcaataa aaaactactt agactcgtac
19201 tgttgatgt atccagcggc ggcgcgcgcc atcgaagcta tgtccaagcg caaaatcaaa
19261 gaagagatgc tccaggtcat cgcgcgggag atctatggcc cccgaagaa ggaagagcag
19321 gattacaagc cccgaaagct aaagcggttc aaaaagaaaa agaaagatga tgatgatgat
19381 gaacttgacg acgaggtgga actgttgac gcgaccgcgc ccaggcgacg ggtacagtgg
19441 aaaggtcgac gcgtaagac tgttttgca ccggcacca ccgtagtctt tacgccggt
19501 gagcgctcca cccgcacct caagcgctg tatgatgagg tgtacggcga cgaggacctg
19561 cttgagcagg ccaacgagcg cctcggggag tttgcctacg gaaagcggca taaggacatg
19621 ctggcgctgc cgctggacga gggcaacca acacctagcc taaagcccg gacactgcag
19681 caggtgctgc ccgcgcttc accgtccgaa gaaaagcgcg gcctaaagcg cgagtctggt

```

FIG. 39A-6

115/126

```

19741 gacttggcac ccaccgtgca gctgatggta cccaagcgtc agcgactgga agatgtcttg
19801 gaaaaaatga ccgtggagcc tgggctggag cccgaggtcc gcgtgcggcc aatcaagcag
19861 gtggcaccgg gactgggctg gcagaccgtg gacgttcaga taccaccac cagtagcact
19921 agtattgcca ctgccacaga gggcatggag acacaaacgt ccccggttgc ctggcggtg
19981 gcagatgccg cggatgcaggc ggccgctgcg gccgcgtcca agacctctac ggaggtgcaa
20041 acggaccctg ggatgtttcg tgtttcagcc ccccggtcgc cgcgcgttc aaggaagtac
20101 ggcgccgcca gcgcgtact gccgaatat gccctacatc cttccatcgc gcctaccccc
20161 ggctatcgtg gctacaccta ccgccccaga agacgagcaa ctaccgacg ccgaaccacc
20221 actggaaccc gccgcgcgcg tcgccgtcgc cagcccggtc tggccccgat ttccgtgcgc
20281 aggggtggctc gcgaaggagg caggaccctg gtgctgcca cagcgcgcta ccacccagc
20341 atcgtttaaa agccggtctt tgtggttctt gcagatatgg cctcacctg ccgcctccgt
20401 ttcccggtgc cgggattccg aggaagaatg caccgtagga ggggcatggc cggccacggc
20461 ctgacgggcg gcatgcgtcg tgcgcaccac cggcggcggc gcgcgtcgca ccgtcgcatg
20521 cgcggcggtg tcctgcccc ccttattcca ctgatcgccg cggcgattgg cgcctgccc
20581 ggaattgcat ccgtggcctt gcaggcgcag agacactgat taaaaacaag ttacatgtgg
20641 aaaaatcaaa ataaaagtct ggactctcac gctcgcttgg tcctgtaact attttgtaga
20701 atggaagaca tcaactttgc gtcactggcc ccgcgacacg gctcgcgccc gttcatggga
20761 aactggcaag atatcggcac cagcaatatg agcgggtggc ccttcagctg gggctcgctg
20821 tggagcggca ttaaaaattt cggttccgcc gttaagaact atggcagcaa agcctggaac
20881 agcagcacag gccagatgct gagggacaag ttgaaagagc aaaatttcca acaaaagggtg
20941 gtagatggcc tggcctctgg cattagcggg gtggtggacc tggccaacca ggcagtgcaa
21001 aataagatta acagtaagct tgatccccgc cctcccgtag aggagcctcc accggccgtg
21061 gagacagtgt ctccagaggg gcgtggcgaa aagcgtccgc gacccgacag ggaagaaact
21121 ctggtgacgc aaatagacga gcctccctcg tacgaggagg cactaaagca aggcctgccc
21181 accacccgtc ccatcgcgcc catggctacc ggagtgtgg gccagcacac acccgtaacg
21241 ctggacctgc ctcccccgcc cgacaccag cagaaacctg tgctgccagg cccgtccgcc
21301 gttgttgtaa cccgtcctag ccgcgcgtcc ctgcgcgcgc ccgccagcgg tccgcgatcg
21361 ttgcggcccc tagccagtgg caactggcaa agcacactga acagcatcgt ggggttgggg
21421 gtgcaatccc tgaagcgccg acgatgcttc tgatagctaa cgtgtcgtat gtgtgtcatg
21481 tatgcgtcca tgtcgccgcc agaggagctg ctgagccgcc gcgcgccgc tttccaagat
21541 ggctaccctc tcgatgatgc cgcagtggtc ttacatgcac atctcgggcc aggacgcctc
21601 ggagtacctg agccccgggc tgggtgcagtt cgcgccgcgc accgagacgt acttcagcct
21661 gaataacaag tttagaaacc ccacggtggc gcctacgcac gacgtgacca cagaccggtc
21721 tcagcgtttg acgctgcggt tcatccccgt ggaccgcgag gatactgcgt actcgtacaa
21781 ggcgcggttc accctagctg tgggtgataa ccgtgtgcta gacatggctt ccacgtactt
21841 tgacatccgc ggcgtgctgg acaggggccc tacttttaag ccctactctg gcaactgccta
21901 caacgcactg gcccccaagg gtgcccccaa ctcgtgcgag tgggaacaaa atgaaactgc
21961 acaagtggat gctcaagaac ttgacgaaga ggagaatgaa gccaatgaag ctcaggcgcg
22021 agaacaggaa caagctaaga aaacctatgt atatgccag gctccactgt ccggaataaa
22081 aataactaaa gaaggctctac aaataggaac tgccgacgcc acagtagcag gtgccggcaa
22141 agaaattttc gcagacaaaa cttttcaacc tgaaccacaa gtaggagaa ctcaatggaa
22201 cgaagcggat gccacagcag ctggtggaag ggttcttaaa aagacaactc ccatgaaacc
22261 ctgctatggc tcatacgcta gaccaccaa ttccaacggc ggacagggcg ttatggttga
22321 acaaatgggt aaattggaaa gtcaagtcga aatgcaattt tttccacat ccacaaatgc
22381 cacaatgaa gttaacaata tacaaccaac agttgtattg tacagcgaag atgtaaacat
22441 ggaaactcca gatactcatc tttcttataa acctaaaatg ggggataaaa atgccaaagt
22501 catgcttggg caacaagcaa tgccaaacag accaaattac attgctttta gagacaattt
22561 tattggtctc atgtattaca acagcacagg taacatgggt gtccttgctg gtcaggcatc
22621 gcagttgaac gctgtttag atttgcaaga cagaaacaca gagctgtcct accagctttt
22681 gcttgattca attggcgaca gaacaagata cttttcaatg tggaatcaag ctggtgacag
22741 ctatgatcca gatgtcagaa ttattgagaa ccatggaact gaggatgagt tgccaaatta
22801 ttgctttcct cttggtggaa ttgggattac tgacactttt caagctgtta aaacaactgc
22861 tgctaacggg gaccaaggca atactacctg gcaaaaagat tcaacatttg cagaacgcaa
22921 tgaaataggg gtgggaaata actttgccat ggaaattaac ctgaatgcca acctatggag
22981 aaatttcctt tactccaata ttgcgctgta cctgccagac aagctaaaat acaacccac
23041 caatgtggaa atatctgaca accccaacac ctacgactac atgaacaagc gagtgggtggc

```

FIG. 39A-7

WO 2006/020480

PCT/US2005/027658

116/126

```

23101 tcctgggctt gtagactgct acattaacct tggggcgcgcgc tgggtctctgg actacatgga
23161 caacgttaat ccctttaacc accaccgcaa tgcgggcctg cgttaccgct ccatgttggt
23221 gggaaacggc cgctacgtgc cctttcacat tcaggtgccc caaaagtttt ttgccattaa
23281 aaacctcctc ctctgccag gctcatacac atatgaatgg aacttcagga aggatgttaa
23341 catggttctg cagagctctc tgggaaacga ccttagagtt gacggggcta gcattaagtt
23401 tgacagcatt tgtctttacg ccaccttctt ccccatggcc cacaacacgg cctccacgct
23461 ggaagccatg ctcagaaatg acaccaacga ccagtccttt aatgactacc tttccgcccgc
23521 caacatgcta tatcccatat ccgccaacgc caccaacgtg cccatctcca tcccatcgcg
23581 caactgggca gcatttcgcg gttgggcctt cacacgcttg aagacaaagg aaacccttc
23641 cctgggatca ggctacgacc cttactacac ctactctggc tccataccat accttgacgg
23701 aaccttctat cttaatcaca cctttaagaa ggtggccatt acttttgact cttctgttag
23761 ctggccgggc aacgaccgcc tgcttactcc caatgagttt gagattaagc gctcagttga
23821 cggggagggc tataacgtag ctcagtgcaa catgacaaag gactggttcc tagtgcagat
23881 gttggccaac tacaatattg gctaccaggg cttctacatt ccagaaagct acaaagaccg
23941 catgtactcg ttcttcagaa acttcagacc catgagccgg caagtgggtg acgatactaa
24001 atacaaagat tatcagcagg ttggaattat ccaccagcat aacaactcag gcttcgtagg
24061 ctacctcgct cccaccatgc gcgagggaca agcttaccct gctaattgtc cctaccact
24121 aataggcaaa accgcggttg atagtattac ccagaaaaag tttctttgcg accgcacct
24181 gtggcgcatc cccttctcca gtaactttat gtccatgggt gcgctcacag acctgggcca
24241 aaaccttctc tacgcaaact ccgcccacgc gctagacatg acctttgagg tggatcccat
24301 ggacgagccc acccttcttt atgttttgtt tgaagtcttt gacgtggtcc gtgtgcacca
24361 gccgcaccgc ggcgtcacgc agaccgtgta cctgcgcacg cccttctcgg ccggcaacgc
24421 cacaacataa agaagcaagc aacatcaaca acagctgccg ccatgggctc cagtgcagag
24481 gaactgaaag ccattgtcaa agatcttggc tgtgggcccac attttttggg cacctatgac
24541 aagcgcttcc caggctttgt tccccacac aagctcgcct gcgccatagt taacacggcc
24601 ggtcgcgaga ctgggggcgt acactggatg gcctttgcct ggaaccgcgc ctcaaaaaca
24661 tgctacctct ttgagccctt tggcttttct gaccaacgtc tcaagcaggt ttaccagttt
24721 gagtacgagt cactcctgcg ccgtagcgcc attgcctctt ccccgaccg ctgtataacg
24781 ctggaaaagt ccacccaaag cgtgcagggg cccaactcgg ccgcctgtgg cctattctgc
24841 tgcatgtttc tccacgcctt tgccaactgg ccccaaactc ccatggatca caaccacc
24901 atgaacctta ttaccggggt acccaactcc atgcttaaca gtcccaggt acagcccacc
24961 ctgcgcccga accaggaaca gctctacagc ttcctggagc gccactcgcc ctacttccgc
25021 agccacagtg cgcaaattag gagcgccact tctttttgtc acttgaaaaa catgtaaaaa
25081 taatgtacta ggagacactt tcaataaagg caaatgtttt tatttgtaca ctctcgggtg
25141 attatttacc cccacccttg ccgtctgcgc cgtttaaaaa tcaaaggggt tctgccgcgc
25201 atcgctatgc gccactggca gggacacgtt gcgatactgg tgtttagtgc tccacttaaa
25261 ctcaggcaca accatccgcg gcagctcggt gaagttttca ctccacaggc tgcgcaccat
25321 caccaacgcg tttagcaggt cgggcgccga tatcttgaag tcgcagttgg ggcctccgcc
25381 ctgcgcgcgc gagttgcgat acacaggggt acagcactgg aacactatca gcgcgggtg
25441 gtgcacgctg gccagcacgc tcttgtcgga gatcagatcc gcgtccaggt cctccgcgtt
25501 gctcagggcg aacggagtca actttggtag ctgccttccc aaaaagggtg catgccagg
25561 ctttgagttg cactcgcacc gtagtggcat cagaaggtga ccgtgcccag tctgggcgtt
25621 aggatacagc gcctgcatga aagccttgat ctgcttaaaa gccacctgag cctttgcgcc
25681 ttcagagaag aacatgccgc aagacttgcc ggaaaactga ttggccggac aggcgcgctc
25741 atgcacgcag caccttgctg cggtgttgga gatctgcacc acatttcggc cccaccggtt
25801 cttcacgatc ttggccttgc tagactgctc cttcagcgcg cgctgcccgt tttcgctcgt
25861 cacatccatt tcaatcacgt gctccttatt tatcataatg ctcccgtgta gacacttaag
25921 ctgccttctg atctcagcgc agcggtgtag ccacaacgcg cagcccgtgg gctcgtgggtg
25981 cttgtaggtt acctctgcaa acgactgcag gtacgcctgc aggaatcgcc ccatcatcgt
26041 cacaaaggct ttgttgctgg tgaaggtcag ctgcaaccgc cggtgctcct cgtttagcca
26101 ggtcttgcac acggccgcca gagcttccac ttggtcaggc agtagcttga agtttgctt
26161 tagatcgtaa tccacgtggt acttgctcat caacgcgcgc gcagcctcca tgcccttctc
26221 ccacgcagac acgatcggca ggctcagcgg gtttatcacc gtgctttcac tttccgcttc
26281 actggactct tccttttctt cttgcatccg cataccccgc gccactgggt cgtcttcatt
26341 cagccgccgc accgtgcgct tacctccctt gccgtgcttg attagaccg gtgggttgct
26401 gaaaccacc atttgtagcg ccacatcttc tctttcttcc tcgctgtcca cgatcacctc

```

FIG. 39A-8

WO 2006/020480

PCT/US2005/027658

117/126

```

26461 tgggggatggc gggcgctcgg gcttgggaga ggggcgcttc tttttctttt tggacgcaat
26521 ggccaaatcc gccgtcgagg tcgatggccg cgggctgggt gtgcgcggca ccagcgcac
26581 ttgtgacgag tcttcttcgt cctcggactc gagacgccgc ctcagccgct tttttggggg
26641 cgcgcgggga ggcggcgggc acggcgacgg ggacgagacg tcctccatgg ttggtggacg
26701 tcgcgccgca ccgcgtccgc gctcgggggt ggtttcgcgc tgctcctctt cccgactggc
26761 catttccttc tcctataggc agaaaaagat catggagtca gtcgagaagg aggacagcct
26821 aaccgcccc tttgagttcg ccaccaccgc ctccaccgat gccgccaacg cgcctaccac
26881 cttecccgtc gaggcacccc cgcttgagga ggaggaagtg attatcgagc aggacccagg
26941 ttttgtaagc gaagacgacg aagatcgctc agtaccaaca gaggataaaa agcaagacca
27001 ggacgacgca gaggcaaacg aggaacaagt cgggcggggg gaccaaaggc atggcgacta
27061 cctagatgtg ggagacgacg tgctgttgaa gcatctgcag cgccagtgcg ccattatctg
27121 cgacgcgttg caagagcgca gcgatgtgcc cctcgccata gcggatgtca gccttgccca
27181 cgaacgccac ctgttctcac cgcgcgtacc ccccaaacgc caagaaaacg gcacatgcga
27241 gcccaaccgg cgcctcaact tctaccccggt atttgccgtg ccagagggtg ttgccaccta
27301 tcacatcttt ttccaaaact gcaagatacc cctatcctgc cgtgccaaac gcagccgagc
27361 ggacaagcag ctggccttgc ggcagggcgc tgcataacct gatatcgctt cgctcgacga
27421 agtgccaaaa atctttgagg gtcttgagac cgacgagaag cgcgcggcaa acgctctgca
27481 acaagaaaac agcgaaaatg aaagtcactg tggagtgtg gtggaacttg agggtgacaa
27541 cgcgcgccta gccgtgctga aacgcagcat cgaggtcacc cactttgcct acccggcact
27601 taacctacc cccaaggtta tgagcacagt catgagcgag ctgatcgtgc gccgtgcacg
27661 acccctggag agggatgcaa acttgcaaga acaaaccgag gagggcctac ccgcagttgg
27721 cgatgagcag ctggcgcgct ggcttgagac gcgcgagcct gccgacttgg aggagcgacg
27781 caagctaata atggccgcag tgcttggtac cgtggagctt gagtgcacgc agcggttctt
27841 tgctgaccgg gagatgcagc gcaagctaga ggaaacgttg cactacacct ttcgccaggg
27901 ctacgtgcgc caggcctgca aaatttccaa cgtggagctc tgcaacctgg tctcctacct
27961 tggaaatttg cacgaaaacc gccttgggca aaacgtgctt cattccacgc tcaagggcga
28021 ggcgcgccgc gactacgtcc gcgactgcgt ttacttattt ctgtgctaca cctggcaaac
28081 ggccatgggc gtgtggcagc agtgccctga ggagcgcaac ctgaaggagc tgcagaagct
28141 gctaaagcaa aacttgaagg acctatggac ggccttcaac gagcgctccg tggccgcgca
28201 cctggcgagc attatcttcc ccgaacgcct gcttaaaacc ctgcaacagg gtctgccaga
28261 cttcaccagt caaagcatgt tgcaaaactt taggaacttt atcctagagc gttcaggaat
28321 tctgcccggc acctgctgtg cgcttcctag cgactttgtg cccattaagt accgtgaatg
28381 ccctccggcg ctttgggggt actgctacct tctgcagcta gccaaactacc ttgcctacca
28441 ctccgacatc atggaagacg tgagcgggtg cggcctactg gagtgtcact gtcgctgcaa
28501 cctatgcacc ccgcaccgct ccctgggtctg caattcacaa ctgcttagcg aaagtcaaat
28561 tatcggtacc tttgagctgc agggctccct gcctgacgaa aagtcgcggg ctccgggggtt
28621 gaaactcact ccggggctgt ggacgtcggc ttaccttcgc aaatttgtac ctgaggacta
28681 ccacgcccac gagattaggt tctacgaaga ccaatccgcg ccgccaatg cggagcttac
28741 cgcctgcgtc attaccaggg gccacatcct tggccaattg caagccatta acaaagcccg
28801 ccaagagttt ctgctacgaa agggacgggg ggtttacttg gacccccagt ccggcgagga
28861 gctcaacca atcccccgcc cgccgcagcc ctatcagcag ccgcggggccc ttgcttccca
28921 ggatggcacc caaaaagaag ctgcagctgc cgccgcggcc acccacggac gaggaggaat
28981 actgggacag tcaggcagag gaggttttgg acgaggagga ggagatgatg gaagactggg
29041 acagcctaga cgaggaagct tccgaggccg aagagggtgc agacgaaaca ccgtcaccct
29101 cggtcgcatt cccctcgccg gcgccccaga aatcggaac cgttcccagc attgctacaa
29161 cctccgctcc tcaggcgccg ccggcactgc ccgttcgccc acccaaccgt agatgggaca
29221 ccaactggaac cagggccgggt aagtctaagc agccgcggcc gttagcccaa gagcaacaac
29281 agcgccaagg ctaccgctcg tggcgcgctg acaagaacgc catagttgct tgcttgcaag
29341 actgtggggg caacatctcc ttgcgccgcc gctttcttct ctaccatcac ggcgtggcct
29401 tccccgtaa catcctgcat tactaccgtc atctctacag cccctactgc accggcgggca
29461 gcggcagcaa cagcagcggc cacgcagaag caaaggcgac cggatagcaa gactctgaca
29521 aagcccaaga aatccacagc ggcggcagca gcaggaggag gagcactgcg tctggcgccc
29581 aacgaaccgg tatcgaccgg cgagcttaga aacaggatth ttcccactct gtatgctata
29641 tttcaacaga gcagggggcca agaacaagag ctgaaaataa aaaacaggtc tctgcgctcc
29701 ctaccccgca gctgcctgta tcacaaaagc gaagatcagc ttcggcgcac gctggaagac
29761 gcggaggctc tcttcagcaa atactgcgcg ctgactctta aggactagtt tcgcgcctt

```

FIG. 39A-9

WO 2006/020480

PCT/US2005/027658

118/126

29821 tctcaaattt aagcgcgaaa actacgtcat ctccagcggc cacacccggc gccagcacct
29881 gtcgtcagcg ccattatgag caaggaaatt cccacgccct acatgtggag ttaccagcca
29941 caaatgggac ttgcggctgg agctgcccaa gactactcaa cccgaataaa ctacatgagc
30001 gcgggacccc acatgatatc ccgggtcaac ggaatccgcg cccaccgaaa ccgaattctc
30061 ctcgaaacagg cggctattac caccacacct cgtaataacc ttaatccccg tagttggccc
30121 gctgccctgg tgtaccagga aagtcccgct cccaccactg tggtaacttc cagagacgcc
30181 caggccgaag ttcagatgac taactcaggg gcgcagcttg cgggcggcctt tcgtcacagg
30241 gtgcggtcgc ccgggcaggg tataactcac ctgaaaatca gagggcgagg tattcagctc
30301 aacgacgagt cggtgagctc ctctcttggg ctccgtccgg acgggacatt tcagatcggc
30361 ggcgctggcc gctcttcatt tacgccccgt caggcgatcc taactctgca gacctcgtcc
30421 tcggagccgc gctccggagg cattggaact ctacaattta ttgaggagtt cgtgccttcg
30481 gtttacttca accccttttc tggacctccc ggccactacc cggaccagtt tattcccaac
30541 tttgacgcgg taaaagactc ggcggacggc tacgactgaa tgaccagtgg agaggcagag
30601 caactgcgcc tgacacacct cgaccactgc cgccgccaca agtgctttgc ccgcggctcc
30661 ggtgagtttt gttactttga attgcccga gagcatatcg agggcccggc gcacggcgtc
30721 cggctcacca cccaggtaga gcttacacgt agcctgattc gggagtttac caagcgcccc
30781 ctgctagtgg agcgggagcg gggctccctgt gttctgaccg tggtttgcaa ctgtcctaac
30841 cctggattac atcaagatct tattccattc aactaacaat aaacacacaa taaattactt
30901 acttaaaatc agtcagcaaa tctttgtcca gcttattcag catcacctcc ttccctcct
30961 cccaactctg gtatttcagc agccttttag ctgcgaactt tctccaaagt ctaaattggga
31021 tgtcaaattc ctcatgttct tgtccctccg caccactat cttcatattg ttgcagatga
31081 aacgcgccag accgtctgaa gacaccttca accctgtgta cccatatgac acggaaaccg
31141 gccctccaac tgtgcctttc cttacccttc cctttgtgtc gccaaatggg ttccaagaaa
31201 gtcccccccg agtgctttct ttgcgtcttt cagaaccttt ggttacctca cacggcatgc
31261 ttgcgctaaa aatgggcagc ggcctgtccc tggatcaggg aggcaacctt acatcaaata
31321 caatcactgt ttctcaaccg ctaaaaaaaa caaagtccaa tataactttg gaaacatccg
31381 cgcccttac agtcagctca ggcgccctaa ccatggccac aacttcgcct ttgggtggtct
31441 ctgacaacac tcttaccatg caatcacaa gaccgctaac cgtgcaagac tcaaaactta
31501 gcattgctac caaagagcca cttacagtgt tagatggaaa actggccctg cagacatcag
31561 cccctctctc tgccactgat aacaacgccc tcactatcac tgccctacct cctcttacta
31621 ctgcaaattg tagtctggct gttaccatgg aaaaccact ttacaacaac aatggaaaac
31681 ttgggctcaa aattggcggg cctttgcaag tggeccaccga ctcacatgca ctaacactag
31741 gtactgggtca ggggggttgca gttcataaca atttgctaca tacaaaagtt acaggcgcaa
31801 tagggtttga tacatctggc aacatggaac ttaaaactgg agatggcctc tatgtggata
31861 gcgcgggtcc taaccaaaaa ctacatatta atctaaatac cacaaaaggc cttgcttttg
31921 acaacaccgc aataacaatt aacgctggaa aagggttgga atttgaaaca gactcctcaa
31981 acggaaatcc cataaaaaa aaaattggat caggcataca atataatacc aatggagcta
32041 tggttgcaaa acttggaaca ggcctcagtt ttgacagctc cggagccata acaatgggca
32101 gcataaacia tgacagactt actcttttga caacaccaga cccatcccca aattgcagaa
32161 ttgcttcaga taaagactgc aagctaactc tggcgctaac aaaatgtggc agtcaaattt
32221 tgggcaactg ttcagctttg gcagtatcag gtaatatggc ctccatcaat ggaactctaa
32281 gcagtgtaaa cttgggttctt agatttgatg acaacggagt gcttatgtca aattcatcac
32341 tggacaaaca gtattggaac tttagaaacg gggactccac taacgggtcaa ccatacactt
32401 atgctgttgg gtttatgcca aacctaaaag cttacccaaa aactcaaagt aaaactgcaa
32461 aaagtaatat tgtagccag gtgtatctta atggtgacaa gtctaaacca ttgcatttta
32521 ctattacgct aaatggaaca gatgaaacca accaagtaag caaatactca atatcattca
32581 gttggtcctg gaacagtga caatacacta atgacaaatt tgccaccaat tcctatacct
32641 tctcctacat tgcccaggaa taaagaatcg tgaacctgtt gcatgttatg tttcaacgtg
32701 tttatttttc aattgcagaa aatttcaagt catttttcat tcagtagtat agccccacca
32761 ccacatagct tatactaate accgtacctt aatcaaactc acagaaccct agtattcaac
32821 ctgccacctc cctcccaaca cacagagtac acagtccttt ctccccggct ggccttaaac
32881 agcatcatat catgggtaac agacatattc ttaggtgtta tattccacac ggtctcctgt
32941 cgagccaaac gctcatcagt gatgttaata aactccccgg gcagctcgct taagttcatg
33001 tcgctgtcca gctgctgagc cacaggctgc tgtccaactt gcggttgctc aacgggcggc
33061 gaaggagaag tccacgccta catgggggta gagtcataat cgtgcatcag gataggcgcg
33121 tgggtgctgca gcagcgcgcg aataaactgc tgccgcgcgc gctccgtcct gcaggaatac

FIG. 39A-10

119/126

33181 aacatggcag tgggtctctc agcgatgatt cgcaccgccc gcagcataag gcgccttgtc
33241 ctccgggcac agcagcgcac cctgatctca cttaagtcag cacagtaact gcagcacagt
33301 accacaatat tgtttaaaat cccacagtgc aaggcgctgt atccaaagct catggcgggg
33361 accacagaac ccacgtggcc atcataccac aagcgcaggt agattaagtg gcgaccctc
33421 ataaacacgc tggacataaa cattacctct tttggcatgt tgtaattcac cacctcccgg
33481 taccatataa acctctgatt aaacatggcg ccatccacca ccatcctaaa ccagctggcc
33541 aaaacctgcc cgccggctat gcactgcagg gaaccgggac tggaacaatg acagtggaga
33601 gcccaggact cgtaaccatg gatcatcatg ctcgatcatga tatcaatgtt ggcacaacac
33661 aggcacacgt gcatacactt cctcaggatt acaagctcct cccgcgtcag aaccatatcc
33721 cagggaacaa cccattcctg aatcagcgta aatcccacac tgcaggggaag acctcgcacg
33781 taactcacgt tgtgcattgt caaagtgtta cattcgggca gcagcggatg atcctccagt
33841 atggtagcgc gtgtctctgt ctcaaaagga ggtaggcgat ccctactgta cggagtgcgc
33901 cgagacaacc gagatcgtgt tggtcgtagt gtcatgccaa atggaacgcc ggacgtagt
33961 atatttcctg aagcaaaacc aggtgcgggc gtgacaaaaca gatctgcgtc tccggtctcg
34021 tcgcttagct cgctctgtgt agtagttgta gtatatccac tctctcaaag catccaggcg
34081 ccccctggct tcgggttcta tgtaaaactc ttcatgcgcc gctgccctga taacatccac
34141 caccgcagaa taagccacac ccagccaacc tacacattcg ttctgcgagt cacacacggg
34201 aggagcggga agagctggaa gaaccatgtt tttttttttt attccaaaag attatccaaa
34261 acctcaaaat gaagatctat taagtgaacg cgctcccctc cgggtggcgtg gtcaaactct
34321 acagccaaag aacagataat ggcattttgt agatgttgca caatggcttc caaaaggcaa
34381 actgccctca cgtccaagtg gacgtaaagg ctaaaccctt caggggtgaat ctcctctata
34441 aacattccag caccttcaac catgcccata taattttcat ctgcgccact tatcaatatg
34501 tctctaagca aatcccgaat attaagtccg gccattgtaa aaatctgctc cagagcgccc
34561 tccaccttca gcctcaagca gcgaatcatg attgcaaaaa ttcaggttcc tcacagacct
34621 gtataagatt caaaagcgga acattaacaa aaataccgcy atcccgtagg tcccttcgca
34681 gggccagctg aacataatcg tgcaggtctg cacgggaccag cgcggccact tccccgccag
34741 gaaccatgac aaaagaaccc acactgatta tgacacgcat actcggagct atgttaacca
34801 gcgtagcccc gatgtaagct tgttgcatgg gcggcgatat aaaatgcaag gtactgctca
34861 aaaaatcagg caaagcctcg cgcaaaaaag caagcacatc gtagtcatgc tcatgcagat
34921 aaaggcaggt aagttccgga accaccacag aaaaagacac catttttctc tcaaacatgt
34981 ctgcggggtc ctgcataaac acaaaataaa ataacaaaaa aaaaaaaaca tttaaacatt
35041 agaagcctgt cttacaacag gaaaaacaac ccttataagc ataagacgga ctacggccat
35101 gccggcgtga ccgtaaaaaa actggtcacc gtgattaaaa agcaccaccg acagttcctc
35161 ggtcatgtcc ggagtcataa tgtaagactc ggtaaacaca tcaggttggg taacatcggt
35221 cagtgcataa aagcgaccga aatagcccgg gggaatacat acccgagggc gtagagacaa
35281 cattacagcc cccataggag gtataacaaa attaatagga gagaaaaaca cataaacacc
35341 tgaaaaaccc tcctgcctag gcaaaatagc accctcccgc tccagaacaa catacagcgc
35401 ttccacagcg gcagccataa cagtcagcct taccagtaaa aaaacctatt aaaaaacacc
35461 actcgacacg gcaccagctc aatcagtcac agtgtaaaaa gggccaagta cagagcgagt
35521 atatatagga ctaaaaaatg acgtaacggg taaagtccac aaaaaccacc cagaaaaccg
35581 cagcgaacc tacgcccaga aacgaaagcc aaaaaacca caacttcctc aaatcttcac
35641 ttccgttttc ccacgatacg tcaactccca ttttaaaaaa aaactacaat tcccaataca
35701 tgcaagttac tccgccctaa aacctacgtc acccgccccg ttcccacgcc ccgcgccacg
35761 tcacaaactc caccctctca ttatcatatt ggcttcaatc caaaataagg tatattattg
35821 atgatg (SEQ ID NO: 22)

FIG. 39A-11

120/126

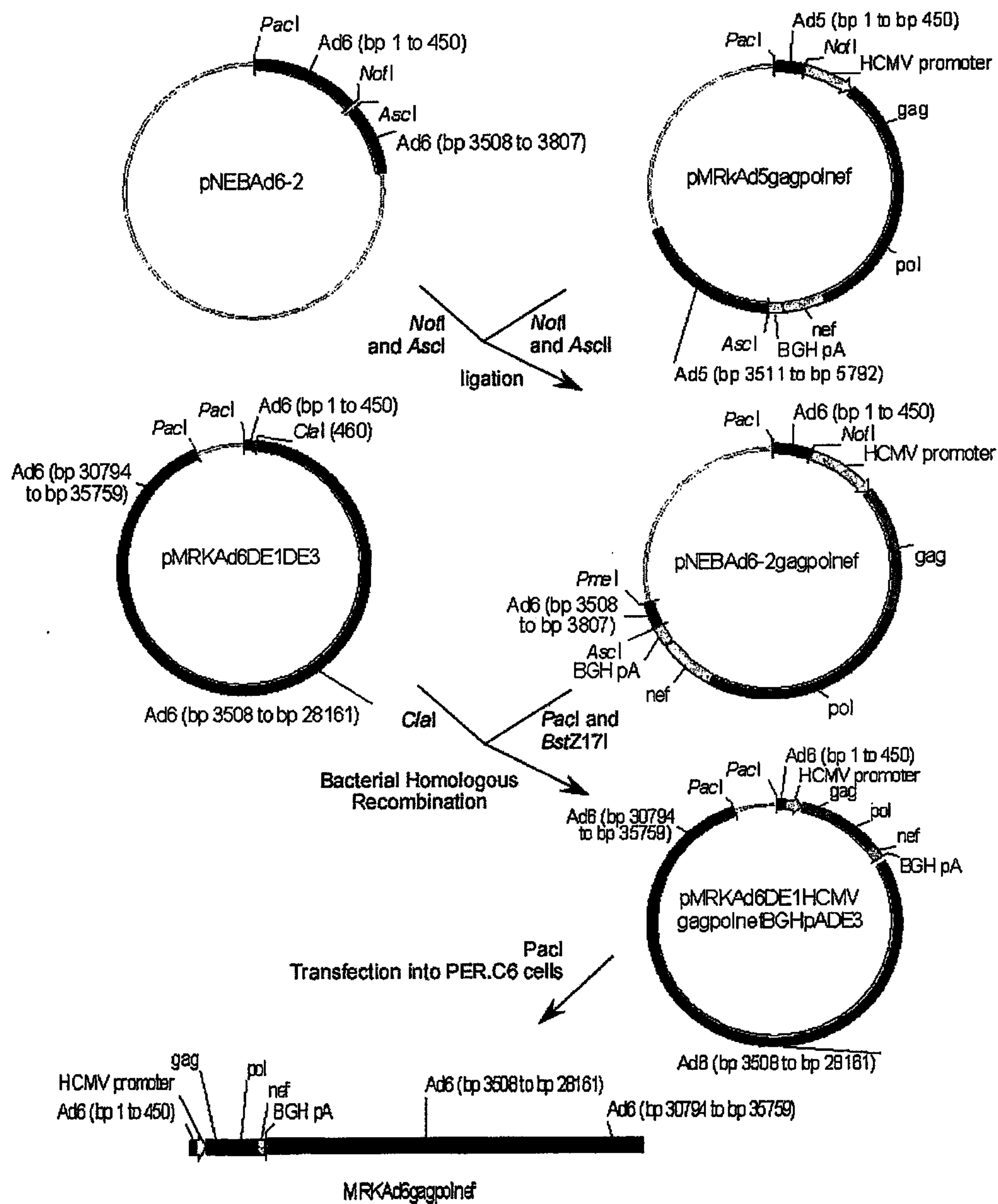


FIG. 40

WO 2006/020480

PCT/US2005/027658

121/126

Group	Animal ID	Pre Ad5 Neut	Vaccine (Wk 0, 4, 30)	Pre	Wk 4	Wk 8	Wk 30	Wk 34	Wk 38
1	037F 00F 99C027	4158 3504 2886	MRKAd5 HIV nef 10 ¹⁰ vp	0	1007	1138	876	688	1326
				4	955	703	515	1238	1298
				0	1029	1161	224	421	439
					997	975	466	710	911
2	00C008 00C017 00C167	nd nd nd	MRKAd5 HIV nef 10 ¹⁰ vp	1	158	334	116	473	883
				2	104	105	21	3	138
				4	584	1595	574	1508	2885
					212	382	112	121	705
3	020F 115F 114F	3297 >4808 3270	MRKAd5 HIV nef 10 ¹⁰ vp	0	137	45	83	70	289
				0	102	128	80	171	426
				0	278	233	148	1085	718
					157	110	99	235	445
4	00C026 00D259 00C039	nd nd nd	MRKAd5 HIV nef 10 ¹⁰ vp	4	575	388	78	1448	1320
				9	130	211	180	106	400
				2	378	148	58	50	94
					305	229	89	197	367
5	V229 99C042 99C044	3537 3322 >4608	MRKAd5 HIV nef + MRKAd5 HIV nef 5X10 ⁹ vp each	4	1644	1558	825	1455	1383
				1	1294	661	311	590	853
				0	1719	970	645	713	380
					1541	1000	549	849	765
6	00C141 00C093 00C175	nd nd nd	MRKAd5 HIV nef + MRKAd5 HIV nef 5X10 ⁹ vp each	5	558	363	183	299	505
				1	780	428	300	1201	1290
				0	658	468	90	953	738
					659	417	170	899	783

FIG. 41

WO 2006/020480

PCT/US2005/027658

122/126

Group	Vaccine Wk 0, 4	Monkey ID	Ad5 Neut titer, Pre	Wk 4		WK 8	
				Mock	Gag	Mock	Gag
1	MRKAd5 gag 10 ¹⁰ vp	98C099	279	4	374	16	693
		97X009	1320	1	173	4	138
		00C039	1948	4	123	1	174
		00C175	4129	3	21	6	161
		Geomean	1312		109		222
2	MRKAd5 gag MRKAd6 gag 10 ¹⁰ vp/vector	57G	804	6	306	0	295
		98C087	1132	9	846	28	426
		99C059	1210	14	340	36	1061
		97X008	3721	6	729	3	455
		Geomean	1423		493		483
3	MRKad5gag 10 ¹⁰ vp	00D257	<18	6	1164	26	740
		00D267	<18	6	1070	6	1215
		00D273	<18	8	1060	21	1056
		Geomean	<18		1090		963

FIG. 42

WO 2006/020480

PCT/US2005/027658

123/126

Vaccine Wk 0, 4	Monkey ID	Wk 4			Wk 8		
		Gag	Pol	Nef	Gag	Pol	Nef
MRKAd5gag + MKRAd5pol + MRKAd5nef each at 10^{10} vp	02D078	1276	1209	375	929	840	334
	02D240	624	243	161	529	213	251
	02D225	458	246	306	383	293	313
	02D249	1226	320	31	334	84	38
	Geomean	817	390	155	500	257	177
MRKAd5hCMVnef mCMVgag + MRKAd5pol each at 10^{10} vp	02D111	535	118	169	333	105	181
	02D116	666	410	1200	169	120	318
	02D119	459	363	200	321	410	494
	02D128	253	86	259	118	129	239
	Geomean	451	197	320	215	161	287
MRKAd5hCMVnef mCMVgagpol at 10^{10} vp	02D145	326	13	320	255	24	301
	02D217	375	90	151	349	134	270
	02D221	36	114	30	98	214	108
	02D228	850	350	660	439	180	602
	Geomean	248	82	176	248	105	269
MRKAd5hCMVgagpolnef at 10^{10} vp	02D177	1118	1189	418	954	771	361
	02D195	460	324	24	239	291	6
	02D201	234	153	75	263	165	103
	02D202	181	490	18	188	480	11
	Geomean	384	412	60	325	365	40

FIG. 43

WO 2006/020480

PCT/US2005/027658

124/126

Vaccine Wk 0, 4	Monkey ID	Wk 4			Wk 8		
		Gag	Pol	Nef	Gag	Pol	Nef
MRKAd5gag + MKRAd5pol + MRKAd5nef each at 10 ⁸ vp	02D094	278	206	178	285	226	219
	02D095	450	215	24	254	211	18
	02D251	303	53	144	240	86	176
	Geomean	336	133	85	259	160	88
MRKAd5hCMVnef mCMVgag + MRKAd5pol each at 10 ⁸ vp	02D132	682	578	338	471	428	371
	02D135	99	271	425	105	134	249
	02D143	33	69	30	30	50	20
	Geomean	130	221	163	114	142	123
MRKAd5hCMVnef mCMVgagpol at 10 ⁸ vp	02D166	16	35	96	41	106	158
	02D168	996	55	286	810	3	293
	02D172	93	24	195	93	41	304
	Geomean	114	36	175	146	22	241
MRKAd5hCMVgagpolnef at 10 ⁸ vp	02D236	134	14	1	74	3	1
	02D207	359	165	290	94	79	73
	02D211	159	270	23	64	161	8
	Geomean	197	85	20	76	32	8

FIG. 44

<u>Vaccine</u> <u>Wk 0, 4</u>	<u>Monkey</u> <u>ID</u>	<u>Wk 4</u>			<u>Wk 8</u>		
		<u>Gag</u>	<u>Pol</u>	<u>Nef</u>	<u>Gag</u>	<u>Pol</u>	<u>Nef</u>
MRKAd5nefgagpol 10 [^] 10 vp	01D450	613	970	85	344	889	233
	02D120	428	573	61	93	164	96
	02D124	1036	264	494	353	125	385
	Geomean	647	527	137	224	263	205
MRKAd6nefgagpol 10 [^] 10 vp	02D163	88	125	33	39	65	25
	02D248	471	953	118	126	143	63
	02D183	630	333	25	123	110	43
	Geomean	296	341	46	84	101	40
MRKAd5nefgagpol+MRKAd6nefgagpol each at 10 [^] 10 vp	02D197	669	1574	356	371	1146	859
	02D208	239	126	416	170	193	556
	02D210	255	21	126	115	31	73
	Geomean	344	162	266	194	190	326

FIG. 45

126/126

Vaccine	Monkey ID	Wk 4			Wk 8		
Wk 0, 4		Gag	Pol	Nef	Gag	Pol	Nef
MRKAd5nefgagpol 10^8 vp	02D147	19	41	274	69	55	366
	02D149	168	29	33	50	24	41
	02D151	19	119	55	31	125	38
	Geomean	39	52	79	48	55	83
MRKAd6nefgagpol 10^8 vp	02D186	33	79	160	28	46	111
	02D193	1	1	58	8	31	154
	02D196	46	46	90	43	39	134
	Geomean	11	17	94	21	38	132
MRKAd5nefgagpol+MRKAd6nefgagpol each at 10^8 vp	02D216	18	503	691	5	95	110
	02D230	3	39	248	15	109	701
	02D238	19	21	96	33	34	103
	Geomean	9	75	254	13	70	199

FIG. 46