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(54) Title :
HIV envelope polypeptides and vaccine.

(57) Abstract :

Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

(56) Documents Cited : **WO 94 28929 A**

HIV ENVELOPE POLYPEPTIDES AND VACCINE

BACKGROUND OF THE INVENTION5 Field of the Invention

This invention relates to HIV envelope polypeptides and vaccines containing the polypeptides.

Description of the Related Art

10 Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus identified as the human immunodeficiency virus (HIV). There have been intense efforts to develop a vaccine that induces a protective
15 immune response based on induction of antibodies or cellular responses. Recent efforts have used subunit vaccines where an HIV protein, rather than attenuated or killed virus, is used as the immunogen in the vaccine for safety reasons. Subunit vaccines generally include gp120, the portion of the HIV envelope protein
20 which is on the surface of the virus.

The HIV envelope protein has been extensively described, and the amino acid and nucleic acid sequences encoding HIV envelope from a number of HIV strains are known (Myers, G. et al., 1992. Human
25 Retroviruses and AIDS. A compilation and analysis of nucleic acid and amino acid sequences. Los Alamos National Laboratory, Los Alamos, New Mexico). The HIV envelope protein is a glycoprotein of about 160 kd (gp160) which is anchored in the membrane bilayer at
30 its carboxyl terminal region. The N-terminal segment, gp120, protrudes into the aqueous environment surrounding the virion and the C-terminal segment, gp41, spans the membrane. Via a host-cell mediated process, gp160 is cleaved to form gp120 and the
35 integral membrane protein gp41. As there is no covalent attachment between gp120 and gp41, free gp120 is sometimes released from the surface of virions and

AP/P/99/01432

infected cells.

The gp120 molecule consists of a polypeptide core of 60,000 daltons which is extensively modified by N-linked glycosylation to increase the apparent molecular weight of the molecule to 120,000 daltons. The amino acid sequence of gp120 contains five relatively conserved domains interspersed with five hypervariable domains. The positions of the 18 cysteine residues in the gp120 primary sequence, and the positions of 13 of the approximately 24 N-linked glycosylation sites in the gp120 sequence are common to all gp120 sequences. The hypervariable domains contain extensive amino acid substitutions, insertions and deletions. Sequence variations in these domains result in up to 30% overall sequence variability between gp120 molecules from the various viral isolates. Despite this variation, all gp120 sequences preserve the ability of the virus to bind to the viral receptor CD4 and to interact with gp41 to induce fusion of the viral and host cell membranes.

gp120 has been the object of intensive investigation as a vaccine candidate for subunit vaccines, as the viral protein which is most likely to be accessible to immune attack. At present, clinical trials using gp120 MN strain are underway. However, to date no human vaccine trial has been of sufficient size to confirm or refute vaccine efficacy.

The development of candidate HIV-1 vaccines is burdened by the lack of in vivo or in vitro models of HIV-1 infection that accurately approximate the conditions of natural infection in humans. Several candidate HIV-1 vaccines [Berman et al.; *J. Virol.* 7:4464-9 (1992); Haigwood et al.; *J. Virol.* 66:172-82 (1992); Salmon-Ceron et al.; *AIDS Res. and Human Retroviruses* 11:1479-86 (1995)] have been described that elicit broadly cross-reactive antibodies able to

neutralize a variety of diverse HIV-1 isolates in vitro. However, the relevance of in vitro assays to protective immunity in vivo is uncertain. Although several vaccines have provided chimpanzees with protection from challenge by homologous and heterologous strains of HIV-1, protection has not always correlated with in vitro neutralization assays carried out in T cell lines, or in lectin- and cytokine-activated peripheral blood mononuclear cells (PBMCs) [Berman et al.; *Nature* 345:622-5 (1990); Bruck et al.; *Vaccine* 12(12):1141-8 (1994); El-Amad et al.; *AIDS* 9:1313-22 (1995); Girard et al.; *J. Virol.* 69:6239-48 (1995); and Fulz et al; *Science* 256:1687-1690 (1992)]. While successful protection of chimpanzees is encouraging and has historically proved to be a reliable indicator of vaccine efficacy, the conditions of infection in all experimental models of HIV-1 infection differ significantly from natural infection in humans.

Experimental HIV-1 infection in vivo and in vitro both suffer from the limitation that the in vitro amplification of HIV-1, which is required to prepare virus stocks for in vitro or in vivo infectivity experiments, imposes a genetic selection that results in a spectrum of virus quasi-species that differ from the spectrum of variants present in the clinical specimens used to establish the culture [Kusumi et al.; *J. Virol.* 66:875 (1992); Meyerhans et al.; *Cell* 58:901-10 (1989)]. Because of these uncertainties, and even greater uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available in vitro or in vivo assays to reliably predict vaccine efficacy is questionable.

One of the candidate HIV-1 vaccines that have

entered human clinical trials is recombinant gp120
 prepared in Chinese hamster ovary (CHO) cells from the
 MN strain of HIV-1 (MN-rgp120) (Berman et al.;
 J. Virol. 7:4464-9 (1992)). To date, approximately 499
 5 adults have participated in Phase 1 and 2
 immunogenicity and safety trials of this vaccine. The
 data collected thus far suggest that MN-rgp120 is safe,
 immunogenic, and elicits high titers of neutralizing
 antibodies in greater than 95% of individuals immunized
 10 according to a 0, 1, and 6 month immunization schedule
 [Belshe et al.; JAMA 272(6):475-80 (1994); McElrath;
 Seminars in Cancer Biol. 6:1-11 (1995)]. However,
 during the course of these trials, nine vaccinees who
 received MN-rgp120 have become infected with HIV-1
 15 through high risk behavior. Small trials, such as
 these, in populations with low rates of infection and
 minimally sized placebo control groups do not have
 sufficient statistical power to confirm or refute
 vaccine efficacy.

20 However, effective vaccines based on gp120 or
 another HIV protein for protection against additional
 strains of HIV are still being sought to prevent the
 spread of this disease.

25 Description of the Background Art

Recombinant subunit vaccines are described in
 Berman et al., PCT/US91/02250 (published as number
 WO91/15238 on 17 October 1991). See also, e.g.
 Hu et al., Nature 328:721-724 (1987) (vaccinia virus-
 30 HIV envelope recombinant vaccine); Arthur et al.,
 J. Virol. 63(12): 5046-5053 (1989) (purified gp120);
 and Berman et al., Proc. Natl. Acad. Sci. USA
 85:5200-5204 (1988) (recombinant envelope glycoprotein
 gp120).

35 Numerous sequences for gp120 are known. The
 sequence of gp120 from the IIIB substrain of HIV-1_{LAJ}

referred to herein is that determined by Muesing et al., "Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus, *Nature* 313:450-458 (1985). The sequences of gp120 from the NY-5, Jrcsf, Z6, Z321, and HXB2 strains of HIV-1 are listed by Myers et al., "Human Retroviruses and AIDS; A compilation and analysis of nucleic acid and amino acid sequences," Los Alamos National Laboratory, Los Alamos, New Mexico (1992). The sequence of the Thai isolate A244 is provided by McCutchan et al., "Genetic Variants of HIV-1 in Thailand," *AIDS Res. and Human Retroviruses* 8:1887-1895 (1992). The MN₁₉₈₄ clone is described by Gurgo et al., "Envelope sequences of two new United States HIV-1 isolates," *Virology* 164: 531-536 (1988). As used herein, MN, MN-rgp120, the MN clone or isolate refers to MN_{GNE}. The MN_{GNE} amino acid sequence is Sequence ID No. 29.

Each of the above-described references is incorporated herein by reference in its entirety.

Summary of the Invention

Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

Brief Description of the Drawings

Figure 1 illustrates the kinetics of antibody response to MN-rgp120 in vaccinees infected with HIV-1.

AP/P/99/01432

Sera were collected at the time points indicated and assayed for antibodies reactive with MN-rgp120 (open circles) or a synthetic peptide derived from the V3 domain of MN-rgp120 (closed circles). Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7, panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

Figure 2 illustrates the kinetics of CD4 blocking antibody response in vaccinees infected with HIV-1. Sera were collected at the time points indicated and assayed for antibodies able to block the binding of [¹²⁵I]-labeled MN-rgp120 to cell surface CD4. Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7, panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

Figure 3 illustrated predicted amino acid sequences of envelope glycoproteins (gp120) from breakthrough viruses. Proviral DNA sequences were amplified by PCR from PBMCs and cloned into the PRK5 expression plasmid. Two clones from each infected vaccinee were sequenced from double stranded plasmid DNA. Sequence numbering is with reference to the initiator methionine residue of gp120. For the purpose of comparison, the sequences shown begin at amino acid 12 of the mature, fully processed, envelope glycoproteins (corresponding to position 41 of the gp120 open reading frame). Shaded areas indicate sequences at neutralizing epitopes, dark boxes indicate polymorphisms thought to be important for the binding of virus neutralizing MAb reactive with MN-rgp120.

Conserved (C) regions and variable (V) regions are indicated above the sequences. Boxes indicate sequence homologies and polymorphisms.

Figure 4 illustrates immunoprecipitation of recombinant gp120 prepared from breakthrough viruses. Recombinant gp120s from the seven breakthrough viruses were prepared by transient transfection of 293s cells. Cells were metabolically labeled with ³⁵S methionine and growth conditioned cell culture supernatants were immunoprecipitated with polyclonal antisera to MN-rgp120. Immunoprecipitates were resolved by SDS-PAGE and visualized by autoradiography. C8 lanes a and b correspond to clones C8.3 and C8.6; C6 lanes a and b correspond to clones C6.1 and C6.5; C7 lanes a and b correspond to clones C7.2 and C7.10; C17 lanes a and b correspond to C17.1 and C17.3; C11 lanes a and b correspond to clones C11.5 and C11.7; C10 lanes a and b correspond to clones C10.5 and C10.7; C15 lanes a and b correspond to clones C15.2 and C15.3.

Figure 5 illustrates binding of monoclonal antibodies to recombinant gp120 from breakthrough viruses. Growth-conditioned cell culture supernatants were collected from 293s cells transiently transfected with plasmids directing the expression of breakthrough virus envelope glycoproteins. The relative rgp120 concentrations were determined by ELISA using MAb 5B6 specific for the HSV-1 glycoprotein D flag epitope at the amino terminus of all of the rgp120 variants described herein. The resulting rgp120 preparations were captured onto wells of microtiter plates coated with a polyclonal antibody specific for a conserved sequence in the C-terminus of gp120. The binding of virus neutralizing monoclonal antibodies reactive with gp120 was determined by ELISA. A, binding by MAb (5B6) specific for the HSV-1 glycoprotein D flag epitope; B, binding by MAb (1034) against the V3 domain of

AP/P/99/01432

MN-rgp120; C binding by MAb (50.1) raised against a synthetic peptide corresponding to the V3 domain of MN-rgp120; D, binding by a human MAb (15e) known to block the binding of gp120 to CD4.

5 Figure 6 depicts the mature envelope glycoprotein (gp120) from the MN clone of the MN strain of HIV-1 (SEQ. ID. NO. 29). Hypervariable domains are indicated in bold, and the V and C regions are indicated (according to Modrow et al., *J. Virology* 61(2):570
10 (1987). Potential glycosylation sites are marked with a (*).

Detailed Description of the Invention

15 The present invention provides gp120 polypeptides from breakthrough isolates of HIV vaccine trials. Novel oligonucleotide sequences encoding gp120 from breakthrough isolates which can be used to express gp120 are also provided. Use of gp120 polypeptides from one or more of the isolates in a subunit vaccine,
20 usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains.

25 In one embodiment, the vaccine is based on the use of the MN-rgp120 polypeptide (Sequence ID No. 29) and gp120 polypeptides from MN-like viruses that include neutralizing epitopes that are not present in the initial vaccine strain, and are sufficiently different
30 from those of the vaccine strain, to have been able to cause HIV-1 infections in MN-rgp120 vaccinated individuals (i.e.; to result in breakthrough infections). Use of the initial vaccine strain empirically determines the viruses present in the
35 population that contain additional neutralizing epitopes sufficiently different from those of the

vaccine strain to escape protection induced by the vaccine strain. Use of an initial representative gp120 polypeptide in a vaccine acts as a sieve so that viruses that are not effectively protected against by the vaccine strain breakthrough the vaccine, empirically resulting in determination of additional strains in a given geographic region that are not protected against by the initial vaccine strain. Use of gp120 from those breakthrough isolates complements the vaccine isolate by providing additional neutralizing epitopes not present in the initial vaccine strain, therefore creating a more complete vaccine that confers protection against multiple different virus strains in the region.

Prior HIV-1 vaccine strategies were based on selection of appropriate candidate vaccine polypeptides based on homology alignment studies. However, since some of the neutralizing epitopes are conformation-dependent and the location of all of these epitopes is not known, this approach necessarily cannot determine all of the neutralizing epitopes that should be included in a vaccine for a particular region. In contrast, the present approach uses a selected representative strain and empirically determines strains that are sufficiently different and therefore breakthrough the barrier of protection provided by the initial vaccination program. Those strains can be included in the vaccine to confer more complete protection from HIV strains in the region. In addition, those strains can be used alone to confer protection against the breakthrough virus.

In another embodiment, the invention comprises a vaccine containing a first HIV gp120 polypeptide sequence and a breakthrough isolate HIV gp120 polypeptide sequence from a vaccinee vaccinated with a vaccine including the first HIV gp120 polypeptide

AP/P/99/01432

sequence, the HIV gp120 polypeptide sequences being in a suitable carrier. Fragments of one or both HIV gp120 polypeptide sequences can be substituted for one or both of the corresponding HIV gp120 polypeptide sequences.

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Preferably, the first gp120 polypeptide sequence contains neutralizing epitopes found in one or more gp120 polypeptides present in isolates from the geographical region where the initial vaccine (i.e., the vaccine that gives rise to the breakthrough isolate) is administered. More preferably, the first gp120 polypeptide sequence contains at least one of the more common neutralizing epitopes for the region, and most preferably the first gp120 polypeptide sequence contains at least one of the three most common neutralizing epitopes.

gp120 polypeptide sequences suitable for use as the first gp120 polypeptide sequence include gp120 MN, the Thai isolate A244 sequence (hereinafter "gp120 A244"), gp120 MN-GNE6 (Sequence ID No. 31; also known in the art as "gp120 GNE6"), and gp120 MN-GNE8 (Sequence ID No. 33; also known in the art as "gp120 GNE8"), and the like. gp120 MN, gp120 MN-GNE6, and gp120 MN-GNE8 are especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for North America. gp120 A244 is especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for Thailand.

In a variation of this embodiment, the vaccine includes two different (i.e., first and second) gp120 polypeptide sequences, or fragments thereof, in combination with a breakthrough isolate HIV gp120 polypeptide sequence. The latter can be from a vaccinee vaccinated with either or both of the first and second HIV gp120 polypeptide sequences.

Exemplary vaccines include those containing

combinations of gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), and gp120 MN-GNE8 (Sequence ID No. 33). Combinations of gp120 MN and gp120 A244 or gp120 MN-GNE8 (Sequence ID No. 33) with a breakthrough isolate HIV gp120 polypeptide sequence are especially preferred.

In vaccines containing gp120 MN, the breakthrough isolate HIV gp120 polypeptide sequence can be an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

The term "subunit vaccine" is used herein, as in the art, to refer to a viral vaccine that does not contain virus, but rather contains one or more viral proteins or fragments of viral proteins. As used herein, the term "multivalent", means that the vaccine contains gp120 from at least two HIV isolates having different amino acid sequences.

The term "breakthrough isolate" or "breakthrough virus" is used herein, as in the art, to refer to a virus isolated from a vaccinee.

The terms "amino acid sequence", "polypeptide sequence", and "polypeptide" are used interchangeably herein as in the art, as are the terms "nucleic acid sequence", "nucleotide sequence", and "oligonucleotide".

Polypeptides from Breakthrough Isolates

The gp120 polypeptides of this invention correspond to the amino acid sequences of seven breakthrough isolates which are illustrated below in Table 1. A polypeptide of this invention includes an HIV gp120 amino acid sequence illustrated in Table 1 (Sequence ID Nos. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27) and fragments thereof. The polypeptides of this invention can include fused

AP/P/99/01432

sequences from two or more HIV gp120 or gp160 amino acid sequences.

The polypeptide can also be joined to another viral protein, such as a flag epitope amino acid sequence. The term "flag epitope" is used herein, as in the art, to denote an amino acid sequence that includes an epitope recognized by a monoclonal antibody. Flag epitopes facilitate using single monoclonal antibody affinity purification of a plurality of different recombinant proteins, each having the flag epitope recognized by the monoclonal antibody. Numerous amino acid sequences can function as flag epitopes. The N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is conveniently used as the flag epitope and its use is described in detail in the examples. The flag epitope is conveniently fused to the N terminus of the HIV gp120 polypeptide sequence. Alternatively, however, monoclonal antibodies that recognize neutralizing epitopes in the rgp120 sequences can be used to affinity purify the amino acid sequences, and a flag epitope can be omitted.

In addition, various signal sequences can be joined to a polypeptide of this invention. Although rgp120 is secreted to some extent in HIV cultures, the amount of the envelope glycoprotein released from (secreted by) the host cells varies widely from strain to strain. Various signal sequences can be introduced into the polypeptide by joining a nucleotide sequence encoding the signal sequence to the nucleotide sequence encoding the rgp120 to facilitate secretion of rgp120 from the cells. For example, Chiron HIV gp120 polypeptides include a signal sequence from tissue plasminogen activator (TPA) that provides good secretion of rgp120. Additional signal sequences are well known and include the N-terminal domain of murine

APC 01282

leukemia virus surface protein gp70 described by Kayman et al., *J. Virol.* 68:400-410 (1984).

Table 1 illustrates the nucleotide and deduced amino acid sequences for two clones of each the seven
5 breakthrough isolates of this invention. The clones are: C6.1; C6.5; C8.3; C8.6; C15.2; C15.3; C7.2; C7.10; C11.5; C11.7; C10.5; C10.7; C17.1; and C17.3. These sequences are SEQ. ID. NOS. 1-28, the first
10 sequence number for each clone being the nucleotide sequence and the second being the amino acid sequence. The amino acid sequence for MN and the nucleotide and deduced amino acid sequences for MN-GNE6 and MN-GNE8 are illustrated in the sequence listing hereinafter. In the listing for MN-GNE6, a stop codon appears at
15 amino acid residue position 51. This stop codon can be replaced with a codon encoding the corresponding amino acid from MN or MN-GNE8 or another isolate.

AP/F/99/01432

CLONE C6.1

AP/P/99/01432

AP001282

	AAT GCT AAA ATC ATA ATA GTA CAG TTG AGG GAA CCT GTA	816
	Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu Pro Val	
	260 265 270	
5	GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA	855
	Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys	
	275 280 285	
	GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA	894
	Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr	
	290 295	
10	GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC	933
	Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn	
	300 305 310	
	ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA	972
	Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val	
	315 320	
15	GTT AAA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA	1011
	Val Lys Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile	
	325 330 335	
20	GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA	1050
	Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val	
	340 345 350	
	ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT	1089
	Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys	
	355 360	
25	AAT ACA ACA AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT	1128
	Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr	
	365 370 375	
	ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA	1167
	Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro	
	380 385	
30	TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA ATA	1206
	Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile	
	390 395 400	
35	GGA AAA GCA ATG TAT GCC CCT CCC ACC AGA GGA GAA ATT	1245
	Gly Lys Ala Met Tyr Ala Pro Thr Arg Gly Glu Ile	
	405 410 415	
	AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ATA AGA	1284
	Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Ile Arg	
	420 425	
40	GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC	1323
	Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe	
	430 435 440	
	AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT	1362
	Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser	
	445 450	
45	GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA	1401
	Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu	
	455 460 465	
	GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG	1440
	Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln	
	470 475 480	
50	AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT	1479
	Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu	
	485 490	
55	GGG TTC TTA GGA GCA TAA AGC TTC	1503
	Gly Phe Leu Gly Ala Xaa Ser Phe	
	495 500 501	
	<u>CLONE C6.5</u>	
60	GGG GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA	36
	Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu	
	1 5 10	
	TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG	75
	Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val	
65	15 20 25	

AP/P/99/01432

	CAT	AAT	GTT	TGG	GCC	ACA	CAT	GCT	TGT	GTA	CCC	ACA	GAC	114
	His	Asn	Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	
					30					35				
5	CCA	AAC	CCA	CAA	GAA	ATG	GTA	TTG	GAA	AAT	GTG	ACA	GAA	153
	Pro	Asn	Pro	Gln	Glu	Met	Val	Leu	Glu	Asn	Val	Thr	Glu	
		40				45					50			
	GAT	TTT	AAC	ATG	TGG	AAA	AAT	CAC	ATG	GTA	GAA	CAG	ATG	192
	Asp	Phe	Asn	Met	Trp	Lys	Asn	Asp	Met	Val	Glu	Gln	Met	
				55					60					
10	CAT	GAG	ANT	ATA	ATC	AGT	TTA	TGG	GAT	CAA	AGC	CTA	AAA	231
	His	Glu	Xaa	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	
		65				70					75			
	CCA	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	ATT	ACT	TTA	AAT	270
	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Ile	Thr	Leu	Asn	
15			80					85				90		
	TGC	ACC	AAT	TGG	AAG	GAG	AAT	GAT	ACT	AAA	ACT	AAT	AGT	309
	Cys	Thr	Asn	Trp	Lys	Glu	Asn	Asp	Thr	Lys	Thr	Asn	Ser	
				95					100					
20	AGT	AGT	ACT	ACA	ACT	AAT	AAT	AGT	AGT	GCT	ACA	GCT	AAT	348
	Ser	Ser	Thr	Thr	Thr	Asn	Asn	Ser	Ser	Ala	Thr	Ala	Asn	
		105				110					115			
	AGT	AGT	AGT	ACT	ACA	ACT	AAT	AGT	AGT	TGG	GGA	GAG	ATA	387
	Ser	Ser	Ser	Thr	Thr	Asn	Ser	Ser	Trp	Gly	Glu	Ile		
				120					125					
25	AAG	GAG	GGA	GAA	ATA	AAG	AAC	TGC	TCT	TTC	AAT	ATC	ACC	426
	Lys	Glu	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	
		130				135					140			
	ACA	GGC	ATA	AGA	GAC	AAG	GTC	AAG	AAA	GAA	TAT	GCA	CTT	465
	Thr	Gly	Ile	Arg	Asp	Lys	Val	Lys	Lys	Glu	Tyr	Ala	Leu	
30								150				155		
	TTT	TAT	AGC	CTT	GAT	GTA	GTA	CCA	ATA	GAA	AAT	GAT	AAT	504
	Phe	Tyr	Ser	Leu	Asp	Val	Val	Pro	Ile	Glu	Asn	Asp	Asn	
					160					165				
35	ACT	AGC	TAT	AGG	TTG	AGA	ACT	TGT	AAC	ACC	TCA	GTC	ATT	543
	Thr	Ser	Tyr	Arg	Leu	Arg	Ser	Cys	Asn	Thr	Ser	Val	Ile	
		170					175				180			
	ACA	CAA	GCC	TGT	CCA	AAG	GTA	ACT	TTT	GAG	CCA	ATT	CCC	582
	Thr	Gln	Ala	Cys	Pro	Lys	Val	Thr	Phe	Glu	Pro	Ile	Pro	
				185					190					
40	ATA	CAT	TAT	TGT	ACC	CCG	GCT	GGT	TTT	GCG	ATT	CTG	AAG	621
	Ile	His	Tyr	Cys	Thr	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	
		195				200				205				
	TGT	AAA	GAT	AAA	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGC	AAA	660
	Cys	Lys	Asp	Lys	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	
45			210					215				220		
	AAT	GTT	AGC	ACA	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AAG	CCA	699
	Asn	Val	Ser	Thr	Val	Gln	Cys	Thr	His	Gly	Ile	Lys	Pro	
				225					230					
50	GTA	GTG	TCA	ACT	CAA	CTG	CTG	TTA	AAT	GGC	AGC	CTA	GCA	738
	Val	Val	Ser	Thr	Gln	Leu	Leu	Asn	Gly	Ser	Leu	Ala		
		235				240					245			
	GAA	GAA	GAG	GTA	ATA	ATT	AGA	TCT	GCC	AAT	TTC	TCA	AAC	777
	Glu	Glu	Glu	Val	Ile	Ile	Arg	Ser	Ala	Asn	Phe	Ser	Asn	
				250					255					
55	AAT	GCT	AAA	ATC	ATA	ATA	GTA	CAG	TTG	AAG	GAA	CCT	GTA	816
	Asn	Ala	Lys	Ile	Ile	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val	
		260				265					27			
	GAA	ATT	AAT	TGT	ACA	AGA	CCC	AGC	AAC	AAT	ACA	ATA	AAA	855
	Glu	Ile	Asn	Cys	Thr	Arg	Pro	Ser	Asn	Asn	Thr	Ile	Lys	
60			275					280				285		
	GGT	ATA	CAC	ATA	GGA	CCA	GGG	AGA	GCA	TTT	TAT	GCA	ACA	894
	Gly	Ile	His	Ile	Gly	Pro	Gly	Arg	Ala	Phe	Tyr	Ala	Thr	
				290					295					

AP/P/99/01432

APC 01282

5 GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
 Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
 300 305 310
 ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
 Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
 315 320
 10 GTT ATA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
 Val Ile Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
 325 330 335
 GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
 Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
 340 345 350
 15 ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
 Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
 355 360
 AAT ACA ACG AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
 Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
 365 370 375
 20 ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
 Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
 380 385
 TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA 1206
 Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val
 390 395 400
 25 GGA AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA GAA ATT 1245
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile
 405 410 415
 AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ACA AGA 1284
 Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Thr Arg
 420 425
 30 GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
 Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
 430 435 440
 AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
 Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
 445 450
 GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
 Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
 455 460 465
 40 GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
 Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
 470 475 480
 AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
 Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
 485 490
 45 GGG TTC TTG GGA GCA TAA AGC TTC 1503
 Gly Phe Leu Gly Ala Xaa Ser Phe
 495 500 501
 50 CLONE C8.3
 G GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
 Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
 1 5 10
 TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
 Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
 15 20 25
 AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
 30 35
 60 AAC CCA CAA GAA GTA TTG GAA AAT GTA ACA GAA AAT 154
 Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
 40 45 50
 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
 Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
 55 60

AP/P/99/01432

	GAG	GAT	ATA	ATC	AGT	TTA	TCG	GAT	CAA	AGT	CTA	AAG	CCA	232
	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	Pro	
	85					70					75			
5	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACT	TTA	AAT	TGC	271
	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys	
			80					85					90	
	ACT	AAT	TTG	GAG	AAT	GCT	AAT	AAT	ACC	GAG	AAT	GCT	AAT	310
	Thr	Asn	Leu	Glu	Asn	Ala	Asn	Asn	Thr	Glu	Asn	Ala	Asn	
					95					100				
10	AAT	ACC	AAT	AAT	TAT	ACC	TTG	GGG	ATG	GAG	AGA	GGT	GAA	349
	Asn	Thr	Asn	Asn	Tyr	Thr	Leu	Gly	Met	Glu	Arg	Gly	Glu	
	105					110						115		
	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	AGC	TTA	AGA	388
	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Leu	Arg	
15				120				125						
	GAT	AAG	GTG	AAA	AAA	GAA	TAT	GCA	TTG	TTT	TAT	AAA	CTT	427
	Asp	Lys	Val	Lys	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu	
	130					135					140			
20	GAT	GTA	GTA	CAA	ATA	GAT	AAT	AGT	ACC	AAC	TAT	AGG	CTG	466
	Asp	Val	Val	Gln	Ile	Asp	Asn	Ser	Thr	Asn	Tyr	Arg	Leu	
			145					150					155	
	ATA	AGT	TGT	AAT	ACC	TCA	GTC	ATT	ACA	CAG	GCC	TGT	CCA	505
	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	Pro	
				160						165				
25	AAG	GTA	TCC	TTT	GAG	CTA	ATT	CCC	ATA	CAT	TAT	TGT	GCC	544
	Lys	Val	Ser	Phe	Glu	Leu	Ile	Pro	Ile	His	Tyr	Cys	Ala	
	170					175						180		
	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TCT	AAA	GAT	AAG	AAG	583
	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Lys	Asp	Lys	Lys	
30				185				190						
	TTC	AAT	GGA	ACA	GGA	CCA	TGT	AAA	AAT	GTC	AGC	ACA	GTA	622
	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	Val	
	195					200					205			
35	CAA	TGT	ACA	CAT	GGA	ATT	AGA	CCA	GTA	GTA	TCA	ACT	CAA	661
	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	
			210					215					220	
	CTA	CTG	TTA	AAT	GCC	AGT	CTA	GCA	GAA	GAA	GAG	ATA	GTA	700
	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Ile	Val	
					225					230				
40	ATT	ACA	TCT	GAA	AAT	ATC	ACA	GAC	AAT	GCT	AAA	ACC	ATA	739
	Ile	Arg	Ser	Glu	Asn	Ile	Thr	Asp	Asn	Ala	Lys	Thr	Ile	
	235					240						245		
	ATA	GTG	CAG	CTA	AAT	GAA	TCT	ATA	GTG	ATT	AAT	TGT	ACA	778
	Ile	Val	Gln	Leu	Asn	Glu	Ser	Ile	Val	Ile	Asn	Cys	Thr	
45				250				255						
	AGA	CCC	AAT	AAC	AAC	ACA	AGA	AAA	AGT	ATA	AAT	ATA	GGA	817
	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Lys	Ser	Ile	Asn	Ile	Gly	
	260					265					270			
50	CCA	GGG	AGA	GCA	TTC	TAT	ACA	ACA	GGA	GAC	ATA	ATA	GGA	856
	Pro	Gly	Arg	Ala	Phe	Tyr	Thr	Thr	Gly	Asp	Ile	Ile	Gly	
			275					280					285	
	GAT	ATA	AGA	CAA	GCA	CAT	TCT	AAC	CTT	AGT	AAA	ACA	CAA	895
	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Leu	Ser	Lys	Thr	Gln	
				290						295				
55	TGG	GAA	AAA	ACG	TTA	AGA	CAG	ATA	GCT	ATA	AAA	TTA	GAA	934
	Trp	Glu	Lys	Thr	Leu	Arg	Gln	Ile	Ala	Ile	Lys	Leu	Glu	
	300					305						310		
	GAA	AAA	TTT	AAG	AAT	AAA	ACA	ATA	GCC	TTT	AAT	AAA	TCC	973
	Glu	Lys	Phe	Lys	Asn	Lys	Thr	Ile	Ala	Phe	Asn	Lys	Ser	
60				315				320						
	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	ATG	CAC	AGT	TTT	AAT	1012
	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Val	Met	His	Ser	Phe	Asn	
	325					330					335			

AP/P/99/01432

APC 01282

TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA AAA CTG 1051
 Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Lys Leu 350
 340
 TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
 Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn 360
 355
 ACC GGG AAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
 Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro 375
 365
 10 TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
 Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val 385
 380
 GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile 400
 390
 15 AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA ACA AGA 1246
 Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg 415
 405
 GAT GGT GGA AGT AAC ACC GGT GAC AAC AGG ACT GAG ACC 1285
 Asp Gly Gly Ser Asn Thr Gly Asp Asn Arg Thr Glu Thr 425
 420
 TTT AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA 1324
 Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg 440
 430
 25 AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
 Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro 450
 445
 TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
 Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val 465
 455
 30 CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
 Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe 480
 470
 CTT GGG TTC TTG GGA GAT AA 1461
 35 Leu Gly Phe Leu Gly Asp 485 486

CLONE C8.6

G GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
 Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe 10
 1
 TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
 Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His 25
 15
 45 AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro 35
 30
 AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
 Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn 50
 40
 50 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
 Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His 60
 55
 GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
 Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro 75
 65
 TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
 Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys 90
 80
 60 ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
 Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn 100
 95
 AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
 Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu 115
 105
 65

AP/P/99/01432

AGA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
 Arg Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
 120 125

5 GAT AAG GGG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
 Asp Lys Gly Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
 130 135 140

GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
 Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
 145 150 155

10 ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
 Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
 160 165

AAG GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC 544
 Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
 170 175 180

15 CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
 Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
 185 190

TTC AAT GCA ACA GGA CCA TGT AAA AAT GTC AGG ACA GTA 622
 Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val
 195 200 205

CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
 Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
 210 215 220

25 CTA CTG GTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
 Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
 225 230

ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
 Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
 235 240 245

30 ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
 Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
 250 255

AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
 Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
 260 265 270

CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
 Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
 275 280 285

40 GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
 Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
 290 295

TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
 Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
 300 305 310

45 GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
 Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
 315 320

TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
 Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
 325 330 335

TGT GGA GGG GGA TTT TTC TAC TGT AGT ACG AGA AAA CTG 1051
 Cys Gly Gly Gly Phe Phe Tyr Cys Ser Thr Arg Lys Leu
 340 345 350

55 TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
 Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
 355 360

ACC GGG GAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
 Thr Gly Asp Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
 365 370 375

60 TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
 Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
 380 385

AP/P/99/01432

APG 01282

GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
 390 395 400
 5 AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA AGG AGA 1246
 Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Arg Arg
 405 410 415
 GAT GGT GGA AGT AAC ACC AGT GAC AAC CAG ACT GAG ACC 1285
 Asp Gly Gly Ser Asn Thr Ser Asp Asn Gln Thr Glu Thr
 420 425
 10 TTT AGA CCT GGG GGA GGA GAT ATG AGG GAC AAG TGG AGA 1324
 Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Lys Trp Arg
 430 435 440
 AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
 Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
 445 450
 15 TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
 Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
 455 460 465
 CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
 Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
 470 475 480
 CTT AGG TTC TTA GGA GAT AAA GCT TCT AGA GTC 1474
 Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
 485 490 491
 25
 CTC GAG GTA CCT GTA TGG AAA GAA GCA ACT ACC ACT 36
 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1 5 10
 30 CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
 Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
 15 20 25
 AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
 Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
 30 35
 GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
 Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
 40 45 50
 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60
 ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
 Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75
 45 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT ACT TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90
 AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
 Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
 95 100
 50 AGT AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
 Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
 105 110 115
 AAG GGG GAA ATG AAA AGA TGC TCT TTC AAT ATC ACC ACA 387
 Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
 120 125
 AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
 Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
 130 135 140
 60 TAT AGA CTT GAT GTA CCA ATA GAT AAT GAT AAT ACC 465
 Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
 145 150 155

CLONE C15.2

AP/P/99/01432

ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
 Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
 160 165
 5 CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
 Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
 170 175 180
 CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
 His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
 185 190
 10 AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
 Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
 195 200 205
 GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
 Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
 210 215 220
 15 GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
 Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
 225 230
 20 GAA GAG GTA ATA ATT AGA TCT GAC AAT ATC ACA GAC AAT 738
 Glu Glu Val Ile Ile Arg Ser Asp Asn Ile Thr Asp Asn
 235 240 245
 ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
 Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
 250 255
 25 ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA AGA AAA AGT 816
 Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser
 250 265 270
 ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
 Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
 275 280 285
 30 GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
 Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
 290 295
 35 AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
 Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
 300 305 310
 ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
 Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
 315 320
 40 AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
 Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
 325 330 335
 GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
 Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
 340 345 350
 45 TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
 Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
 355 360
 50 AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
 Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
 365 370 375
 ACA GGA GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
 Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
 380 385
 55 CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
 Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
 390 395 400
 TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
 Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
 405 410 415
 60 AAC ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
 Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
 420 425

AP/P/99/01432

APC 01282

AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
 Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
 430 435 440
 5 GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
 Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
 445 450
 AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
 Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
 455 460 465
 10 CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
 Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
 470 475 480
 AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
 Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
 485 490
 15 TTG GGA GCA TAA AGC TTC TAG AGT CGA CCT GCA 1512
 Leu Gly Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
 495 500 504
 20 CLONE C15.3
 CTC GAG GTA CCT GTG TGG AAA GAA GCA ACT ACC ACT 36
 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1 5 10
 25 CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
 Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
 15 20 25
 AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
 Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
 30 30 35
 GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
 Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
 40 45 50
 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60
 35 ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
 Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75
 40 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90
 AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
 Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
 95 100
 45 AGC AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
 Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
 105 110 115
 AAG GGG GAA ATG AAA AGG TGC TCT TTC AAT ATC ACC ACA 387
 Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
 120 125
 50 AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
 Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
 130 135 140
 TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
 Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
 145 150 155
 55 ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
 Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
 160 165
 60 CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
 Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
 170 175 180
 CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
 His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
 185 190
 65

AP/P/99/01432

AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
 Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
 195 200 205
 5 GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
 Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
 210 215 220
 GTC TCA ACT CAA CTG CTC TTA AAT GGC AGT CTA GCA GAA 699
 Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
 225 230
 10 GAA GAG GTA ATA ATT AGA TCT GGC AAT ATC ACA GAC AAT 738
 Glu Glu Val Ile Ile Arg Ser Gly Asn Ile Thr Asp Asn
 235 240 245
 ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
 Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
 250 255
 15 ATT AAT TGT ACA AGA TCC AAC AAC AAT ACA AGA AAA AGT 816
 Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg Lys Ser
 260 265 270
 20 ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
 Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
 275 280 285
 GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
 Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
 290 295
 25 AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
 Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
 300 305 310
 ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
 Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
 315 320
 30 AAA ACA ATA GTC TTT AAT CCA TCC TCA GGA GGG GAC CCG 1011
 Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
 325 330 335
 35 GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
 Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
 340 345 350
 TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
 Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
 355 360
 40 AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
 Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
 365 370 375
 ACA GGG GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
 Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
 380 385
 45 CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
 Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
 390 395 400
 50 TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
 Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
 405 410 415
 AAT ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
 Asn Ile Thr Gly Leu Leu Thr Arg Asp Gly Gly Ser
 420 425
 55 AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
 Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
 430 435 440
 GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
 Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
 445 450
 60 AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA CGC 1401
 Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
 455 460 465

AP/P/99/01432

APC 01282

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CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
470 475 480
5 AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
485 490
TTA GGA GCA TAA AGC TTC TAG A 1501
Leu Gly Ala Xaa Ser Phe Xaa
495 500

10 CLONE C7.2
GG GAA TTC GGA TCC GGG GTA CCT GTG TGG AAG GAA GCA 38
Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala
1 5 10
15 ACC ACC ACT CTA TTC TGT GCA TCA GAT GCT AGA GCA TAT 77
Thr Thr Thr Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr
15 20 25
GAC ACA GAG GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT 116
Asp Thr Glu Val His Asn Val Trp Ala Thr His Ala Cys
30
20 GTA CCC ACA GAC CCT AGT CCA CAA GAA GTA GTT TTG GAA 155
Val Pro Thr Asp Pro Ser Pro Gln Glu Val Val Leu Glu
40 45 50
AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG 194
Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met
55 60
25 GTA GAA CAA ATG CAT GAG GAT ATA ATT AGT TTA TGG GAT 233
Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
65 70 75
30 CAA AGC TTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT 272
Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
80 85 90
GTT ACT TTA AAT TGC AGT GAT TAT AGG AAT GCT ACT GAT 311
Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp
95 100
35 TAT AAG AAT GCT ACT GAT ACC ACT AGT AGT AAC GAG GGA 350
Tyr Lys Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly
105 110 115
40 AAG ATG GAG ACA GGA GAA ATA AAA AAC TGC TCT TTC AAT 389
Lys Met Glu Arg Gly Glu Ile Lys Asn Cys Ser Phe Asn
120 125
ATT ACC ACA AGC ATA AAA AAT AAG ATG CAG AAA GAA TAT 428
Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys Glu Tyr
130 135 140
45 GCA CTT TTC TAT AAA CTT GAT ATA GTA CCA ATA GAT AAT 467
Ala Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asn
145 150 155
ACA AGC TAT ACA TTG ATA AGT TGT AAC ACC TCA GTC ATT 506
Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile
160 165
50 ACA CAG GCC TGT CCA AAG GTA TCC TTT GAA CCA ACT CCC 545
Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr Pro
170 175 180
ATA CAT TAT TGT GCT CCG GCT GGT TTT GCG ATT CTA AAG 584
Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys
185 190
55 TGT AAT GAT AAG AAG TTC AGT GGA AAA GGA GAA TGT AAA 623
Cys Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys
195 200 205
60 AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA 662
Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro
210 215 220
GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA 701
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
225 230
65

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AP/P/99/01432

GAA GAA GAG GTG GTA ATT AGA TCT GAC AAT TTC ATA GAC 740
 Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Ile Asp
 235 240 245
 5 AAT ACT AAA ACC ATA ATA GTA CAG CTG AAA GAA TCT GTA 779
 Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val
 250 255
 GAA ATT AAT TGT ATA AGA CCC AAC AAT AAT ACA AGA AAA 818
 Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys
 260 265 270
 10 GGT ATA CAT ATA GGA CCA GGG AGA GCA TGG TAT GCA ACA 857
 Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
 275 280 285
 GGA GAA ATA GTA GGA GAT ATA AGA AAG GCA TAT TGT AAC 896
 Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn
 290 295
 15 ATT AGT AGA ACA AAA TGG AAT AAC ACT TTA ATA CAG ATA 935
 Ile Ser Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile
 300 305 310
 GGT AAC AAA TTA AAA GAA AAA TAT AAT ACA ACA ATA AGC 974
 Ala Asn Lys Leu Lys Glu Lys Tyr Asn Thr Thr Ile Ser
 315 320
 20 TTT AAT CCA TCC TCA GGA GGG GAC CCA GAA ATT GTA ACC 1013
 Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Thr
 325 330 335
 CAT AGT TTT AAT TGT GGA GGG GAG TTT TTC TAC TGT GAT 1052
 His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asp
 340 345 350
 TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT TTA AAT GGT 1091
 Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly
 355 360
 30 ACT TGG AAT TTT ACT GCA GGG TCA AAT GAA ACT GAA GGC 1130
 Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly
 365 370 375
 AAT ATC ACA CTC CCA TGC AGA ATA AAA CAA ATT ATA AAC 1169
 Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn
 380 385
 35 AGG TGG CAG GAA GTA GGG AAA GCA ATG TAT GCC CCT CCC 1208
 Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro
 390 395 400
 40 ATC AGT GGA CAA ATA AAA TGC TCA TCA AAC ATT ACA GGG 1247
 Ile Ser Gly Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly
 405 410 415
 ATG ATA ATA ACA AGG GAT GGT AAC GAG AAC AAT AAT 1286
 Met Ile Leu Thr Arg Asp Gly Gly Asn Glu Asn Asn Asn
 420 425
 45 GAG AGC AGT ACT ACT GAG ACC TTC AGA CCG GGA GGA GGA 1325
 Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly Gly
 430 435 440
 GAT ATG AGG AAC AAT TGG AGA AGT GAA TTA TAT AAA TAT 1364
 Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
 445 450
 AAA GTA GTA AAA ATT GAA CCA TTA GCA GTA GCA CCC ACC 1403
 Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr
 455 460 465
 55 AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA 1442
 Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
 470 475 480
 GTC GGA CCG CTA GGA GGT ATG TTC CTT GGG TTC TTA GGA 1481
 Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly
 485 490
 60 GCA TAA AGC TTC TAG ACC GAC TCT AGA GGA TCC 1514
 Ala Xaa Ser Phe Xaa Thr Asp Ser Arg Gly Ser
 495 500 504

AP/P/99/01432

AP001282

CLONE C7.10

	G	GTA	CCT	GTG	TGG	AAG	GAA	GCA	ACC	ACC	ACT	CTA	TTC	37
		Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	Phe	
		1				5					10			
5	TGT	GCA	TCA	GAT	GCT	AGA	GCA	TAT	GAC	ACA	GAG	GTA	CAT	76
	Cys	Ala	Ser	Asp	Ala	Arg	Ala	Tyr	Asp	Thr	Glu	Val	His	
		15						20			25			
	AAT	GTT	TGG	GCC	ACA	CAT	GCC	TGT	GTA	CCC	ACA	GAC	CCT	115
	Asn	Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	
10					30					35				
	AGT	CCA	CAA	GAA	GTA	TTT	TTG	GGA	AAT	GTG	ACA	GAA	AAT	154
	Ser	Pro	Gln	Glu	Val	Phe	Leu	Gly	Asn	Val	Thr	Glu	Asn	
		40					45				50			
	TTT	AAT	ATG	TGG	AAA	AAT	AAC	ATG	GTA	GAA	CAA	ATG	TAT	193
15	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	Val	Glu	Gln	Met	Tyr	
				55					60					
	GAG	GAT	ATA	ATT	AGT	TTA	TGG	GAT	CAA	AGC	TTA	AAG	CCA	232
	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	Pro	
		65				70					75			
20	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACT	TTA	AAT	TGC	271
	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys	
		80						85			90			
	AGT	GAT	TAT	AGG	AAT	GCT	ACT	GAT	TAT	AAG	AAT	GCT	ACT	310
	Ser	Asp	Tyr	Arg	Asn	Ala	Thr	Asp	Tyr	Lys	Asn	Ala	Thr	
25					95					100				
	GAT	ACC	ACT	AGT	AGT	AAC	GAG	GGA	AAG	ATG	GAG	AGA	GGA	349
	Asp	Thr	Thr	Ser	Ser	Asn	Glu	Gly	Lys	Met	Glu	Arg	Gly	
		105					110				115			
	GAA	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	AGC	ATA	388
30	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Ile	
			120					125						
	AAA	AAT	AAG	ATG	CAG	AAA	GAA	TAT	GCA	CTT	TTC	TAT	AAA	427
	Lys	Asn	Lys	Met	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	
		130				135					140			
35	CTT	AAT	ATA	GTA	CCA	ATA	GAT	AAT	ACA	AGC	TAT	ACA	TTG	466
	Leu	Asn	Ile	Val	Pro	Ile	Asp	Asn	Thr	Ser	Tyr	Thr	Leu	
		145					150				155			
	ATA	AGT	TGT	AAC	ACC	TCA	GTC	ATT	ACA	CAG	GCC	TGT	CCA	505
	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	Pro	
40					160					165				
	AAG	GTA	TCC	TTT	GAA	CCA	ATT	CCC	ATA	CAT	TAT	TGT	GCT	544
	Lys	Val	Ser	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	Ala	
		170					175				180			
	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAT	GAT	AAG	AAG	583
45	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp	Lys	Lys	
			185					190						
	TTC	AGT	GGA	AAA	GGA	GAA	TGT	AAA	AAT	GTC	AGC	ACA	GTA	622
	Phe	Ser	Gly	Lys	Gly	Glu	Cys	Lys	Asn	Val	Ser	Thr	Val	
		195				200				205				
50	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	CAA	661
	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	
		210					215				220			
	CTG	CTG	TTA	AAT	GGC	AGT	CTA	GCA	GAA	GAA	GAG	GTG	GTA	700
	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	Val	
55					225					230				
	ATT	AGA	TCT	GAC	AAT	TTC	ACA	GAC	AAT	ACT	AAA	ACC	ATA	739
	Ile	Arg	Ser	Asp	Asn	Phe	Thr	Asp	Asn	Thr	Lys	Thr	Ile	
		235				240				245				
	ATA	GTA	CAG	CTG	AAA	GAA	TCT	GTA	GAA	ATT	AAT	TGT	ATA	778
60	Ile	Val	Gln	Leu	Lys	Glu	Ser	Val	Glu	Ile	Asn	Cys	Ile	
			250					255						
	AGA	CCC	AAC	AAT	AAT	ACA	AGA	AAA	GGT	ATA	CAT	ATA	GGA	817
	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Lys	Gly	Ile	His	Ile	Gly	
		260			265					270				

AP/P/99/01432

GCA GGG AGA GCA TGG TAT GCA ACA GGA GAA ATA GTA GGA 256
 Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly
 275 280 285
 5 GAT ATA AGA CAG GCA TAT TGT AAC ATT AGT AGA ACA AAA 895
 Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys
 290 295
 TGG AAT AAC ACT TTA ATA CAG ATA GCT AAC AAA TTA AAA 934
 Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys
 300 305 310
 10 GAA AAA TAT AAT ACA ACA ATA AGC TTT AAT CGA TCC TCA 973
 Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser
 315 320
 GGA GGG GAC CCA GAA ATT GTA ACC CAT AGT TTT AAT TGT 1012
 Gly Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys
 325 330 335
 15 GGA GGG GAA TTT TTC TAC TGT AAT TCA ACA CAA CTG TTT 1051
 Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe
 340 345 350
 AAT AGT ACT TGG AAT TTA AAT GGT ACT TGG AAT TTT ACT 1090
 Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp Asn Phe Thr
 355 360
 20 GCA GGG TCA AAT GAA ACT GAA GGC AAT ATC ACA CTC CCA 1129
 Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu Pro
 365 370 375
 25 TGC AGA ATA AAA CAA ATT ATA AAC AGG TGG CAG GAA GTA 1168
 Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val
 380 385
 GCA AAA GCA ATG TAT GCC CCT CCC ATC AGT GGA CAA ATA 1207
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile
 390 395 400
 AGA TGC TCA TCA AAC ATT ACA GGG ATG ATA TTA ACA AGG 1246
 Arg Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
 405 410 415
 35 GAT GGT GGT AAC GAG AAC AAT AAT GAG AGC AGT ACT ACT 1285
 Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr
 420 425
 GAG ACC TTC AGA CCG GGA GGA GGA GAT ATG AGG AAC AAT 1324
 Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn
 430 435 440
 40 TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT 1363
 Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile
 445 450
 CAG CCA TTA GGA GTA GCA CCC ACC GAC TCT AGA GGA TCC 1402
 Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg Gly Ser
 455 460 465
 45 TCT AGA 1408
 Ser Arg
 469
 50 CLONE C11.5
 GAG GTA CCT GTG TGG AAA GAA GCA ACC ACT ACT CTA 36
 Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
 1 5 10
 55 TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GGG GTG 75
 Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val
 15 20 25
 CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
 His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
 30 35
 60 CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
 Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
 40 45 50
 GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
 Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
 55 60

AP/P/99/01432

APC 01282

	CAT	GAG	GAT	ATA	ATC	AGT	TTA	TGG	GAT	GAA	AGC	CTA	AAG	231
	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Glu	Ser	Leu	Lys	
	65					70					75			
5	CCA	TGT	GTA	AAG	TTA	ACC	CCA	CTT	TGT	GTT	ACT	CTA	AAC	270
	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	
	80							85					90	
	TGC	AGT	GAT	GTG	AAC	AAT	TCC	ACA	AAT	CCT	AAT	GAT	ACT	309
	Cys	Ser	Asp	Val	Asn	Ser	Thr	Asn	Pro	Asn	Asp	Thr		
					95					100				
10	AAT	ACT	AAT	TCC	ACT	AAT	ACT	ACT	TCC	TCT	ACT	CCT	ACG	348
	Asn	Thr	Asn	Ser	Thr	Asn	Thr	Thr	Ser	Ser	Thr	Pro	Thr	
	105						110					115		
	GCC	ACT	ACT	AGT	AGC	GAG	GAA	AAG	ATG	GAG	AAG	GGA	GAA	387
	Ala	Thr	Thr	Ser	Ser	Glu	Glu	Lys	Met	Glu	Lys	Gly	Glu	
15														
	120							125						
	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	CAC	ATG	AAA	426
	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	His	Met	Lys	
	130					135					140			
20	GAT	AAG	GCA	CAG	AAA	GAA	TAT	GCA	CTT	TTT	TAT	AAA	CTT	465
	Asp	Lys	Ala	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu	
	145							150				155		
	GAT	ATA	GTA	CCA	ATA	GAT	GAT	AAT	GCC	AGC	TAT	AGG	504	
	Asp	Ile	Val	Pro	Ile	Asp	Asp	Asn	Asn	Ala	Ser	Tyr	Arg	
						160				165				
25	TTG	ATA	AGT	TGT	AAT	ACC	TCA	GAC	ATT	ACA	CAG	GCC	TGT	543
	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Asp	Ile	Thr	Gln	Ala	Cys	
	170						175					180		
	CCA	AAG	GTG	ACC	TTT	GAG	CCA	ATT	CCC	ATA	CAT	TAT	TGT	582
	Pro	Lys	Val	Thr	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	
30														
	185							190						
	GCC	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAA	GAT	AAG	621
	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Lys	Asp	Lys	
	195					200					205			
35	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	TCA	AAG	GTC	AGC	ACA	660
	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Ser	Lys	Val	Ser	Thr	
	210						215					220		
	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	699
	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	
					225					230				
40	CAA	CTG	TTG	TTA	AAT	GGC	AGT	CTT	GCA	GAA	GAA	GAA	GTA	738
	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	
	235						240					245		
	GTA	ATT	AGA	TCT	GTC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ATC	777
	Val	Ile	Arg	Ser	Val	Asn	Phe	Thr	Asp	Asn	Ala	Lys	Ile	
45														
	250							255						
	ATA	ATA	GTA	CAG	CTG	AAA	GAA	CCT	GTA	GCA	ATT	AAT	TGT	816
	Ile	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val	Ala	Ile	Asn	Cys	
	260					265					270			
50	ACA	AGA	CCC	AAC	AAC	AAT	ACA	AGA	AAA	GGT	ATA	CAT	CTA	855
	Thr	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Lys	Gly	Ile	His	Leu	
	275							280				285		
	GGA	CCA	GGG	AGC	ACA	TTT	TAT	ACA	ACA	GGA	GAA	ATA	ATA	894
	Gly	Pro	Gly	Ser	Thr	Phe	Tyr	Thr	Thr	Gly	Glu	Ile	Ile	
					290					295				
55	GGA	GAC	ATA	AGA	AAA	GCA	TAT	TGC	AAG	ATT	AGT	AAA	GAA	933
	Gly	Asp	Ile	Arg	Lys	Ala	Tyr	Cys	Lys	Ile	Ser	Lys	Glu	
	300						305					310		
	AAA	TGG	AAT	AAC	ACT	TTA	AGA	CAG	GTA	GTT	AAA	AAA	TTA	972
	Lys	Trp	Asn	Asn	Thr	Leu	Arg	Gln	Val	Val	Lys	Lys	Leu	
60														
	315							320						
	AGA	GAA	CAA	TTT	GGG	AAT	AAA	ACA	ATA	ATT	TTT	AAT	CGA	1011
	Arg	Glu	Gln	Phe	Gly	Asn	Lys	Thr	Ile	Ile	Phe	Asn	Arg	
	325					330					335			

AP/P/99/01432

TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
 Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
 340 345 350
 5 AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
 Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
 355 360
 CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
 Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
 365 370 375
 10 AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
 Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
 380 385
 ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA CTA GGA AAA 1206
 Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
 390 395 400
 15 GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
 Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
 405 410 415
 20 ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
 Ile Ser Asn Ile Thr Gly Leu Leu Thr Arg Asp Gly
 420 425
 GGT AGG AAT GTC ACA AAC AAT ACC GAA ACC TTC AGA CCT 1323
 Gly Arg Asn Val Thr Asn Asn Thr Glu Thr Phe Arg Pro
 430 435 440
 25 GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
 Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
 445 450
 TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
 Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
 455 460 465
 30 GCA CCC ACC AAG GCA AAG ACA AGA GTG GTG CAC AGA GAC 1440
 Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
 470 475 480
 35 AAA AGA GCA GCA CTA GGA GCC TTG TTC CTT GGG TTC TTA 1479
 Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
 485 490
 GGA GCA TAA AAG CTT CTA GA 1499
 Gly Ala Ala Lys Leu Leu
 495 499
 40
 CLONE C11.7
 GAG GTA CCT GTA TGG AAA GAA GCA ACC ACT ACT CTA 36
 Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
 1 5 10
 45 TTT TGT GCA TCA GAT GCT AAA GCA TAT CAC ACA GAG GTG 75
 Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
 15 20 25
 CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
 His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
 30 35
 50 CCC AAC GCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
 Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
 40 45 50
 GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
 Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
 55 60
 CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA ACC CTA AAG 231
 His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
 65 70 75
 60 CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
 Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
 80 85 90
 TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
 Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
 95 100

AP001282

	AAT	ACT	AAT	TCC	ACT	AAT	ACT	ACT	TCC	TCT	ACT	CCT	ACG	348
	Asn	Thr	Asn	Ser	Thr	Asn	Thr	Thr	Ser	Ser	Thr	Pro	Thr	
	105					110						115		
5	GCC	ACT	ACT	AGT	AGC	GAG	GAA	AAG	ATG	GAG	AAG	GGA	GAA	387
	Ala	Thr	Thr	Ser	Ser	Glu	Glu	Lys	Met	Glu	Lys	Gly	Glu	
	120									125				
	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	CAC	ATG	AAA	426
	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	His	Met	Lys	
	130					135					140			
10	GAT	AAG	GTA	CAG	AAA	GAA	TAT	GCA	CTT	TTT	TAT	AAA	CTT	465
	Asp	Lys	Val	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu	
	145							150				155		
	GAT	ATA	GTA	CCA	ATA	GAT	GAT	AAT	AAT	ACC	AGC	TAT	AGG	504
	Asp	Ile	Val	Pro	Ile	Asp	Asp	Asn	Asn	Thr	Ser	Tyr	Arg	
15	TTG	ATA	AGT	TGT	AAT	ACC	TCA	GTC	ATT	ACA	CAG	GCC	TGT	543
	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	
	170					175					180			
20	CCA	ATG	GTG	ACC	TTT	GAG	CCA	ATT	CCC	ATA	CAT	TAT	TGT	582
	Pro	Met	Val	Thr	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	
	185							190						
	GCC	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAA	GAT	AAG	621
	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Lys	Asp	Lys	
	195					200				205				
25	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	TCA	AAG	GTC	AGC	ACA	660
	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Ser	Lys	Val	Ser	Thr	
	210							215				220		
	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	699
	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	
30	CAA	CTG	TTG	TTA	AAT	GGC	AGT	CTT	GCA	GAA	GAA	GAA	GTA	738
	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	
	235					240					245			
35	GTA	ATT	AGA	TCT	GTC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ATC	777
	Val	Ile	Arg	Ser	Val	Asn	Phe	Thr	Asp	Asn	Ala	Lys	Ile	
	250								255					
	ATA	ATA	GTA	CAG	CTG	AAA	GAA	CCT	GTA	GCA	ATT	AAT	TGT	816
	Ile	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val	Ala	Ile	Asn	Cys	
	260					265					270			
40	ACA	AGA	CCC	AAC	AAC	AAT	ACA	AGA	AAA	GGT	ATA	CAT	CTA	855
	Thr	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Lys	Gly	Ile	His	Leu	
	275							280				285		
	GGA	CCA	GGG	AGC	ACA	TTT	TAT	ACA	ACA	GGA	GAA	ATA	ATA	894
	Gly	Pro	Gly	Ser	Thr	Phe	Tyr	Thr	Thr	Gly	Glu	Ile	Ile	
45	GGA	GAC	ATA	AGA	AAA	GCA	TAT	TGC	AAG	ATT	AGT	AAA	GAA	933
	Gly	Asp	Ile	Arg	Lys	Ala	Tyr	Cys	Lys	Ile	Ser	Lys	Glu	
	300					305					310			
50	AAA	TGG	AAT	AAC	ACT	TTA	AGA	CAG	GTA	GTT	AAA	AAA	TTA	972
	Lys	Trp	Asn	Asn	Thr	Leu	Arg	Gln	Val	Val	Lys	Lys	Leu	
	315							320						
	AGA	GAA	CAA	TTT	GGG	AAT	AAA	ACA	ATA	ATT	TTT	AAT	CGA	1011
	Arg	Glu	Gln	Phe	Gly	Asn	Lys	Thr	Ile	Ile	Phe	Asn	Arg	
	325					330					335			
55	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	ATG	CAC	AGT	TTT	1050
	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Val	Met	His	Ser	Phe	
	340							345				350		
	AAC	TGT	GGA	GGG	GAG	TTT	TTC	TAC	TGT	AAT	ACA	ACA	CAA	1089
	Asn	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Thr	Thr	Gln	
60	CTG	TTT	AAT	AGT	ACT	TGG	AAT	AAT	ACT	GAA	GGG	ACA	AAT	1128
	Leu	Phe	Asn	Ser	Thr	Trp	Asn	Asn	Thr	Glu	Gly	Thr	Asn	
	365					370						375		

AP/P/99/01432

AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
 Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
 380 385
 5 ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
 Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
 390 395 400
 GCA AGC TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
 Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
 405 410 415
 10 ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
 Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
 420 425
 GGT AGG AAT GTC ACA AAC AAT ACC GAN NCC TTC AGA CCT 1323
 Gly Arg Asn Val Thr Asn Asn Thr Xaa Xaa Phe Arg Pro
 430 435 440
 15 GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA ACT GAA TTA 1362
 Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
 445 450
 TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
 Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
 455 460 465
 20 GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
 Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
 470 475 480
 25 AAA AGA GCA GCA CTA GGA CCT TTG TTC CTT GGG TTC TTA 1479
 Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
 485 490
 GGA GCA TAA AAG CTT CTA GA 1499
 Gly Ala Xaa Lys Leu Leu
 495 499
 30

CLONE C10.5
 35 G GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
 Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
 1 5 10
 TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
 Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
 15 20 25
 40 AAT GTT TGG GCA ACA CAT GGC TGT GTA CCC ACA GAC CCC 115
 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
 30 35
 AAC CCA CAA GAA ATA GTA TGG GGA AAT GTG ACA GAA AAT 154
 Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
 40 45 50
 45 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
 Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
 55 60
 GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
 Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
 65 70 75
 50 TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
 Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
 80 85 90
 55 AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
 Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
 95 100
 ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
 Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
 105 110 115
 60 ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
 Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
 120 125
 AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
 Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
 130 135 140

AP001282

	GTA	GTA	CCA	ATA	GAA	GAA	GAT	GAC	AAT	ACT	AGC	TAT	AGA	466
	Val	Val	Pro	Ile	Glu	Glu	Asp	Asp	Asn	Thr	Ser	Tyr	Arg	
			145					150					155	
5	TTG	ATA	AGT	TGT	AAC	ACC	TCA	GTC	ATT	ACA	CAG	GCT	TGT	505
	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	
				160					165					
	CCA	AAG	ACA	TCC	TTT	GAG	CCA	ATT	CCC	ATA	CAT	TAT	TGT	544
	Pro	Lys	Thr	Ser	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	
		170					175					180		
10	GCC	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAT	GAT	AAG	583
	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp	Lys	
				185					190					
	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	AAA	AAT	GTC	AGC	ACA	622
15	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	
		195				200				205				
	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	661
	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	
			210					215				220		
20	CAA	CTG	TTG	TTA	AAT	GGC	AGT	CTA	GCA	GAA	GAA	GAG	GTA	700
	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	
					225					230				
	GTA	ATC	AGA	TCT	GCC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ACC	739
	Val	Ile	Arg	Ser	Ala	Asn	Phe	Thr	Asp	Asn	Ala	Lys	Thr	
		235					240					245		
25	ATA	ATA	GTA	CAT	CTA	AAT	GAA	ACT	GTA	AAA	ATT	AAT	TGT	778
	Ile	Ile	Val	His	Leu	Asn	Glu	Thr	Val	Lys	Ile	Asn	Cys	
				250					255					
	ACA	AGA	CTT	GGC	AAC	AAT	ACA	AGA	AAA	AGT	ATA	AAT	ATA	817
	Thr	Arg	Leu	Gly	Asn	Asn	Thr	Arg	Lys	Ser	Ile	Asn	Ile	
30		260				265				270				
	GGA	CCA	GGG	AGA	GTA	CTC	TAT	GCA	ACA	GGA	GAA	ATA	ATA	856
	Gly	Pro	Gly	Arg	Val	Leu	Tyr	Ala	Thr	Gly	Glu	Ile	Ile	
			275					280				285		
35	GGA	GAC	ATA	AGA	CAA	GCA	CAT	TGT	AAC	ATT	AGT	AGA	GCA	895
	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Ile	Ser	Arg	Ala	
					290					295				
	CAA	TGG	AAT	AAG	ACT	TTA	GAA	AAG	GTA	GTT	GAC	AAA	TTA	934
	Gln	Trp	Asn	Lys	Thr	Leu	Glu	Lys	Val	Val	Asp	Lys	Leu	
		300					305					310		
40	AGA	AAA	CAA	TTT	GGG	GAT	AAT	ACA	ACA	ATA	GCT	TTT	AAT	973
	Arg	Lys	Gln	Phe	Gly	Asp	Asn	Thr	Thr	Ile	Ala	Phe	Asn	
				315					320					
	CGA	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	ATG	CAC	ACT	1012
	Arg	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Val	Met	His	Thr	
45		325				330					335			
	TTT	AAT	TGT	GGA	GGG	GAA	TTT	TTC	TAC	TGT	AAT	ACA	ACA	1051
	Phe	Asn	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Thr	Thr	
			340					345				350		
	CAA	CTG	TTT	AAT	AGT	ACT	TGG	AAT	AAT	ACT	TGG	AAG	GAT	1090
50	Gln	Leu	Phe	Asn	Ser	Thr	Trp	Asn	Asn	Thr	Trp	Lys	Asp	
					355					360				
	CCT	AAC	AGG	AGT	GAC	AAT	ATC	ACA	CTC	CCA	TGC	AGA	ATA	1129
	Pro	Asn	Arg	Ser	Asp	Asn	Ile	Thr	Leu	Pro	Cys	Arg	Ile	
		365					370					375		
55	AAA	CAA	ATT	ATA	AAC	ATG	TGG	CAG	GAA	GTA	GGA	AAA	GCA	1168
	Lys	Gln	Ile	Ile	Asn	Met	Trp	Gln	Glu	Val	Gly	Lys	Ala	
				380					385					
	ATG	TAC	GCC	CCT	CCC	ATC	AGA	GGG	GAA	ATT	AGA	TGT	TCA	1207
	Met	Tyr	Ala	Pro	Pro	Ile	Arg	Gly	Glu	Ile	Arg	Cys	Ser	
60		390				395					400			
	TCA	AAT	ATC	ACA	GGG	CTG	CTA	CTA	ACA	AGA	GAT	GGT	GGT	1246
	Ser	Asn	Ile	Thr	Gly	Leu	Leu	Thr	Arg	Asp	Gly	Gly		
				405				410				415		

AP/P/99/01432

AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
 Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
 420 425
 5 ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
 Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
 430 435 440
 AGA ACT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
 Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
 445 450
 10 GCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
 Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
 455 460 465
 GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
 Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
 470 475 480
 15 TTC CTT GGG T TCTTAGGAG CATAAAGCTT CTAGA 1475
 Phe Leu Gly
 483
 20 CLONE C10.7
 G GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
 Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
 1 5 10
 25 TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
 Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
 15 20 25
 AAT GTT TGG GCA ACA CAT GCG TGT GTA CCC ACA GAC CCC 115
 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
 30 35
 30 AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
 Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
 40 45 50
 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
 Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
 55 60
 35 GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
 Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
 65 70 75
 40 TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
 Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
 80 85 90
 AAG GAT CTC GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
 Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
 95 100
 45 ACC AAT AAT AGT AGT TTG GAG GCA CTA AGA GAA CAA ATG 349
 Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
 105 110 115
 ACA AAC TGC TCT TTC AAC ATC ACC ACA ACT ATA AGA GAT 382
 Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
 120 125
 50 AAG GTG CAG AAA GAA TAT GCA GTT TTC TAT AAA CTT GAT 427
 Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
 130 135 140
 GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
 Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
 145 150 155
 55 TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
 Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
 160 165
 60 CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
 Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
 170 175 180
 GGC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
 Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
 185 190

AP/P/99/01432

AP001282

	AAG	TTC	AAT	GGA	ACA	GGA	CCA	TGT	AAA	AAT	GTC	AGC	ACA	622
	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	
	195					200					205			
5	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	GTA	GTA	TCA	ACT	661
	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	
	210						215						220	
	CAA	CTG	TTG	TTA	AAT	GGC	AGT	CTA	GCA	GAA	GAA	GAG	GTA	700
	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	
					225					230				
10	GTA	ATC	AGA	TCT	GCC	AAT	TTC	ACA	GAC	AAT	GCT	AAA	ACC	739
	Val	Ile	Arg	Ser	Ala	Asn	Phe	Thr	Asp	Asn	Ala	Lys	Thr	
	235					240						245		
	ATA	ATA	GTA	CAT	CTA	AAT	GAA	ACT	GTA	AAA	ATT	AAT	TGT	778
	Ile	Ile	Val	His	Leu	Asn	Glu	Thr	Val	Lys	Ile	Asn	Cys	
15					250					255				
	ACA	AGA	CTT	GGC	AAC	AAT	ACA	AGA	AAA	AGT	ATA	AAT	ATA	817
	Thr	Arg	Leu	Gly	Asn	Asn	Thr	Arg	Lys	Ser	Ile	Asn	Ile	
	260					265					270			
20	GGA	CCA	GGG	AGA	GTA	CTC	TAT	GCA	ACA	GGA	GAA	ATA	ATA	856
	Gly	Pro	Gly	Arg	Val	Leu	Tyr	Ala	Thr	Gly	Glu	Ile	Ile	
			275				280					285		
	GGA	GAC	ATA	AGA	CAA	GCA	CAT	TGT	AAC	ATT	AGT	AGA	GCA	895
	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Ile	Ser	Arg	Ala	
					290					295				
25	CAA	TGG	AAT	AAG	ACT	TTA	GAA	AAG	GTA	GTT	GAC	AAG	TTA	934
	Gln	Trp	Asn	Lys	Thr	Leu	Glu	Lys	Val	Val	Asp	Lys	Leu	
	300					305						310		
	AGA	AAA	CAA	TTT	GGG	GAT	AAT	ACA	ACA	ATA	GCT	TTT	AAT	973
	Arg	Lys	Gln	Phe	Gly	Asp	Asn	Thr	Thr	Ile	Ala	Phe	Asn	
30					315					320				
	CGA	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	ATG	CAC	ACT	1012
	Arg	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Val	Met	His	Thr	
	325					330					335			
35	TTT	AAT	TGT	GGA	GGG	GAA	TTT	TTC	TAC	TGT	AAT	ACA	ACA	1051
	Phe	Asn	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Thr	Thr	
			340				345					350		
	CAA	CTG	TTT	AAT	AGT	ACT	TGG	AAT	AAT	ACT	TGG	AAG	GAT	1090
	Gln	Leu	Phe	Asn	Ser	Thr	Trp	Asn	Asn	Thr	Trp	Lys	Asp	
					355					360				
40	CCT	AAC	AGG	AGT	GAC	AAT	ATC	ACA	CTC	CCA	TGC	AGA	ATA	1129
	Pro	Asn	Arg	Ser	Asp	Asn	Ile	Thr	Leu	Pro	Cys	Arg	Ile	
		365				370					375			
	AAA	CAA	ATT	ATA	AAC	ATG	TGG	CAG	GAA	GTA	GGA	AAA	GCA	1168
	Lys	Gln	Ile	Ile	Asn	Met	Trp	Gln	Glu	Val	Gly	Lys	Ala	
45					380					385				
	ATG	TAC	GCC	CCT	CCC	ATC	AGA	GGG	GAA	ATT	AGA	TGT	TCA	1207
	Met	Tyr	Ala	Pro	Pro	Ile	Arg	Gly	Glu	Ile	Arg	Cys	Ser	
	390					395					400			
50	TCA	AAT	ATC	ACA	GGG	CTG	CTA	CTA	ACA	AGA	GAT	GGT	GGT	1246
	Ser	Asn	Ile	Thr	Gly	Leu	Leu	Leu	Thr	Arg	Asp	Gly	Gly	
			405				410					415		
	AAT	GAC	GAT	GGT	AAT	GAC	ACG	ACC	ACA	AAC	AGG	ACC	GAG	1285
	Asn	Asp	Asp	Gly	Asn	Asp	Thr	Thr	Thr	Asn	Arg	Thr	Glu	
					420					425				
55	ATC	TTC	AGA	CCT	GGA	GGA	GAT	ATG	AGG	GAC	AAT	TGG		1324
	Ile	Phe	Arg	Pro	Gly	Gly	Asp	Met	Arg	Asp	Asn	Trp		
		430				435					440			
	AGA	AGT	GAA	TTA	TAT	AGA	TAT	AAA	GTA	GTA	AAA	ATT	GAA	1363
	Arg	Ser	Glu	Leu	Tyr	Arg	Tyr	Lys	Val	Val	Lys	Ile	Glu	
60					445				450					
	CCA	TTA	GGA	ATA	GCA	CCC	ACC	AGG	GCA	AAG	AGA	AGA	GTG	1402
	Pro	Leu	Gly	Ile	Ala	Pro	Thr	Arg	Ala	Lys	Arg	Arg	Val	
	455					460					465			

AP/P/99/01432

GTG CAC AGA GAA AAA AGA GGA GTA GGA CTA GGA GCT TTG 1441
 Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
 470 475 480
 TTC CTT GGG TTC TTG GGA GGA TAA AGC TTC TAG A 1475
 5 Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
 485 490 491

CLONE C17.1

10 CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1 5 10
 CTA TTT TGT GCA TCA GAT GGT AAA GCA TAT GAT TCA GAG 75
 Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
 15 15 20 25
 GCA CAT AAT GTT TGG GCG ACA GAT GCC TGT GTA CCC ACA 114
 Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
 30 35
 GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
 Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
 20 40 45 50
 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60
 ATC CAT GGG GAT ATA ATT ACT TTA TGG GAT CAA AGC CTA 231
 Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75
 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90
 30 AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
 95 100
 ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
 Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
 105 110 115
 35 ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
 Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
 120 125
 CTT TTT CAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
 Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
 130 135 140
 AAT ACT AGC TAT AGG TTG ATA ACT TGT AAC ACC TCA GTC 465
 Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
 145 150 155
 45 ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
 Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
 160 165
 CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
 Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
 170 175 180
 50 AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
 Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
 185 190
 ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
 Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
 195 200 205
 CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
 Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
 210 215 220
 60 GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
 Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
 225 230
 GAG AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 739
 Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
 65 235 240 245

AP/P/99/01432

AD/P/99/01432

-37-

GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
 Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
 40 45 50
 5 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60
 ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
 Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75
 10 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90
 AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
 95 100
 15 ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 345
 Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
 105 110 115
 20 ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
 Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
 120 125
 CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
 Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
 130 135 140
 25 AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
 Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
 145 150 155
 ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
 Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
 160 165
 30 CCC ATA CAT TAT TGT GCC CCC GCT GGT TTT GCG ATT CTA 543
 Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
 170 175 180
 35 AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
 Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
 185 190
 ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
 Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
 195 200 205
 40 CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
 Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
 210 215 220
 GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
 Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
 225 230
 45 GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
 Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
 235 240 245
 50 GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
 Val Thr Met Asn Cys Thr Arg Pro Asn Asn Thr Met
 250 255
 AAA AGT ATA CAT ATA GGA CCA GCC AGA GCA TTT TAT GCA 816
 Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
 260 265 270
 55 ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
 Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
 275 280 285
 AAC ATT AGT GGA ACA AAA TGC AAT GAC ACT TTG AAA AAG 894
 Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
 290 295
 60 ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
 Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
 300 305 310

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GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
315 320
5 ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
325 330 335
AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
340 345 350
10 GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
355 360
CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
365 370 375
15 ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
380 385
ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
390 395 400
AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
405 410 415
25 ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
420 425
AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
430 435 440
30 CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
445 450
GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
455 460 465
35 TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
470 475 478

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In addition to the listing in Table 1, Figure 3 shows the alignment of the amino acid sequences of the clones of each of the seven isolates. Corresponding residues from various clones are in boxes. In the figure, the amino acid sequences are aligned against MN-rgp120 (SEQ. ID. NO. 29).

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In one embodiment, a gp120 polypeptide of this invention has the same amino acid sequence as the sequence of one of the breakthrough isolates. In another embodiment, the amino acid sequence is truncated, as described in detail hereinafter. In another embodiment, a gp120 polypeptide sequence of this invention contains a substitution, insertion, or

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AP/P/99/01432

deletion (alteration) of one or more amino acids in the sequence of a breakthrough isolate. Usually, with the exception of amino acids that are not present in a truncated amino acid sequence and eliminate an epitope, a gp120 polypeptide of this invention will include alterations in the amino acid sequence of a breakthrough isolate that do not alter the polypeptide's ability to induce the same neutralizing antibodies as the amino acid sequence of the isolate.

In general, substitutions in the amino acid sequence of a gp120 polypeptide of this invention are conservative substitutions, particularly for amino acid residues in the V2, V3, and C4 domains of gp120, which domains contain neutralizing epitopes. However, non-conservative substitutions, particularly in domains that do not contain neutralizing epitopes are contemplated.

Conservative substitutions replace an amino acid with an amino acid of similar size and character. For example, a hydrophobic residue or hydrophilic residue is replaced with another hydrophobic residue or hydrophilic residue, respectively. Amino acids can be divided into the following groups: positively charged residues (K, R and H); negatively charged residues (D and E); amides (N and Q); aromatics (F, Y, and W); hydrophobics (P, G, A, V, L, I, and M); and uncharged residues (S and T). Usually, residues within a group are replaced with another member of the group.

In one embodiment, critical amino acid residues in the V2, V3, and C4 domains of gp120 are identical to the corresponding residues in a breakthrough isolate sequence. Critical amino acid residues in the V2, V3, and C4 domains of gp120 are described in the experimental section. In another embodiment, all amino

acid residues in the V2, V3, and C4 domains of gp120 are identical to corresponding residues in a breakthrough isolate sequence.

5 Oligonucleotide Encoding gp120 from Breakthrough Isolates

The present invention also provides novel oligonucleotides encoding gp120 from the breakthrough isolates which can be used to express gp120. An
10 oligonucleotide of this invention encodes a polypeptide of this invention. The oligonucleotide can be DNA or RNA, usually DNA. Although numerous nucleotide sequences can encode the same amino acid sequence due to the degeneracy of the genetic code, conveniently,
15 the oligonucleotides of this invention include a nucleotide sequence of a breakthrough isolate as illustrated in Table 1 (Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28). Usually, an oligonucleotide of this invention is less than about
20 5 kilobases (kb), preferably less than about 3 kb.

To express the encoded amino acid sequence, the oligonucleotide can be inserted into a transcription unit. The transcription unit can be inserted into a plasmid for production of cell lines, inserted into a
25 virus (e.g.; vaccinia) or can be used directly as a DNA vaccine. Suitable transcription units for production of vaccine proteins are well known. A preferred expression vector, designated psvI6B5, is illustrated in Sequence ID No. 32. The vector includes an HSV-1
30 gD1 signal sequence joined to a linker sequence. The gp120 nucleotide sequence to be expressed starts with the Kpn I site of the gene. Since all gp120 or gp160 sequences contain this site, any gp120 nucleotide sequence can be analogously inserted into the vector
35 and expressed. The vector ends with a polyA tail from SV40.

AP/P/99/01432

In addition to being useful to express a polypeptide sequence of this invention, the oligonucleotides of this invention can also be used in diagnostics to detect HIV isolates. For example, the oligonucleotide or a portion thereof encoding a neutralizing epitope can be used in branched chain DNA diagnostics or as a probe in in situ hybridization studies.

10 Vaccine preparation

A gp120 polypeptide of this invention from a selected breakthrough isolate(s) in a suitable carrier is used to make a subunit vaccine. The polypeptide can be used alone, but is generally administered in a multivalent subunit vaccine that includes gp120 MN. In addition to one or more gp120 polypeptides of this invention, the vaccine generally includes the MN polypeptide (hereinafter, MN-rgp120). The vaccine usually includes about 3 to about 5 different gp120 polypeptides, but 30 or more different gp120 polypeptides can be used.

Preparation of gp120 polypeptides for use in a vaccine is well known and is described hereinafter. With the exception of the use of the selected HIV isolate, the gp120 subunit vaccine prepared in the method does not differ from gp120 subunit vaccines of the prior art.

As with prior art gp120 subunit vaccines, gp120 at the desired degree of purity and at a sufficient concentration to induce antibody formation is mixed with a physiologically acceptable carrier. A physiologically acceptable carrier is nontoxic to a recipient at the dosage and concentration employed in the vaccine. Generally, the vaccine is formulated for injection, usually intramuscular or subcutaneous injection. Suitable carriers for injection include

AP/P/99/01432

sterile water, but preferably are physiologic salt solutions, such as normal saline or buffered salt solutions such as phosphate-buffered saline or ringer's lactate. The vaccine generally contains an adjuvant.

5 Useful adjuvants include QS21 (Quillaja saponaria, commercially available from Cambridge Biotech, Worcester, MA), which stimulates cytotoxic T-cells, and alum (aluminum hydroxide adjuvant). Formulations with different adjuvants which enhance cellular or local

10 immunity can also be used. In particular, immunopotentiators such as cytokines can be included in the vaccine. Examples of suitable immunopotentiating cytokines include interleukins, such as interleukin-2 (IL-2) and interleukin-12 (IL-12), and tumor necrosis

15 factor-alpha (TNF- α).

Additional excipients that can be present in the vaccine include low molecular weight polypeptides (less than about 10 residues), proteins, amino acids, carbohydrates including glucose or dextrans, chelating

20 agents such as EDTA, and other excipients that stabilize the protein or inhibit growth of microorganisms.

The vaccine can also contain other HIV proteins. In particular, gp41 or the extracellular portion of

25 gp41 or HIV-1 core proteins such as P24, P17, and P55 can be present in the vaccine. Although the amino acid sequence of gp41 is more conserved than that of gp120, gp41 contains neutralizing epitopes. Preferably, any gp41 present in the vaccine is from an HIV isolate

30 present in the vaccine. gp160 from an isolate used in the vaccine can replace gp120 in the vaccine or be used together with gp120 from the isolate. Alternatively, gp160 from a different isolate than those in the vaccine can additionally be present in the vaccine.

35 Vaccines according to the invention can also contain one or more soluble gp120 polypeptide

AP/P/99/01432

sequences, or fragments thereof, in combination with an engineered virus specifically designed to express proteins that induce a cytotoxic T-cell response. Suitable engineered viruses are derived from, for example, Canary Pox virus, vaccinia viruses, attenuated human herpes viruses (such as, e.g., herpes simplex viruses), and Varicella Zoster. Exemplary engineered viruses are modified to express any HIV protein capable of inducing a cytotoxic T-cell response, such as those described above. Typically, immunization with the gp120/engineered virus vaccine is followed by administration of one or more doses of the gp120 polypeptide sequence(s) to boost the immune response. If desired, viruses can be engineered to express one or more gp120 polypeptide sequences of the invention, or fragments thereof, and used in vaccines with or without soluble gp120 polypeptide sequences.

Vaccine formulations generally include a total of about 300 to 600 μ g of gp120, conveniently in about 1.0 ml of carrier. Preferred formulations include use of twice the weight of a gp120 polypeptide in twice as much alum. However, formulations having smaller amounts (e.g.; 50 μ g per dose) are also used, generally with alum or other adjuvants. The amount of gp120 for any isolate present in the vaccine will vary depending on the immunogenicity of the gp120. For example, gp120 from some strains of HIV may be less immunogenic than gp120 from the MN strain (Sequence ID No. 29). If two strains having different immunogenicity are used in combination, empirical titration of the amount of each virus would be performed to determine the percent of the gp120 of each strain in the vaccine. For isolates having similar immunogenicity, approximately equal amounts of each isolate's gp120 would be present in the vaccine. For example, in a preferred embodiment, the vaccine includes gp120 from the MN and a strain of this

AP/P/99/01432

invention at concentrations of about 300 μ g per strain in about 1.0 ml of carrier. When the vaccine includes gp120 from about 30 isolates, about 10 to about 50 μ g can be used. Methods of determining the relative amount of an immunogenic protein in multivalent vaccines are well known and have been used, for example, to determine relative proportions of various isolates in multivalent polio vaccines.

The vaccines of this invention are administered in the same manner as prior art HIV gp120 subunit vaccines. In particular, the vaccines are generally administered at 0, 1, and at 6, 8 or 12 months, depending on the protocol. A preferred protocol includes administration at 0, 1, 6, and 12 months. Following the immunization procedure, annual or bi-annual boosts can be administered. However, during the immunization process and thereafter, neutralizing antibody levels can be assayed and the protocol adjusted accordingly.

The vaccine is administered to uninfected individuals. In addition, the vaccine can be administered to seropositive individuals to augment immune response to the virus, as with prior art HIV vaccines. It is also contemplated that DNA encoding the strains of gp120 for the vaccine can be administered in a suitable vehicle for expression in the host. In this way, gp120 can be produced in the infected host, eliminating the need for repeated immunizations. Preparation of gp120 expression vehicles is described hereinafter.

Although the gp120 isolates described herein can be used as a vaccine as described above, the amino acid sequences can also be used alone or in combinations in the same type of formulation for use as an immunogen, to induce antibodies that recognize the isolate(s) present in the immunogen. Immunogens are formulated in

AP/P/99/014'32

the same manner as vaccines and can include the same excipients, etc. Antibodies induced by the immunogens can be used in a diagnostic to detect the HIV strain in the immunogen or to affinity purify the strain.

5

gp120 Polypeptide Sequences and Chemokine Receptors

While CD4 is the primary cellular receptor for HIV-1, it is not sufficient for entry of HIV-1 into cells. Co-receptors required in conjunction with CD4 have been identified. These co-receptors are members of the chemokine receptor family of seven-transmembrane G-protein coupled receptors. The chemokine superfamily is subdivided into two groups based on the amino terminal cysteine spacing. The CXC chemokines are primarily involved in neutrophil-mediated inflammation, and the CC chemokines tend to be involved in chronic inflammation. At least five CC chemokine receptors, designated CC-CKR1-5 (also known in the art as CCR1-5), and at least four CXC chemokine receptors, designated CXC-CKR1-4 (also known as CXCR-1-4), have been identified.

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CXC-CKR-4 (CXCR-4), which has also been called the alpha-chemokine receptor fusin, serves as an entry cofactor for T-cell-tropic HIV-1 strains. CC-CKR-5 (CC-R5), which has been called beta-chemokine receptor, together with its related family members, such as CC-CKR-2b and CC-CKR3, serve as entry cofactors for macrophage-tropic HIV-1 strains. T-cell-tropic strains can infect primary T-cells and T-cell lines, but not macrophages, whereas macrophage-tropic strains can infect macrophages and primary T-cells, but not T-cell lines. T-cell- and macrophage-tropic strains are discussed more fully in Deng et. al., Nature 381:661-666 (1996), which is hereby incorporated by reference in its entirety. Examples of T-cell-tropic strains include laboratory isolates, such as IIIB and MN.

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AP/P/99/01432

Macrophage-tropic strains include primary isolates, including but not limited to A244, GNE6, GNE8, and breakthrough viruses from vaccinees immunized with gp120-based vaccines. Dual-tropic strains can use both types of co-receptors, entering cells via CXC-CKR-4 or via one or more CC-CKR family members, preferably CC-CKR-5, CC-CKR-2b, or CC-CKR-3. While the present invention is not intended to be bound or limited by any one theory, the entry of T-cell tropic and macrophage-tropic HIV-1 strains is believed to provide a unifying explanation of the differences in cell tropism between viral strains, the resistance to HIV-1 infection by many CD4-transfected nonprimate cells, and the HIV-1-infection resistance of a portion of the human population.

Accordingly, in one embodiment is a vaccine containing (1) a first gp120 polypeptide sequence, or fragment thereof, from a macrophage-tropic HIV-1 strain and/or a second gp120 polypeptide sequence, or fragment thereof, from a T-cell tropic strain, in combination with (2) a breakthrough isolate HIV gp120 polypeptide sequence, or fragment thereof, from a vaccinee vaccinated with the first and/or second HIV gp120 polypeptide sequence. Preferably, the vaccine includes at least two gp120 polypeptide sequences that bind to different chemokine receptors. In one embodiment, the vaccine includes first and second gp120 polypeptide sequences that bind to different chemokine receptors. In addition, the breakthrough isolate gp120 polypeptide sequence can bind to a different chemokine receptor than the chemokine receptor(s) bound by either or both of the first and second gp120 polypeptide sequence(s).

A preferred T-cell tropic strain is a laboratory isolate, most preferably MN. Preferred macrophage-tropic viruses for use in the invention are GNE6 and GNE8, which are representative of the breakthrough

AP/P/99/01432

viruses disclosed herein and differ from MN in that
their gp120s induce the formation of antibodies that
recognize the gp120 sequences (e.g., the V3 domain)
involved in binding to CC chemokine receptors, such as
5 CXC-CR-5.

In one embodiment, HIV infection is prevented by
administering one or more chemokine receptor-binding
gp120 polypeptide sequences, or fragment(s) thereof
containing appropriate chemokine receptor-binding
10 domains, in a vaccine, such as those described above.
Preferably, the vaccine also includes one or more
CD4-binding gp120 polypeptide sequences or appropriate
fragments thereof. Such vaccines induce anti-HIV
antibodies that inhibit viral gp120-chemokine receptor
15 or -CD4 binding. In addition, such gp120 polypeptides
can directly inhibit HIV infection by binding to one or
more co-receptors for HIV infection, such as CD4 or a
chemokine receptor, thus providing a prophylactic or
therapeutic effect in treating HIV infection.
20 Preferably, gp120 polypeptide sequences useful in this
regard contain the T-cell binding (TCB) domain.

Various uses of chemokine receptor-binding gp120
polypeptides are discussed below with regard to the CC
chemokine receptor family. However, those skilled in
25 the art recognize that this discussion applies equally
to CXC chemokine receptors that act as cofactors in HIV
infection.

The gp120 polypeptides can be used as a
composition containing one or more gp120 polypeptides,
30 as described for use as a vaccine or immunogen. The
composition can be administered, prophylactically or
therapeutically, to a patient at risk of infection or
in need of such treatment using the dosages and routes
and means of administration described herein. However,
35 chronic administration may be preferred and dosages can
be adjusted accordingly. It is noted that in vivo

administration can also induce antibodies that bind viral gp120, further inhibiting virus binding to CC-CKR.

5 The gp120 polypeptides can also be used in screening assays to identify antagonists of CC-CKR. For example, candidate antagonists can be screened for inhibition of binding of gp120 to a CC-CKR CC-CKR receptor that is isolated and attached to a surface (e.g., plastic dish) or recombinantly or naturally
10 expressed on the surface of a cell. Antagonists can either bind gp120 or bind receptor. Preferred candidate antagonists include gp120 compounds, small gp120 peptides (5 to 20 amino acids in length, preferably 7 to 10 amino acids in length) or
15 peptidomimetics of gp120 that bind receptor, monoclonal antibodies that bind gp120, and small organic molecules that bind either gp120 or receptor.

The antibodies induced by the gp120 polypeptides can also be used to induce anti-idiotypic antibodies
20 that bind CC chemokines. These anti-idiotypic antibodies can be screened for binding to an anti-gp120 polypeptide antibody and inhibiting gp120 from binding CC-CKR receptor. Such anti-idiotypic antibodies mimic gp120 by binding to CC-CKR receptor. Such antibodies,
25 preferably human antibodies, can be obtained in a number of ways, such as human antibodies from combinatorial libraries (e.g., Burton et al. Adv. Immunolo. (1994) 57:191-280). It is now possible to produce transgenic animals (e.g., mice) that are
30 capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice
35 results in complete inhibition of endogenous antibody production. Transfer of the human germ-line

immunoglobulin gene array in such germ-line mutant mice results in the production of human antibodies upon antigen challenge as described in Jakobovitis et al., *Proc. Natl. Acad. Sci. USA* 90: 2551 (1993); Jakobovits et al., *Nature* 362:255-258 (1993); Bruggermann et al., *Year in Immuno.* 7: 33 (1993).

Alternatively, phage display technology as described by McCafferty et al., *Nature* 348:552-553 (1990) can be used to produce human antibodies and antibody fragments in vitro from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are closed in-frame either into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Phage display can be performed in a variety of formats as reviewed by, for example, Johnson, et al., *Current Opinion in Structural Biology* 3:564-571 (1993).

Several sources of V-gene segments can be used for phage display. Clackson et al., *Nature*, 352: 624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors (or embryonic cells) can be constructed. It has been demonstrated that antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., *J. Mol. Biol.*, 222: 581-597 (1991), or Griffith et al., *EMBO J.*, 12: 725-734 (1993).

In a natural immune response, antibody genes accumulate mutations at a high rate (somatic hypermutation). Some of the changes introduced confer higher affinity, and B cells displaying high-affinity surface immunoglobulin are preferentially replicated and differentiated during subsequent antigen challenge. This natural process can be mimicked by employing the technique known as "chain shuffling" (Marks et al., *Bio/Technol.* 10:779-783 [1992]). In this method, the affinity of "primary" human antibodies obtained by phage display can be improved by sequentially replacing the heavy and light chain V region genes with repertoires of naturally occurring variants (repertoires) of V domain genes obtained from unimmunized donors. This technique allows the production of antibodies and antibody fragments with affinities in the nM range. A strategy for making very large phage antibody repertoires has been described by Waterhouse et al., *Nucl. Acids Res.*, 21: 2265-2266 (1993).

Accordingly, antibodies that bind CC-CKR can be obtained by screening antibodies or fragments thereof expressed on the surface of bacteriophage in combinatorial libraries or in other systems as described above with a gp120 monoclonal antibody that inhibits gp120 binding to receptor.

In addition to screening antibodies with a gp-120 antibody, random or combinatorial peptide libraries can be screened with either a gp120 antibody or the gp120 compounds of the invention. Approaches are available for identifying peptide ligands from libraries that comprise large collections of peptides, ranging from 1 million to 1 billion difference sequences, which can be screened using monoclonal antibodies or target molecules. The power of this technology stems from the chemical diversity of the amino acids coupled with the

AP/P/99/01432

large number of sequences in a library. See for example, Scott et al., *Cur. Open. Biotechnol.* 5(1):40-8 (1994); Kenan et al. *Trends Biochem. Sci.* (1994) 19(2):57-64. Accordingly, the monoclonal antibodies, preferably human monoclonals or fragments thereof, generated as discussed herein, find use in treatment by inhibiting or treating HIV infection or disease progression, as well as in screening assays to identify additional pharmaceuticals.

Production of gp120

gp120 for a vaccine can be produced by any suitable means, as with prior art HIV gp120 subunit vaccines. Recombinantly-produced or chemically synthesized gp120 is preferable to gp120 isolated directly from HIV for safety reasons. Methods for recombinant production of gp120 are described below.

Oligonucleotides encoding gp120 from breakthrough isolates and capable of expressing gp120 can be prepared by conventional means. For example, the nucleotide sequence can be synthesized. Alternatively, another HIV nucleotide sequence encoding gp120 can be used as a backbone and altered at any differing residues as by site-directed mutagenesis.

Site-directed mutagenesis is described in Kunkel et al, *Proc. Natl. Acad. Sci. (USA)* 82:488-492 (1985) and Zoller et al, *Nuc. Acids Res.* 10:6487-6500 (1982) and is well known.

In a preferred embodiment, the nucleotide sequence is present in an expression construct containing DNA encoding gp120 under the transcriptional and translational control of a promoter for expression of the encoded protein. The promoter can be a eukaryotic promoter for expression in a mammalian cell. In cases where one wishes to expand the promoter or produce gp120 in a prokaryotic host, the promoter can be a

AP/P/99/01432

prokaryotic promoter. Usually a strong promoter is employed to provide high-level transcription and expression.

5 The expression construct can be part of a vector capable of stable extrachromosomal maintenance in an appropriate cellular host or may be integrated into host genomes. Normally, markers are provided with the expression construct which allow for selection of a host containing the construct. The marker can be on
10 the same or a different DNA molecule, desirably, the same DNA molecule.

The expression construct can be joined to a replication system recognized by the intended host cell. Various replication systems include viral
15 replication systems such as those from retroviruses, simian virus, bovine papilloma virus, or the like. In addition, the construct may be joined to an amplifiable gene, e.g. the DHFR gene, so that multiple copies of the gp120 DNA can be made. Introduction of the
20 construct into the host will vary depending on the construct and can be achieved by any convenient means. A wide variety of prokaryotic and eukaryotic hosts can be employed for expression of the proteins.

Preferably, the gp120 is expressed in mammalian
25 cells that provide the same glycosylation and disulfide bonds as in native gp120. Expression of gp120 and fragments of gp120 in mammalian cells as fusion proteins incorporating N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is
30 described in Lasky, L. A. et al., 1986 (Neutralization of the AIDS retrovirus by antibodies to a recombinant envelope glycoprotein) Science 233: 209-212 and Haffar, O.K. et al., 1991 (The cytoplasmic tail of HIV-1 gp160 contains regions that associate with cellular
35 membranes.) Virol. 180:439-441, respectively. A preferred method for expressing gp120 is described in

AP/P/99/01432

the examples. In the examples, a heterologous signal sequence was used for convenient expression of the protein. However, the protein can also be expressed using the native signal sequence.

5 An isolated, purified gp120 polypeptide having one of the amino acid sequences illustrated in Table 1 can be produced by conventional methods. For example, the proteins can be chemically synthesized. In a preferred embodiment, the proteins are expressed in mammalian
10 cells using an expression construct of this invention. The expressed proteins can be purified by conventional means. A preferred purification procedure is described in the examples.

15 gp120 Fragments

The present invention also provides gp120 fragments that are suitable for use in inducing antibodies for use in a vaccine formulation. A truncated gp120 sequence, as used herein, is a fragment
20 of gp120 that is free from a portion of the intact gp120 sequence beginning at either the amino or carboxy terminus of gp120. A truncated gp120 sequence of this invention is free from the C5 domain. The C5 domain of gp120 is a major immunogenic site of the molecule.
25 However, antibodies to the region do not neutralize virus. Therefore, elimination of this portion of gp120 from immunogens used to induce antibodies for serotyping is advantageous.

In another embodiment, the truncated gp120
30 sequence is additionally free from the carboxy terminal region through about amino acid residue 453 of the gp120 V5 domain. The portion of the V5 domain remaining in the sequence provides a convenient restriction site for preparation of expression
35 constructs. However, a truncated gp120 sequence that is free from the entire gp120 V5 domain is also

suitable for use in inducing antibodies.

In addition, portions of the amino terminus of gp120 can also be eliminated from the truncated gp120 sequence. In particular, the truncated gp120 sequence
5 can be free from the gp120 signal sequence. The truncated gp120 sequence can be free from the carboxy terminus through amino acid residue 111 of the gp120 C1 domain, eliminating most of the C1 domain but preserving a convenient restriction site. However, the
10 portion of the C1 domain through the V2 cysteine residue that forms a disulfide bond can additionally be removed, so that the truncated gp120 sequence is free from the carboxy terminus through amino acid residue 117 of the gp120 C1 domain. In a preferred embodiment,
15 the truncated gp120 sequence is free from the amino terminus of gp120 through residue 111 of the C1 domain and residue 453 through the carboxy terminus of gp120.

The truncated gp120 sequences can be produced by recombinant engineering, as described previously.
20 Conveniently, DNA encoding the truncated gp120 sequence is joined to a heterologous DNA sequence encoding a signal sequence.

It is understood that the application of the teachings of the present invention to a specific
25 problem or situation is within the capabilities of one having ordinary skill in the art in light of the teachings contained herein. Examples of the products of the present invention and representative processes for their isolation, use, and manufacture appear below, but should not be construed to limit the invention.
30 All literature citations herein are expressly incorporated by reference.

35

EXAMPLES Materials and Methods

Specimen collection from human volunteers. Blood was collected from MN-rgp120-immunized individuals who were infected with HIV-1 while participating in Phase I (NIH Protocol AVEG 016) and Phase II (NIH Protocol AVEG 201) HIV-1 vaccine trials sponsored by the National Institutes of Health (NIH). The demographics of the subjects in the study, and the study design have been described in McElrath; *Seminars in Cancer Biol.* 6:1-11 (1995); McElrath et al.; *Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS*. Bethesda, MD 216 (1996). Specimens were obtained according to an informed consent protocol approved by the institutional review boards of the participating institutions. In the experimental section, the time of HIV-1 infection is specified with regard to data provided by the NIH AIDS Vaccine Evaluation Network where PCR (RNA) and/or serologic assays were used to detect HIV-1 infection.

Sample preparation for cloning HIV-1 envelope glycoproteins. Peripheral blood mononuclear cells (PBMCs) from HIV-1 infected vaccinees were prepared from heparinized venous blood by FICOLL-HYPAQUE gradient centrifugation. Cell number and viability were determined. After separation, PBMCs were washed twice in phosphate-buffered saline and suspended at a cell density of 6×10^6 cells/ml in PCR lysis buffer (50 mM KCl, 10 mM Tris (pH 8.4), 2.5 mM MgCl₂, 0.1 mg/ml gelatin (Sigma), 0.45% NONIDET P40 detergent, 0.45% TWEEN 20 detergent (both detergents are commercially available from United States Biochemical Corp.) and 0.06 mg/ml Proteinase K (Gibco BRL) to lyse the cells. The lysate was incubated at 50-60°C for 1 hour, followed by inactivation of the Proteinase K at 95°C for 10 minutes. Lysates were shipped frozen and stored at -70°C until use.

AP/P/99/01432

Polymerase chain reaction (PCR) amplification.

Samples were subjected to two rounds of PCR amplification using the nested primers described below. In the first round, 25 μ l aliquots of PBMC lysates (containing about 1 μ g genomic DNA) were mixed with an equal volume of a PCR reaction mix containing 400 μ M each dNTP, 200 μ g/ml BSA (Sigma Chemical Corporation, RIA grade) and about 100 pmoles of each primer in 50 mM KCl, 20 mM Tris (pH 8.4) and 3 mM MgCl₂. After an initial 10 minute denaturation step at 95°C, 5 units of *Tag* polymerase (AMPLITAQ, Perkin Elmer Cetus) were added during an 55°C soak step, and samples were overlayed with mineral oil.

The PCR profile was as follows: 2 cycles having 1 minute at 55°C, 2.5 minutes at 72°C and 1 minute at 94°C, followed by 28 cycles with 30 seconds at 55°C, 2.5 minutes at 72°C and 45 seconds at 94°C, and an extension step at 72°C for 5 minutes.

Aliquots of 10 μ l from the first-round reactions were re-amplified with appropriate nested primers in a final reaction volume of 100 μ l, using either the reagents and profile described above or the reagents and profile described in the PCR Optimizer Kit (Invitrogen.) PCR reaction products were purified using QIAQUICK-spin columns (Qiagen Inc.) The primer pair used in the first round was either 120.os.F (5'-gggaattcggatccAGAGCAGAAGACAGTGGCAATGA with homologous sequence at position 6248-6270 of HIVPV22) (SEQ. ID. NO. 34) or JM11A (5'-ctcgag-CTCCTGAAGACAGTCAGACTCATCAAG at position 6048-6074) (SEQ. ID. NO. 35) in the forward direction [Kusumi et al.; *J. Virol.* 66:875 (1992)] combined with 120.os.R (5'-ggtctagaagctttaGCCCATAGTGCTTCCTGCTGCT-CC at position 7836-7859) (SEQ. ID. NO. 36) in the reverse direction. The internal nested primers were 120.BX.F (5'-gggcggatcctcgaGGTACCTGTRTGAAAGAAGCA at position

AP/P/99/01432

6389-6410; R: A or G) (SEQ. ID. NO. 37) and 120.is.R
(5'-ggtctagaagctttatGCTCCYAAGAACCCAAGGAACA at position
7819-7841; Y: T or C) (SEQ. ID. NO. 38). Heterologous
primer sequences are shown in lower case letters.

5

Subcloning of PCR products and the expression of
recombinant envelope glycoproteins as fusion proteins.
The HIV-1 envelope glycoprotein gp120 sequences were
cloned and expressed as chimeric genes and fusion
10 proteins, where the signal sequence and 27 amino acids
from the mature N terminus of herpes simplex virus
type 1 (HSV-1) were fused to the N-terminal sequences
of the gp120 genes, corresponding to amino acid 13 of
the mature gp120 sequence. PCR products containing
15 gp120 sequences from the breakthrough specimens were
cloned into pRK5 expression plasmid as chimeric genes
using combinations of restrictions sites engineered
into the heterologous PCR primer tails and the Xho I
site engineered into the N-terminal sequence of
20 HSV-1 gD.

The resulting double-stranded DNA was sequenced
with Sequenase and the dGTP Reagent Kit (United States
Biochemical Corp.). Sequences from glycoprotein D were
provided to enhance expression and to provide a flag
25 epitope to facilitate protein analysis, as described in
Berman et al.; *J. Virol.* 7:4464-9 (1992); Nakamura et
al.; *AIDS and Human Retroviruses* 8:1875-85 (1992); and
Nakamura et al.; *J. Virol.* 67:6179-91 (1993).

Briefly, isolated DNA fragments generated by the
30 PCR reaction were ligated into a plasmid (pRK.gD-5,
pRKgDstop) designed to fuse the gp120 fragments, in
frame, to the 5' sequences of the glycoprotein D (gD)
gene of Type 1 Herpes Simplex Virus (gD-1) and the 3'
end to translational stop codons. The fragment of the
35 gD-1 gene encoded the signal sequence and 25 amino
acids of the mature form of HSV-1 protein. To allow

AP/P/99/01432

for expression in mammalian cells, chimeric genes fragments were cloned into the pRK5 expression plasmid (Eaton et al., *Biochemistry* 291:8343-8347 (1986)) that contained a polylinker with cloning sites and
 5 translational stop codons located between a cytomegalovirus promotor and a simian virus 40 virus polyadenylation site.

The resulting plasmids were transfected into the 293s embryonic human kidney cell line (Graham et al.,
 10 *J. Gen. Virol.* 36:59-77 (1977)) using a calcium phosphate technique (Graham et al., *Virology* 52:456-467 (1973)). Growth conditioned cell culture media was collected 48 hr after transfection, and the soluble proteins were detected by ELISA or by specific
 15 radioimmunoprecipitation where metabolically labeled proteins from cell culture supernatants were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (PAGE) and visualized by autoradiography as described in Berman et al.,
 20 *J. Virol.* 63:3489-3498 (1989) and Laemmli, *Nature* 227:680-685 (1970).

Serologic assays. Sera were assayed for antibodies to rgp120, antibodies to synthetic gp120 V3
 25 domain peptides corresponding to sequences from the gp120 V3 domain, and antibodies able to inhibit the binding of MN-rgp120 to cell surface CD4 using serologic assays described in Berman et al.; *J. Virol.* 7:4464-9 (1992); Nakamura et al.; *AIDS and*
 30 *Human Retroviruses* 8:1875-85 (1992); and Nakamura et al.; *J. Virol.* 67:6179-91 (1993). Endpoint titers of antibody binding to gp120 and V3 peptides were determined using three fold-serial dilutions of sera. The endpoint dilution titer was defined as the last
 35 dilution that produced an optical density value that was two times higher than the mean of the optical

AP/P/99/01432

densities of 1:50 diluted, pooled, normal human sera. Antibody titers were calculated by a computer program that interpolated values between antibody dilutions. The inter-assay coefficient of variation of positive control standard sera was 35%.

Binding of monoclonal antibodies to rgp120 from breakthrough viruses. An ELISA similar to that described by Moore et al.; *AIDS* 3:155-63 (1989) was used to measure the binding of various monoclonal antibodies (MAbs) to rgp120s from breakthrough viruses. Briefly, Nunc-Immuno plates (Maxisorp, certified) were coated (100 μ l at 5 μ g/ml in PBS at 4°C overnight) with an affinity-purified sheep polyclonal antiserum to a peptide at the C terminus of gp120 (D7324, International Enzymes, Fallbrook, CA). After washing once with PBS-0.05% TWEEN-20 detergent, the plates were blocked with PBS-1.0% BSA for 30-60 minutes at room temperature. Cell culture supernatants from 293s cells, diluted to contain equivalent amounts of the gD-rgp120 fusion protein, were added and incubated for 2 hours at room temperature followed by three washes with PBS-0.05% TWEEN-20 detergent. Various MAbs were diluted in PBS-1.0% BSA and 100 μ L of the diluted MAbs were added to each well and incubated for 1 hour at room temperature.

The plates were washed 3 times and incubated with 100 μ l of a horseradish peroxidase-conjugated second antibody (goat anti-mouse or anti-human IgG, Cappel) for 1 hour at room temperature. After 3 washes the plates were developed and the OD₄₉₂ (optical density at 492 nm) read in a plate reader. Growth conditioned cell culture supernatants were normalized by dilution based on binding by MAb 5B6 which is specific for HSV-1 glycoprotein D fusion protein.

Virus neutralization assays. The ability of vaccinee sera to inhibit infection of MT4 cells by HIV-1_{MN} was measured in a cytopathicity assay where cell viability was quantitated using a calorimetric indicator dye, as described in Robertson et al.; *J. Virol. Methods* 20:195-202 (1988). Briefly, a virus stock of HIV-1_{MN} (obtained from Dr. Michael Norcross, U.S. Food and Drug Administration) was prepared as the clarified supernatant from chronically infected H9/HIV-1_{MN} cell culture. H9 cells chronically infected with HIV-MN were pelleted and resuspended in one-tenth the original volume of medium. Cell-associated virus was released by the mechanical shearing effects of rapid vortexing of the cells as described in Wrin et al.; *J. Virol.* 69:39-48 (1995).

An amount of virus sufficient to ensure complete cell lysis killing in 7 days was incubated with three-fold serial dilutions of test antisera, and then used to challenge MT4 T-lymphoid cells in 10% FCS/RPMI-1640 cell culture media. The cultures were incubated for 7 days at 37°C in 5% CO₂, and then cell viability was tested by the dye MTT, as described by Robertson et al.; *J. Virol. Methods* 20:195-202 (1988). Virus neutralization endpoints were quantitated by measurement of OD at 570-650 nm, and then the endpoint titers were calculated as the reciprocal of the antiserum dilution giving a signal that was two-fold above the control signal with unprotected (killed) cells. These titers were typically twice those calculated at 50% protection.

Results

Immunization history of infected subjects. Since 1992, 499 adults have been immunized with MN-rgp120 in Phase I trials in low or moderate risk individuals and in a Phase II clinical trial involving moderate to high

AP/P/99/01432

5 risk individuals. The studies described herein entail the genetic and immunologic characterization of the first seven of nine individuals who became infected with HIV-1 through high risk behavior during the course of these trials. A listing of the trials and summary of the status of the vaccinees is presented in Table 2A. A listing of the analysis of the vaccinees is presented in Table 2B.

10

TABLE 2A
Description of Vaccinees Infected with HIV-1
After Immunization with MN-rgp120

	<u>Study No.</u>	<u>Case No.</u>	<u>*Risk Group</u>	<u>†Antigen dose/ Adjuvant</u>
15	016	C6	M/H	300/QS21
	016	C8	M/H	600/QS21
	016	C15	M/H	300/QS21
	201	C7	M/H	600/Alum
	201	C11	M/H	600/Alum
20	201	C10	M/IDU	600/Alum
	201	C17	M/IDU	600/Alum

* - M/H indicates male homosexual; M/IDU indicate male intravenous drug user.

25 † - numbers indicate dose in micrograms of MN-rgp120 injected per immunization; QS21 indicates antigen was formulated in QS21 adjuvant; Alum indicates MN-rgp120 formulated in aluminum hydroxide.

AP/T/99/01432

TABLE 2B
Description of Vaccinees Infected with HIV-1
After Immunization with MN-rgp120

	Case	Injection Schedule (months)	Injections before HIV-1+	Time of HIV-1+ (months)	Interval: to HIV-1+ (months)
5	No.				
	C6	0,1,10.5	2	4.00	2.00
	C8	0,1	2	4.00	3.00
	C15	0,1,2	3	6.25	4.00
10	C7	0,1,6,12	3	9.25	3.00
	C11	0,1,6,12	4	19.50	6.75
	C10	0,1,6,19	3	19.50	13.50
	C17	0,1,6,18	4	24.75	6.25

□ - indicates interval between last immunization and detection of HIV-1 infection.

Three of the infections occurred in a Phase I trial (NIH Protocol AVEG 201) that compared the safety and immunogenicity of MN-rgp120 formulated in two different adjuvants (alum and QS21), and four of the infections occurred in a Phase II trial aimed at establishing the safety and immunogenicity of MN-rgp120 in various high risk groups (e.g., intravenous drug users, homosexual and bisexual males, and partners of HIV-1 infected individuals).

Of the seven infections studied (Table 3), two (C6 and C8) occurred after two injections, three (C7, C10 and C15) occurred after three injections, and two (C11 and C17) occurred after receiving the four scheduled injections. The interval between receiving the last immunization and becoming infected was 2 to 13.5 months.

AP/P/99/01432

TABLE 3
Peak Post Boost MN-rgp120 Antibody Titers
in Vaccinees that Became Infected with HIV-1

5	<u>Injections</u>	<u>C6</u>	<u>C8</u>	<u>C15</u>	<u>C7</u>	<u>C11</u>	<u>C10</u>	<u>C17</u>
	1	<50	2185	79	<50	1890	na	na
	2	21539	10125	na	413	32696	7771	7056
	3	#	#	4460	9707	34728	11627	1841
								3
	4	#	#	#	#	#	#	1134
								0
10	# - indicates specimen not analyzed because of HIV-1 infection.							
	na - indicates the sample was not available for testing.							
15	boldface - indicates unusually low antibody titers.							

Antibody response to gp120 in vaccinated individuals. The magnitude and specificity of the antibody response to MN-rgp120 was measured by ELISA in all infected individuals throughout the course of the immunization regime (Figure 1). Five of the seven

AP/P/99/01432

subjects exhibited normal antibody response kinetics that included a small but reproducible primary response (1:100-1:2,000) and a strong secondary (booster) response (titers ranging from 1:7,000-1:32,000), and antibody responses following third and fourth injections that were similar or marginally higher than those achieved after the second immunization (Figure 1, Table 3).

The antibody response observed in C7 (Figure 1C) was unusual in that no antibodies were detectable after the primary injection and a titer of only 1:350 was detected after the second injection. It thus appeared that C7 did not respond to the primary immunization, and that the antibody response obtained after the second injection represented a primary immune response. Consistent with this hypothesis, the third injection elicited a titer of only 1:9,707, typical of those normally seen after two immunizations.

An atypical antibody response was also seen in subject C15 (Figure 1G) who was immunized according to an accelerated immunization schedule of 0, 1, and 2 months. As expected, the antibody titer seen in this subject (1:4,460) was at the low end of what is typically achieved after two immunizations and was far below normal values for three immunizations. The lack of an effective booster response after the third immunization of C15 was not surprising in view of previous studies where an accelerated 0, 1, and 2 month immunization schedule in baboons [Anderson et al.; *J. Infect. Dis.* 160:960-9 ((1989))] similarly prolonged the secondary response and failed to elicit an effective tertiary booster response.

Retrospective analysis of serum and plasma from subjects C6 (Figure 1A) and C8 (Figure 1B) indicated that they became infected with HIV-1 at some point between the second and third immunizations. Serologic

AP/P/99/01432

evidence of HIV-1 infection was evident in the gp120 antibody assays where the titers failed to decline two weeks after the second injection and instead formed an uncharacteristic high titer plateau (Figures 1A and 1B). A similar plateau in MN-rgp120 titer after the third injection, suggested that subject C7 became infected around week 36, approximately 16 weeks after receiving the third injection (Figure 1C). Subjects C10 (Figure 1E), C11 (Figure 1D), C15 (Figure 1G), and C17 (Figure 1F) developed unexpected increases in gp120 titers, typical of HIV-1 infection, after either the third or fourth immunizations. The data obtained demonstrate that immunologic priming for MN-rgp120 antibody responses is insufficient to provide universal protection from HIV-1 infection.

Antibody titers to the V3 domain. To further characterize the antibody response to gp120, antibody titers were measured to a synthetic V3 domain peptide of MN-rgp120 containing the principal neutralizing determinant (PND). Five of the seven subjects developed good V3 titers (1:400 to 1:4000) after the second immunization, however two subjects (C7 and C15) required three immunizations before developing significant tiers (Figures 1C and 1G). As had been observed previously (11), the peak V3 titers in some individuals (e.g. C11, C10, C17) appeared to decline with each successive immunization (Figures 1D, 1E, and 1F). After HIV-1 infection, two patterns of V3 reactivity were observed. Three subjects (C6, C7, and C10) showed large increases in titer to V3 domain peptides (Figures 1A, 1C, and 1E) whereas C8 (Figure 1B) showed a large decrease in V3 titer. At the time of analysis, the data were insufficient to

AP/P/99/01432

draw any conclusions regarding the changes in V3 titers in response to HIV-1 infection in subjects C11, C15 and C17.

5 The results obtained indicate that the ability to form antibodies reactive with the V3 domain at various time-points prior to HIV-1 infection is not a valid correlate of protective immunity against all strains of HIV-1.

10 **CD4 Inhibition titers.** Antibodies that block the binding of gp120 to CD4 represent a heterogeneous class of virus neutralizing antibodies. Some are known to bind to the C4 domain of gp120 [Nakamura et al.; *J. Virol.* 67:6179-91 (1993); Anderson et al.; *J.*
15 *Infect. Dis.* 160:960-9 ((1989))], and some are known to recognize conformation dependent discontinuous epitopes [Berman et al.; *J. Virol.* 7:4464-9 (1992); Nakamura et al.; *J. Virol.* 67:6179-91 (1993); McKeating et al.; *AIDS Research and Human Retroviruses*
20 8:451-9 (1992); Ho et al.; *J. Virol.* 65:489-93 (1991); Barbas et al.; *Proc. Natl. Acad. Sci. USA* 91:3809-13 (1994)].

One way to detect antibodies to both types of epitopes is to measure the ability of vaccinee sera to
25 prevent the binding of [¹²⁵I]-labeled gp120 to cell surface CD4 [[Nakamura et al.; *AIDS and Human Retroviruses* 8:1875-85 (1992); Nakamura et al.; *J. Virol.* 67:6179-91 (1993)]. CD4 blocking titers were detected in all seven of the vaccinees prior to
30 infection (Figure 2) with peak titers that ranged from 1:10-1:300. At the last time point prior to infection, the CD4 titers in five of the seven vaccinees was low (1:30 or less). One vaccinee (C17), however, possessed a CD4 blocking titer of about 1:300 prior to infection
35 (Figure 2F). Thus, the lack of antibodies that block the binding of MN-rgp120 to CD4 cannot account for all

AP/P/99/01432

of the infections. Large increases in CD4 blocking titers (1:100-1:1,000) were seen in five of the seven subjects after HIV-1 infection. These included vaccinees C6, C7, C8, C10, and C11. These results demonstrate that the CD4 blocking titers elicited by MN-rgp120 were lower than those elicited by natural infection.

Virus neutralizing activity. The virus neutralizing activity of antisera from MN-rgp120-immunized subjects was measured using a colorimetric assay that measured the viability of MT-4 cells after incubation with antibody treated virus (HIV-1_{MIN}). Since the actual date of infection was not known for any of the breakthrough infections, and serum samples were collected infrequently, the magnitude of the neutralizing antibody response at the time of infection is not known for any of the vaccinees.

Of the seven infections examined, the serum sample closest to the time of infection was that obtained from C7, where a neutralizing titer of 1:15 to HIV-1_{MIN} was present three weeks prior to detection of HIV-1 infection (Table 4). In all other cases, however, the interval between the last injection and the time of infection was 10 to 25 weeks.

AP/P/99/01432

AP001282

TABLE 4
Neutralization Activity of Sera from Vaccinees
Infected with HIV-1

	<u>Week</u>	<u>C6</u>	<u>C8</u>	<u>C15</u>	<u>C7</u>	<u>C11</u>	<u>C10</u>	<u>C17</u>
5	0	<10*	<10*	<10*	<10*	<10*	<10*	<10*
	2	<10	<10	<10	-	-	-	-
	4	<10*	<10*	nd*	<10*	<10*	<10*	<10*
	6	10	80	-	<10	30	150	150
	8	-	-	nd*	-	-	-	-
10	10	-	-	35	-	-	-	-
	15	-	-	-	<10	-	-	-
	16	150#	250#	-	-	30	10	<10
	24			150#	<10*	20*	<10*	<10*
	26				70	500	200	400
15	30				-	-	40	100
	33				15	-	-	-
	35				-	100	-	-
	36				30#	-	10	40
	52					30*	<10	<10
20	54					250	-	-
	57					100	-	-
	63					90	-	-
	64					-	-	<10
	77					40#	-	-
25	78						500#	10*
	80							100
	84							60

AP/P/99/01432

90

150

104

150#

* - indicates immunization.

5 # - indicates HIV-1 positive.

nd - indicates not done.

- - indicates sample not available.

When sera from the two early infections were
10 examined (Table 4), one individual (C6) had a peak
neutralizing titer of 1:10 ten weeks prior to detection
of HIV-1 infection, whereas the other individual (C8)
had a neutralizing titer of 1:80 ten weeks prior to
detection of HIV-1 infection. Subject C15, who was
15 immunized according to an accelerated immunization
schedule, developed a neutralizing titer of 1:35 after
the third injection, 14 weeks prior to HIV-1 infection.
Subject C10, who had a peak neutralizing titer of 1:200
following the third immunization (week 24), had no
20 detectable titer at week 52, six months prior to the
first indication of HIV-1 infection (week 78).

Subject C11 possessed a neutralizing titer of 1:90
at fourteen weeks prior to detection of HIV-1 and a
peak titer of 1:500 following the third immunization.
25 Similarly vaccinee C17 had a neutralizing titer of
1:150 fourteen weeks prior to infection and a peak
titer of 1:400 at two weeks after the third
immunization.

Based on the rate of decay of the gp120 response
30 of approximately two months [Belshe et al.; JAMA
272(6):475-80 (1994)], as well as the observation that
neutralizing titers of 1:150 decayed to 1:10 in 10
weeks in vaccinees C10 and C17, it appears that
neutralizing titers in C8, C15, C11, and C17 could have
35 declined to 1:10 or less in the intervals between the
last pre-infection serum sample and the time of HIV-1

AP/P/99/01432

detection.

The results of these studies demonstrated that all vaccinees developed some level of virus-neutralizing antibodies at some time prior to HIV-1 infection, and that the magnitude of the neutralizing response was probably low at the time of infection. In general, the magnitude of the virus-neutralizing response observed in the individuals that became infected with HIV-1 was comparable to that seen in non-infected vaccinees as described in Belshe et al.; *JAMA* 272(6):475-80 (1994).

Sequences of Viruses. To evaluate the similarity of the breakthrough viruses with the vaccine antigen, nucleotide sequences for gp120 from all seven breakthrough viruses were determined. Envelope glycoprotein genes were amplified from proviral DNA using the polymerase chain reaction. Sequences were obtained by direct amplification of DNA from lysates of gradient-purified lymphocytes obtained directly from patient blood without any intermediate tissue culture or amplification step.

A listing of the complete gp120 sequences (two clones per specimen) is provided in Figure 3. All seven envelope glycoproteins possessed sequences typical of subtype (clade) B viruses. The overall homology with MN-rgp120 ranged from 69-80% (Table 5).

AP/P/99/01432

TABLE 5
Comparison of MN-rgp120 Sequence with Sequences
from Infected Vaccinees*

		MN	C6.1	C8.3	C7.2	C11.5	C10.5	C17.1	C15.2
5	MN	100	79	78	70	75	69	80	72
	C6.1		100	78	70	81	75	90	79
	C8.3			100	68	80	76	84	83
	C7.2				100	80	73	76	73
	C11.5					100	75	70	80
10	C10.5						100	70	72
	C17.1							100	87
	C15.2								100

* - Data indicate percent identity.

- 15 Interestingly, a high percentage (four of seven) of the breakthrough viruses differed from MN-rgp120 by 25-30% [Myers et al.; *Retroviruses and AIDS Database*, Los Alamos National Laboratory (1992 and 1995)].
- 20 Historically this degree of sequence variation is typical of inter-subtype (intra-clade) variation rather than intra-subtype variation which is expected to be in the 10-20% range [Myers et al.; *Retroviruses and AIDS Database*, Los Alamos National Laboratory (1992 and 1995)]. Of the viruses with the greatest homology to
- 25 MN-rgp120, two (C6 and C8) occurred as early infections, prior to complete immunization, and one (C17) occurred as a late infection.

- 30 **Polymorphism in the V3 Domain.** Of particular interest were polymorphisms in regions known to contain epitopes recognized by virus neutralizing antibodies. The best characterized neutralizing epitope, the principal neutralizing determinant (PND), occurs at the

tip of the V3 loop. In subtype B viruses, approximately 60% possess the MN serotype-defining signature sequence, IGPGRF (SEQ. ID. NO. 39), based on identity with the prototypic MN strain of HIV-1

- 5 [Berman et al.; *J. Virol.* 7:4464-9 (1992);
Myers et al.; *Retroviruses and AIDS Database*, Los
Alamos National Laboratory (1992 and 1995);
La Rosa et al.; *Science* 249:932-5 (1990)].

- 10 Three of the viruses (C6, C8, and C17) possessed
the MN serotype signature sequence (Figure 3). In
contrast, four viruses possessed sequences with radical
amino acid substitutions in the PND [IGPGRAW (C7),
LGPGSTF (C11), IGPGRL (C10), and IGPGSAF (C15)]
(SEQ. ID. NOS. 40-43, respectively), and therefore were
15 classified as "non-MN like" viruses. Of note, each of
the four "non-MN-like" sequences were rare (Table 6)
and were not typical of the most common "non-MN"
variants of subtype B viruses [Myers et al.;
Retroviruses and AIDS Database, Los Alamos National
20 Laboratory (1992 and 1995)].

AP/P/99/01432

TABLE 6
Frequency of Polymorphisms at the Principal
Neutralizing Determinant in HIV-1 Infected
Individuals Immunized with MN-rgp120*

Sequence	n	Observed Frequency	Dataset Frequency			
			GNE (n=52)	LANL (n=519)	LANL.1 (n=160)	LaRosa (n=245)
GPGRAF	3	0.42	0.67	0.57	0.66	0.60
GPGRAW	1	0.14	0.03	0.013	0.06	0.010
GPGRVL	1	0.14	<0.02	0.004	<0.006	<0.008
GPGSTF**	1	0.14	<0.02	<0.002	<0.006	<0.004
GPGSAF	1	0.14	0.02	0.011	<0.006	<0.004

* - Data set GNE refers to a collection of 52 independent isolates collected in 1992; dataset LANL refers to a collection of 519 sequences reported by Myers et al., *Retroviruses and AIDS Database*, Los Alamos National Laboratory 1992 and 1995; LANL.1 refers to a collection of 160 epidemiologically unlinked individuals provided by B. Korber (personal communication); dataset La Rosa refers to sequence data reported by La Rosa et al., *Science* 249:932-5 (1990).

** - Sequences were not present in the data sets examined.

The prevalence of viruses with PND sequences matching the breakthrough viruses ranged from a high of 1.3% (C7) to a low of 0.2% (C11) in a listing of 519 subtype B sequences compiled by the Los Alamos National Laboratory [Myers et al.; *Retroviruses and AIDS Database*, Los Alamos National Laboratory (1992 and 1995)]. Similarly low frequencies were observed in

three other independently derived data sets (Table 6).
The occurrence of these sequences did not differ
significantly between data sets collected prior to 1985
[La Rosa et al.; *Science* 249:932-5 (1990)] and data
5 collected 1992, or from a set of 160 epidemiologically
unlinked individuals (B. Korber, personal
communication). All four sets of data agreed that the
prevalence of viruses with MN-like PND sequences was in
the range of 60%. Based on this data, four of the
10 seven breakthrough infections were determined to be
caused by viruses that fell outside of the spectrum of
viruses that the vaccine was expected to prevent.

Other features of breakthrough virus V3 domains.

15 Like MN-rgp120, the V3 domains of all of the
breakthrough viruses were 36 amino acids in length.
However, all seven viruses differed from MN-rgp120 with
respect to the number of glycosylation sites and with
respect to the syncytium-inducing (SI) signature
20 sequence.

The sequence of MN-rgp120 is somewhat unusual
[Myers et al.; *Retroviruses and AIDS Database, Los
Alamos National Laboratory* (1992 and 1995)] in that it
lacks an N-linked glycosylation site at position 306 in
25 the V3 domain. The lack of this glycosylation site
does not appear to be antigenically significant since
antisera to MN-rgp120 are known to neutralize a variety
of viruses (e.g. SF-2, DU6587-5, DU4489-5, CC) that
possess a glycosylation site at this position
30 [Berman et al.; *J. Virol.* 7:4464-9 (1992)]

In addition, the V3 domain of MN-rgp120 possessed
sequence polymorphisms (R at position 311, K at
position 324, K at position 328) typical of syncytium
inducing viruses [Fouchier et al.; *J. Virol.* 66:3183-87
35 (1992)], whereas all seven breakthrough viruses
possessed sequences associated with non-syncytium-

AP/P/99/01432

- inducing viruses. Syncytium-inducing viruses have been associated with rapid disease progression [Tersmette et al.; *J. Virol.* 62:2026-32 (1988)] and T cell tropism [O'Brien et al.; *Nature (London)* 348:69-73 (1990);
- 5 Shioda et al.; *Nature (London)* 349:167-9 (1991)]. To date viruses with these properties have not been recovered from any of the MN-rgp120 immunized volunteers.
- 10 **Polymorphism in the V1, V2 and C4 domains.**
Previous investigations have identified additional neutralizing epitopes in the V1, V2 and C4 domains of gp120 [Nakamura et al.; *J. Virol.* 67:6179-91 (1993);
- 15 McKeating et al.; *AIDS Research and Human Retroviruses* 8:451-9 (1992); Ho et al.; *J. Virol.* 65:489-93 (1991); Barbas et al.; *Proc. Natl. Acad. Sci. USA* 91:3809-13 (1994); McKeating et al.; *J. Virol.* 67:4932-44 (1993);
- 20 Moore et al.; *J. Virol.* 67:6136-6151 (1993); Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993)].
- The best characterized of these neutralizing epitopes is in the C4 domain which has attracted special attention because antibodies binding to this area are known to block the binding of gp120 to CD4 [Moore et al.; *AIDS* 3:155-63 (1989); McKeating et al.;
- 25 *AIDS Research and Human Retroviruses* 8:451-9 (1992)]. Because the epitope is located in a conserved (C) domain, naturally-occurring polymorphism in this region is far more limited than in other neutralizing epitopes. Nakamura et al.; *J. Virol.* 67:6179-91 (1993)
- 30 reported that the binding of a number of neutralizing MAbs was dependent on K at position 429.
- Comparison of the sequence of MN-rgp120 with other strains of HIV-1 showed that a common polymorphism, involving the substitution of E for K, occurs at this
- 35 position. Indeed, substrains of the same virus isolate often show polymorphism at this position. The HXB2

AP/P/99/01432

substrain of HIV-1_{LA1} contains K at position 429, whereas the BH10, IIIB, and LAV substrains of the HIV-1_{LA1} contain E at this position [Nakamura et al.; *J. Virol.* 67:6179-91 (1993)]. Similarly, the 1984 isolate of HIV-1_{MN} exhibited E at this position, while the 1990 isolate of HIV-1_{MN}, used to produce MN-rgp120, possessed K at this position.

When the sequences of the infected vaccine recipients were examined (Figure 3), the virus from subject C17, like MN-rgp120 contained K at position 429, whereas the six other viruses that differed from the vaccine immunogen possessed E at this position. These results demonstrated that six of the seven breakthrough viruses differed from the vaccine immunogen at the CD4-blocking, neutralizing epitope in the C4 domain of gp120.

Studies with monoclonal antibodies have defined neutralizing epitopes in the V1 and V2 domains of gp120 [McKeating et al.; *J. Virol.* 67:4932-44 (1993); Moore et al.; *J. Virol.* 67:6136-6151 (1993); Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993)]. Like the polymorphisms that occur in the C4 domain, the V2 domains exhibit several common polymorphisms that affect the binding of virus neutralizing antibodies. One such polymorphism occurs at position 171 which is critically important for the binding of murine MAb 1025, whereas residue 187 is important for the binding of MAb several MABs represented by 1088.

When the V2 domain sequences were examined (Figure 3), all of the infected-vaccine viruses differed from MN-rgp120 in that R replaced G at position 171 and I or V replaced E at position 187. Antibodies recognizing these adjacent sites in the V2 domain of MN-rgp120 would not be expected to neutralize viruses with radical amino acid substitutions at these position. Thus, all seven

AP/P/99/01432

breakthrough viruses differed from MN-rgp120 at a neutralizing epitope in the V2 domain of gp120.

Other neutralizing epitopes have been reported in the V1 domain of gp120 [O'Brien et al.; *Nature (London)* 348:69-73 (1990); McKeating et al.; *J. Virol.* 67:4932-44 (1993)]. Although the neutralizing epitopes in the V1 domain of MN-rgp120 have not been characterized, the polymorphism seen among the breakthrough viruses in this region was interesting. Particularly striking (Figure 3) was that the length of this domain ranged from 20 amino acids (C17) to 45 amino acids (C6), and the number of N-linked glycosylation sites ranged from 2 to 6. In contrast, the V1 domain of MN-rgp120 is 31 amino acids in length and encodes three N-linked glycosylation sites.

Although examination of sequence databases suggest that variation in the V2 region is comparable to the V1 region, the V2 region of the breakthrough viruses showed less variation than expected. Specifically, the length of the V2 region ranged from 36 amino acids (C7) to 39 amino acids in length, with six of seven viruses containing three N-linked glycosylation sites in this domain. A high degree of polymorphism was found in the V4 region where sequences ranged from 26 (C10) to 33 (C15, C7) amino acids in length and contained either 4 or 5 N-linked glycosylation sites.

Antigenicity of envelope glycoproteins from breakthrough viruses. To determine the significance of sequence variation on glycoprotein antigenicity, recombinant gp120 was prepared from the viruses of all seven infected vaccinees (Figure 4). In these studies a series of MAbs was assembled and their binding to MN-rgp120 was compared to that of rgp120 from the vaccinee isolates by ELISA (Table 7).

AP001282

TABLE 7
Relative Reactivity* of MAb Binding to rgp120 from
Infected Subjects Compared with Binding to MN-rgp120

		<u>V3</u>		<u>Discontinuous</u>		<u>C8</u>	<u>V2</u>
5	gp120	1034	50.1	1.5E	1025	1024	1088
	MN	1.0	1.00	1.00	1.00	1.00	1.00
	C6.1	0.37	0.37	0.17	0.00	0.00	0.00
	C6.5	0.33	0.33	0.75	0.00	0.00	0.00
	C8.3	0.11	0.37	0.38	0.00	0.00	0.00
10	C8.6	0.14	0.34	0.29	0.00	0.00	0.00
	C7.2	0.47	0.60	0.71	0.00	0.00	0.00
	C11.5	0.00	0.00	0.17	0.00	0.00	0.00
	C11.7	0.00	0.00	0.17	0.00	0.00	0.00
	C10.5	0.33	0.40	0.46	0.24	0.03	0.04
15	C10.7	0.42	0.48	0.50	0.29	0.07	0.09
	C17.1	0.33	0.52	0.33	0.00	0.30	0.07
	C17.3	0.37	0.56	0.33	0.00	0.38	0.06
	C15.2	0.00	0.47	0.92	0.00	0.00	0.00
	C15.3	0.00	0.37	0.63	0.00	0.00	0.00

* - Relative reactivity values represent ratio of optical densities obtained with rgp120 from patient isolates divided by optical density obtained for MN-rgp120 at a MAb concentration of 2 micrograms per milliliter.

In control experiments, the binding of MAb 5B6 (which is specific for the HSV gD-1 flag epitope fused to the N terminus of all of the rgp120 protein) was used to standardize the amount of gp120 from each isolate (Figure 5A). These studies demonstrated that the assay was carried out under conditions where equivalent amount of rgp120s were captured onto wells of microtiter plates.

The antigenic structure of the V3 domain was examined using the 1034 MAb (isolated from mice immunized with MN-rgp120 as described in Nakamura et al.; *J. Virol.* 67:6179-91 (1993) and the 50.1 MAb (prepared from mice immunized with a synthetic V3 domain peptide as described in Rini et al.; *Proc.*

AP/P/99/01432

Natl. Acad. Sci. USA 90:6325-9 (1993). Both MAbs are known to exhibit potent virus neutralizing activity. When binding to the recombinant proteins was examined, the MAb binding to MN-rgp120 was at least 10-fold greater than to any of the breakthrough virus envelope proteins (Figure 5 B and C). Surprisingly, rgp120 from the three patient isolates (C8, C6, and C17) that possessed the MN serotype-defining sequence, IGPGRAF (SEQ. ID. NO. 39), varied from one another in their MAb binding activity. Thus, the binding of MAb 1034 and MAb 50.1 to rgp120 from C17 was significantly greater than the binding to rgp120s from C6 and C8.

A distinction in the epitopes recognized by these MAbs was evident since C6-rgp120 and C8-rgp120 gave comparable binding with 50.1, whereas 1034 bound better to the C6-derived protein than the C8-derived protein. The poorest MAb reactivity was with rgp120s from C11 and C15. This result was consistent with sequence analysis demonstrating that these two viruses both possessed the radical substitution of S for R at position 18 in the V3 domain. Surprisingly, both of these MAbs exhibited better than expected binding to rgp120 from the C7 and C10 viruses. Like MN-rgp120, both proteins contained the penta-peptide, IGPGR sequence (SEQ. ID. NO. 44) in the V3 loop, but differed from MN-rgp120 in that V and L replaced A and F at positions 319 and 320 in gp120 from C10, and W replaced F at position 320 in gp120 from C7. These results indicate that R at position 318 is essential for the binding of these two MAbs, and that the epitopes recognized by 1034 and 50.1 are not completely destroyed by the hydrophobic substitutions at positions 319 and 320.

As predicted from the sequence data, there was little if any binding to the breakthrough virus rgp120s using MAbs (1088 and 1025) directed to the V2 region of

MN-rgp120. Also consistent with sequence data was the observation that MAb 1024 directed to the C4 domain of MN-rgp120 gave some reactivity with C17-rgp120 which, like MN-rgp120 contained K at position 429, but gave no reactivity with the other isolates that contained E at residue 429.

Together, these studies demonstrated that the antigenic structure of all seven breakthrough viruses differed from the vaccine immunogen at three well characterized neutralizing epitopes.

A totally different pattern of reactivity was observed with the human hybridoma, MAb 15e, prepared from an HIV-1 infected individual as described in Ho et al.; *J. Virol.* 65:489-93 (1991). With this MAb, the greatest binding was achieved with MN-rgp120 and rgp120 from C7, and the poorest reactivity was seen with the two clones of rgp120 from the C11. Moderate, but comparable reactivity was seen with rgp120s from the C10 and C17.

These results demonstrate that the 15e epitope is polymorphic, and that the epitope is conserved on MN-rgp120 and rgp120 from C7, but has been lost on rgp120s from C11. Interestingly, the two different clones of gp120 derived from C6 gave strikingly different patterns of antibody binding. Thus, rgp120 from clone C6.5 exhibited strong reactivity with this antibody, whereas rgp120 from clones C6.1 exhibited significantly weaker activity with this MAb.

Comparison of sequence data (Figure 3) showed that the two C6 clones differed at 6 amino acid positions. Based on comparative binding to the other viral proteins of known sequence, it appeared that the substitution of K for I at position 351 in the C3 domain of gp120 could account for the difference in binding activity. This result is also consistent with both clones of C11 similarly containing a positively-

AP/P/99/01432

charged K at this position, and also being poorly reactive with this MAb. Alternatively, a T for I substitution at position 439 in the C4 domain could account for the difference in 15e binding between C6.1 and C6.5. Although the inability of the two C11 clones to bind 15e cannot be explained by polymorphism at this position in the C4 domain, they could be affected by the adjacent T for M substitution at position 434.

10

Discussion

In these studies, the viruses and immune responses in seven of nine vaccinees who became infected with HIV-1 through high risk activity while participating in Phase I or Phase 2 trials of MN-rgp120, a candidate HIV-1 vaccine were analyzed. Such infections would be expected to occur for one of two reasons: 1) lack of sufficient immune response at the time of infection; or 2) infection with viruses that fall outside of the antigenic spectrum expected to be covered by the vaccine immunogen. The data indicate that both explanations may be involved with the infections observed (Table 8).

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AP/P/99/01432

TABLE 8
Summary of Breakthrough Infections

5	Case No.	Adequate Immunization	Homologous to MN-rgp120			
			MN-rgp120 Homology (%)	V3 PND	C4 Epitope	V2 Epitope
	C6	-	79	+	-	-
	C8	-	78	+	-	-
	C15	-	72	-	-	-
	C7	-	70	-	-	-
10	C11	+	75	-	-	-
	C10	+	69	-	-	-
	C17	+	80	+	+	-

15 Two of the infections occurred in individuals who failed to receive the minimum three doses of vaccine typically required for the induction of protective immunity with protein subunit vaccines (e.g. hepatitis B virus formulated in alum adjuvant as described in Francis et al.; *Ann. Int. Med.* 97:362-6 (1982). Two additional breakthrough infections occurred in vaccinees who had weak or undetectable primary (C7) and booster (C15) responses. Of the three individuals who became infected with HIV-1 after receiving three or more productive immunizations (C10, C11, and C17), at least two, and possibly all three, appear to have become infected more than six months after receiving their last immunization. Because antibody titers to MN-rgp120 typically decay with a half-time of 2 to 2.5 months [Belshe et al.; *JAMA* 272(6):475-80 (1994); Berman et al.; *AIDS* 8:591-601 (1994)], antibody titers would be expected to have decayed at least eight-fold and possibly as much as sixty four-fold at the time of infection. Thus, the lack of a sufficient immune

response at the time of infection represents a potential explanation for at least six of the seven breakthrough infections.

5 Data from vaccine efficacy studies in gp160 immunized chimpanzees [McElrath et al.; Longitudinal Vaccine-Induced Immunity and Risk Behavior of Study Participants in AVEG Phase II Protocol 201. In: Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Bethesda, MD 1996:216] challenged with HIV-1, and
10 gp120-immunized rhesus macaques challenged with a chimeric SIV/HIV-1 virus (SHIV) suggest that the magnitude of the neutralizing antibody response at the time of infection is a critical correlate of protective
15 immunity. If maintaining neutralizing antibody titers proves to be a valid correlate of protective immunity in humans, then formulations (e.g. novel adjuvants) or immunization regimes (frequent boosting) designed to maximize the antibody responses may be required to
20 achieve long lasting protection. Use of a booster every six months may be advantageous.

The other likely explanation for the late infections is the antigenic difference between the vaccine and the breakthrough virus envelope
25 glycoproteins. This explanation is supported by the observation that four of the seven breakthrough viruses possessed envelope glycoproteins that differed from the MN-rgp120 by 25-30% at the amino acid level. Differences of this magnitude have historically
30 [Myers et al.; *Retroviruses and AIDS Database*, Los Alamos National Laboratory (1992 and 1995)] been associated with inter-subtype variation and far exceeds the average 10-20% variation expected for viruses within the same subtype.

35 Although the biologic significance of sequence variation in many regions of the envelope glycoprotein

AP/P/99/01432

is unclear, polymorphism at neutralizing epitopes is an important factor that affects vaccine efficacy.

Previous studies [Salmon-Ceron et al.; *AIDS Res. and Human Retroviruses* 11:1479-86 (1995); Javaherian et al.; *Science* 250:1590-3 (1990)] have demonstrated that the breadth of neutralizing activity that could be elicited by HIV-1 envelope derived vaccines was critically dependent on the sequence of epitopes in the V3 domain (e.g.; the PND). Thus, candidate vaccines based on the LAI strain of HIV-1 (the prototypic "non-MN-like" subtype B virus), exhibited little or no cross neutralizing activity with subtype B viruses, whereas vaccines that contained the "MN-like-" PND sequence (IGPGRAF) (SEQ. ID. NO. 44) exhibited broad cross neutralizing activity. That four of the seven breakthrough viruses possessed envelope glycoproteins with radical amino acid substitutions in the PND is consistent with the explanation that differences in antigenic structure explain some of these infections.

Over the last few years, it has become clear that polymorphism among "MN-like" viruses occurs at neutralizing epitopes outside of the PND. The best example occurs in the C4 domain where two antigenically distinct variants are distinguished by the presence of either K or E at position 429 [Moore et al.; *AIDS* 3:155-63 (1989)]. Because six of the seven breakthrough viruses differed from the vaccine strain in that they contained E rather than K at position 429, antibodies raised to the C4 domain of MN-rgp120 were unlikely to neutralize the viruses infecting in six of the seven vaccinees.

Other neutralizing epitopes are known to be present in the V1 and V2 domains of gp120. Although these regions are highly variable, due to insertions and deletions, neutralizing epitopes have been described by McKeating et al.; *J. Virol.* 67:4932-44

AP/P/99/01432

(1993); Moore et al.; *J. Virol.* 67:6136-6151 (1993);
 and Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993).
 Several of these epitopes overlap an amino terminal
 sequence of the V2 domain containing the tri-peptide
 5 sequence RDK at positions corresponding to 142 to 144
 of MN-rgp120 [McKeating et al.; *J. Virol.* 67:4932-44
 (1993); Moore et al.; *J. Virol.* 67:6136-6151 (1993)].
 Like the C4 epitope, variation in this sequence is
 10 known to occur between different substrains derived
 from the same parental isolate. Since all seven
 breakthrough viruses differed from MN-rgp120 in that
 they possessed the RDK sequence, rather than the GDK
 sequence present in the vaccine antigen, neutralizing
 antibodies to the V2 domain of MN-rgp120 would not have
 15 been expected neutralize any of the viruses recovered
 from the vaccinees immunized with MN-rgp120.

Although polymorphisms at neutralizing epitopes
 might account for the lack of protection in most of the
 infections, this does not appear to explain the
 20 infection of vaccinee C17, who was infected by a virus
 that matched MN-rgp120 in the V3 and C4 domains. If a
 difference in sequence was responsible for the lack of
 protection in this case, the critical difference might
 relate to the unusual sequence in the V1 domain of
 25 gp120 from this breakthrough virus. Several studies
 have shown that the V1 domain possesses epitopes
 recognized by virus neutralizing monoclonal antibodies
 [McKeating et al.; *J. Virol.* 67:4932-44 (1993);
 Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993);
 30 Kayman et al.; *J. Virol.* 68:400-410 (1994)].

Although far less is known about the V1 epitopes
 relative to other neutralizing sites, the V1 epitopes
 appear to be conformation-dependent, and antisera from
 HIV-1 infected individuals recognize epitopes in the V1
 35 and V2 domains [McKeating et al.; *J. Virol.* 67:4932-44
 (1993); Kayman et al.; *J. Virol.* 68:400-410 (1994)].

The V1 sequence of the virus from C17 is noteworthy because it is smaller and contains fewer N-linked glycosylation sites than that of MN-rgp120 or any of the other breakthrough viruses. By the same token, the envelope glycoproteins from C11 and C6 are noteworthy because they are significantly larger and contain more glycosylation sites than MN-rgp120 or the other breakthrough viruses.

While differences in amino acid sequence can provide clues to differences in antigenic structure, the consequences of such polymorphism can only be proven through antibody binding studies. To correlate differences in sequence with differences in antigenic structure, gp120 from two clones each of all seven breakthrough viruses was expressed and the antigenicity of the clones with a panel of monoclonal antibodies was examined. As predicted from the sequence data, none of the breakthrough virus envelope glycoproteins reacted with neutralizing MAbs to the V2 domain of MN-rgp120. When MAbs to the C4 domain were examined, only the C17 envelope glycoprotein (that matched MN-rgp120 with respect to K429) showed significant, albeit lower, binding. Surprisingly, the three breakthrough envelope glycoproteins that contained the subtype B PND consensus sequence, IGPGRAF (SEQ. ID. NO. !!), gave poor reactivity with all three PND directed MAbs, even though they possessed PND sequences closely related to the vaccine immunogen. Thus, all three of the vaccine isolates appeared to possess changes outside of the recognition site that interfered with MAb binding.

It has been known for many years that resistance to neutralization in vitro can sometimes be attributed to mutations in remote sequences that alter the conformation of neutralizing epitopes and interfere with recognition by virus neutralizing antibodies [Nara et al.; *J. Virol.* 64:3779-91 (1990); Cordonnier

AP/P/99/01432

et al.; *Nature* 340:571-4 (1989)]. Together, these results indicate that the antigenic structure of the envelope glycoproteins recovered from the breakthrough viruses differed significantly from that of the vaccine antigen.

A novel result was the localization of residues in the C3 domain that appeared to affect the binding of the virus neutralizing human MAb, 15e. This MAb is known to recognize a discontinuous epitope, block CD4 binding, and neutralize a variety of laboratory and primary isolates of HIV-1 [Ho et al.; *J. Virol.* 65:489-93 (1991); Thali et al.; *J. Virol.* 66:5635-5641 (1992); Moore et al.; *AIDS Res. Hum. Retroviruses* 9:1179-1187 (1993)].

Comparative binding to envelope glycoproteins from the breakthrough viruses indicated that recognition by this antibody is critically dependent on residues in the C3 or C4 domains of gp120. The unique occurrence of a positively charged K at position 351 in the C3 domain provides a common explanation for the inability of the C11.5, C11.7 and C6.1 strains of HIV-1 to bind to 15e. Alternatively, it is possible that different amino acid substitutions in different locations account for the failure of 15e to bind to rgp120s from the C6 and C11 clones. The only obvious positions where substitutions of this type occur are in the C4 domain where T replaces M at 434 (C11) and T replaces I at 439.

The present studies demonstrate that the current formulation of MN-rgp120 is less than 100% effective against HIV-1 infection. Based on previous in vitro and in vivo studies with MN-rgp120, protection from natural HIV-1 infection in humans is expected to depend on a threshold concentration of virus-neutralizing antibodies, and antigenic similarity between the vaccine immunogen and the challenge virus.

In this regard, only one of the seven breakthrough infections (C17) was unexpected. This individual received a full course of immunizations yet became infected with a virus similar to MN-rgp120 at at least
5 two important neutralizing epitopes (V3 and C4 domains). This infection might be related to the magnitude of the antibody response at the time of infection, or antigenic differences between the breakthrough virus and the vaccine strain, or
10 circumstances of infection (e.g., ulcerative lesions, infection by donor with acute infection or high viremia), not monitored in this protocol. Alternatively this individual may represent a true vaccine failure, without clear explanation.

15 On balance, the analysis of breakthrough infections described herein did not uncover any data that would discourage the continued development of MN-rgp120 as a vaccine to prevent HIV-1 infection. The results support speculation that enhancing vaccine
20 immunogenicity (as by additional booster immunizations) may be required to maintain long term protective immunity, and that the addition of rgp120 from other antigenically different strains of virus in addition to MN-rgp120 are useful to expand the breadth of
25 protection.

The availability of viruses and viral glycoproteins derived from breakthrough infections may provide an important means to streamline the process of identifying new antigens for inclusion into a
30 multivalent vaccine. Recombinant viral glycoproteins prepared from breakthrough viruses, by definition, possess antigenic structures that are significantly different from MN-rgp120, and are be representative of
viruses currently being transmitted. Thus, combining
35 rgp120 from breakthrough viruses with MN-rgp120 is an effective way complement and significantly expand

AP/T/99/01432

antigenic complexity and increase breadth of cross
neutralizing activity.

AP/F/99/01432

AP001282

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Berman, Phillip W.

(ii) TITLE OF INVENTION: HIV ENVELOPE POLYPEPTIDES AND VACCINE

(iii) NUMBER OF SEQUENCES: 44

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: SKJERVEN, MORRILL, MACPHERSON, ET AL.

(B) STREET: 25 Metro Drive, Suite 700

(C) CITY: San Jose

(D) STATE: California

(E) COUNTRY: USA

(F) ZIP: 95110

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: WinPatin (Genentech)

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Terlizzi, Laura

(B) REGISTRATION NUMBER: 31,307

(C) REFERENCE/DOCKET NUMBER: M-3897 US

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (408) 453-9200

(B) TELEFAX: (408) 453-7979

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1503 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GGG GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA 36
Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
1 5 10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
15 20 25

CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
30 35

CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
40 45 50

GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
55 60

CAT GAG GAT ATA ATC AGT TTA TGG CAT CAA AGC CTA AAA 231
His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
65 70 75

AP/P/99/01432

CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
 Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
 80 85 90

5 TGC ACC AAT TGG AAG AAG AAT GAT ACT AAA ACT AAT AGT 309
 Cys Thr Asn Trp Lys Lys Asn Asp Thr Lys Thr Asn Ser
 95 100

10 AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
 Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
 105 110 115

15 AGT AGT AGT ACT ACA ACT AAT AGT AGT TGG GCA GAG ATA 387
 Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
 120 125

20 AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
 Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
 130 135 140

ACA AGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
 Thr Ser Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
 145 150 155

25 TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
 Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
 160 165

30 ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
 Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
 170 175 180

35 ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
 Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
 185 190

40 ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
 Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
 195 200 205

TGT ACA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
 Cys Arg Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
 210 215 220

45 AAT GTT AGC ACA GTA CAA TGT GCA CAT GGA ATT AAG CCA 699
 Asn Val Ser Thr Val Gln Cys Ala His Gly Ile Lys Pro
 225 230

50 GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
 Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
 235 240 245

55 GAA GAA GAG GTA ATA ATT AGA TCT GCC AAT TTC TCA AAC 777
 Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
 250 255

60 AAT GCT AAA ATC ATA ATA GTA CAG TTG AGG GAA CCT GTA 816
 Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu Pro Val
 260 265 270

GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
 Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
 275 280 285

AP/P/99/01432

AP001282

GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
290 295

5 GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
300 305 310

10 ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
315 320

15 GTT AAA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
Val Lys Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
325 330 335

20 GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
340 345 350

25 ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
355 360

30 AAT ACA ACA AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
365 370 375

35 ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
380 385

40 TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA ATA 1206
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile
390 395 400

45 GGA AAA GCA ATG TAT GCC CCT CCC ACC AGA GGA GAA ATT 1245
Gly Lys Ala Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile
405 410 415

50 AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ATA AGA 1284
Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Ile Arg
420 425

55 GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
430 435 440

60 AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
445 450

GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
455 460 465

GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
470 475 480

AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
485 490

AP/P/99/01432

GGG TTC TTA GCA GCA TAA AGC TTC 1503
 Gly Phe Leu Gly Ala Xaa Ser Phe
 495 500 501

5 (2) INFORMATION FOR SEQ ID NO:2:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 501 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear
 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
 Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
 1 5 10 15
 15 Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
 20 25 30
 Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Met Val
 20 35 40 45
 Leu Glu Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Asp Met
 50 55 60
 25 Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser
 65 70 75
 Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
 80 85 90
 30 Cys Thr Asn Trp Lys Lys Asn Asp Thr Lys Thr Asn Ser Ser Ser
 95 100 105
 Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn Ser Ser Ser Thr
 110 115 120
 35 Thr Thr Asn Ser Ser Trp Gly Glu Ile Lys Glu Gly Glu Ile Lys
 125 130 135
 Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Lys
 40 140 145 150
 Lys Glu Tyr Ala Leu Phe Tyr Ser Leu Asp Val Val Pro Ile Glu
 155 160 165
 45 Asn Asp Asn Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val
 170 175 180
 Ile Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile
 185 190 195
 50 His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys Cys Arg Asp
 200 205 210
 Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
 215 220 225
 Gln Cys Ala His Gly Ile Lys Pro Val Val Ser Thr Gln Leu Leu
 230 235 240
 60 Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Ile Ile Arg Ser Ala
 245 250 255
 Asn Phe Ser Asn Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu
 260 265 270
 65

AP/P/99/01432

AP001282

Pro Val Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
275 280 285

5 Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr Gly Asp
290 295 300

Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Gly Ala
305 310 315

10 Lys Trp Asn Asn Thr Leu Lys Lys Val Val Lys Lys Leu Lys Glu
320 325 330

Gln Phe Pro Asn Lys Thr Ile Val Phe Asn His Ser Ser Gly Gly
335 340 345

15 Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gln Gly Glu Phe
350 355 360

20 Phe Tyr Cys Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp
365 370 375

Thr Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro Cys
380 385 390

25 Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile Gly Lys Ala
395 400 405

Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile Lys Cys Ser Ser Asn
410 415 420

30 Ile Thr Gly Leu Leu Leu Ile Arg Asp Gly Gly Ile Asn Thr Ser
425 430 435

Asp Ala Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp
440 445 450

35 Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
455 460 465

40 Pro Leu Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
470 475 480

Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu Gly Phe
485 490 495

45 Leu Gly Ala Xaa Ser Phe
500 501

(2) INFORMATION FOR SEQ ID NO:3:

- 50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1503 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

55 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GGG GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA 36
Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
1 5 10

60 TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
15 20 25

AP/P/99/014/32

CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
30 35

5 CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
40 45 50

10 GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
55 60

15 CAT GAG ANT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
65 70 75

20 CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
80 85 90

TGC ACC AAT TGG AAG GAG AAT GAT ACT AAA ACT AAT AGT 309
Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser
95 100

25 AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
105 110 115

30 AGT ACT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
120 125

35 AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
130 135 140

40 ACA GGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
Thr Gly Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
145 150 155

TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
160 165

45 ACT AGC TAT AGG TTC AGA AGT TGT AAC ACC TCA GTC ATT 543
Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
170 175 180

50 ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
185 190

55 ATA CAT TAT TGT ACC GCG GCT GGT TTT GCG ATT CTG AAG 621
Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
195 200 205

TGT AAA GAT AAA AAG TTC AAT GGA ACA GCA CCA TGC AAA 660
Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
210 215 220

60 AAT GTT ACC ACA GTA CAA TGT ACA CAT GGA ATT AAG CCA 699
Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro
225 230

AP/P/99/01432

APU 01282

	GTA	GTG	TCA	ACT	CAA	CTG	CTG	TTA	AAT	GCC	AGC	CTA	GCA	738
	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	
	235						240					245		
5	GAA	GAA	GAG	GTA	ATA	ATT	AGA	TCT	GCC	AAT	TTC	TCA	AAC	777
	Glu	Glu	Glu	Val	Ile	Ile	Arg	Ser	Ala	Asn	Phe	Ser	Asn	
			250					255						
10	AAT	GCT	AAA	ATC	ATA	ATA	GTA	CAG	TTG	AAG	GAA	CCT	GTA	816
	Asn	Ala	Lys	Ile	Ile	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val	
	260					265					270			
15	GAA	ATT	AAT	TGT	ACA	AGA	CCC	AGC	AAC	AAT	ACA	ATA	AAA	855
	Glu	Ile	Asn	Cys	Thr	Arg	Pro	Ser	Asn	Asn	Thr	Ile	Lys	
			275					280					285	
20	GGT	ATA	CAC	ATA	GGA	CCA	GGG	AGA	GCA	TTT	TAT	GCA	ACA	894
	Gly	Ile	His	Ile	Gly	Pro	Gly	Arg	Ala	Phe	Tyr	Ala	Thr	
					290					295				
25	GGA	GAC	ATA	CGA	GGA	GAT	ATA	AGA	CAA	GCA	CAT	TGT	AAC	933
	Gly	Asp	Ile	Arg	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	
		300					305					310		
30	ATT	AGT	GGA	GCA	AAA	TGG	AAT	AAC	ACT	TTA	AAG	AAG	GTA	972
	Ile	Ser	Gly	Ala	Lys	Trp	Asn	Asn	Thr	Leu	Lys	Lys	Val	
				315					320					
35	GTT	ATA	AAA	TTA	AAA	GAA	CAA	TTT	CCA	AAT	AAA	ACA	ATA	1011
	Val	Ile	Lys	Leu	Lys	Glu	Gln	Phe	Pro	Asn	Lys	Thr	Ile	
	325					330					335			
40	GTC	TTT	AAC	CAT	TCC	TCA	GGA	GGG	GAC	CCA	GAA	ATT	GTA	1050
	Val	Phe	Asn	His	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Val	
			340					345					350	
45	ATG	CAC	AGT	TTT	AAT	TGT	CAA	GGG	GAA	TTT	TTC	TAC	TGT	1089
	Met	His	Ser	Phe	Asn	Cys	Gln	Gly	Glu	Phe	Phe	Tyr	Cys	
					355					360				
50	AAT	ACA	ACG	AAG	CTG	TTT	AAT	AGT	ACT	TGG	AAT	GAT	ACT	1128
	Asn	Thr	Thr	Lys	Leu	Phe	Asn	Ser	Thr	Trp	Asn	Asp	Thr	
		365					370					375		
55	ACA	GAG	TCA	AAT	AAC	AAT	GAT	AGT	ACT	ATT	ACA	CTC	CCA	1167
	Thr	Glu	Ser	Asn	Asn	Asn	Asp	Ser	Thr	Ile	Thr	Leu	Pro	
				380					385					
60	TGC	AGA	ATA	AAA	CAA	ATT	ATA	AAC	ATG	TGG	CAG	GAA	GTA	1206
	Cys	Arg	Ile	Lys	Gln	Ile	Ile	Asn	Met	Trp	Gln	Glu	Val	
	390					395					400			
65	GGA	AAA	GCA	ATG	TAT	GCC	CCT	CCC	ATC	AGA	GGA	GAA	ATT	1245
	Gly	Lys	Ala	Met	Tyr	Ala	Pro	Pro	Ile	Arg	Gly	Glu	Ile	
			405					410					415	
70	AAA	TGT	TCA	TCA	AAT	ATT	ACA	GGA	CTA	CTG	TTA	ACA	AGA	1284
	Lys	Cys	Ser	Ser	Asn	Ile	Thr	Gly	Leu	Leu	Leu	Thr	Arg	
					420					425				
75	GAT	GGT	GGT	ATT	AAC	ACT	AGC	GAT	GCC	ACC	GAG	ACC	TTC	1323
	Asp	Gly	Gly	Ile	Asn	Thr	Ser	Asp	Ala	Thr	Glu	Thr	Phe	
		430					435					440		

AP/P/99/01432

AGA CCG GGA GGA GGA CAT ATG AGG GAC AAT TGG AGA AGT 1362
 Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
 445 450

5 GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
 Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
 455 460 465

10 GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
 Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
 470 475 480

15 AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
 Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
 485 490

20 GGG TTC TTG GGA GCA TAA AGC TTC 1503
 Gly Phe Leu Gly Ala Xaa Ser Phe
 495 500 501

(2) INFORMATION FOR SEQ ID NO:4:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 501 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:
 Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
 1 5 10 15
 Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
 20 25 30
 Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Met Val
 35 40 45
 Leu Glu Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Asp Met
 50 55 60
 Val Glu Gln Met His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser
 65 70 75
 Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
 80 85 90
 Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser Ser Ser
 95 100 105
 Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn Ser Ser Ser Thr
 110 115 120
 Thr Thr Asn Ser Ser Trp Gly Glu Ile Lys Glu Gly Glu Ile Lys
 125 130 135
 Asn Cys Ser Phe Asn Ile Thr Thr Gly Ile Arg Asp Lys Val Lys
 140 145 150
 Lys Glu Tyr Ala Leu Phe Tyr Ser Leu Asp Val Val Pro Ile Glu
 155 160 165
 Asn Asp Asn Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val
 170 175 180
 Ile Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile
 185 190 195

AP/P/99/01432

AP001282

	His Tyr Cys Thr	Pro Ala Gly Phe Ala	Ile Leu Lys Cys Lys	Asp
		200	205	210
5	Lys Lys Phe Asn	Gly Thr Gly Pro Cys	Lys Asn Val Ser Thr	Val
		215	220	225
	Gln Cys Thr His	Gly Ile Lys Pro Val	Val Ser Thr Gln Leu	Leu
		230	235	240
10	Leu Asn Gly Ser	Leu Ala Glu Glu Glu	Val Ile Ile Arg Ser	Ala
		245	250	255
	Asn Phe Ser Asn	Asn Ala Lys Ile Ile	Ile Val Gln Leu Lys	Glu
		260	265	270
15	Pro Val Glu Ile	Asn Cys Thr Arg Pro	Ser Asn Asn Thr Ile	Lys
		275	280	285
	Gly Ile His Ile	Gly Pro Gly Arg Ala	Phe Tyr Ala Thr Gly	Asp
20		290	295	300
	Ile Arg Gly Asp	Ile Arg Gln Ala His	Cys Asn Ile Ser Gly	Ala
		305	310	315
25	Lys Trp Asn Asn	Thr Leu Lys Lys Val	Val Ile Lys Leu Lys	Glu
		320	325	330
	Gln Phe Pro Asn	Lys Thr Ile Val Phe	Asn His Ser Ser Gly	Gly
		335	340	345
30	Asp Pro Glu Ile	Val Met His Ser Phe	Asn Cys Gln Gly Glu	Phe
		350	355	360
	Phe Tyr Cys Asn	Thr Thr Lys Leu Phe	Asn Ser Thr Trp Asn	Asp
35		365	370	375
	Thr Thr Glu Ser	Asn Asn Asn Asp Ser	Thr Ile Thr Leu Pro	Cys
		380	385	390
40	Arg Ile Lys Gln	Ile Ile Asn Met Trp	Gln Glu Val Gly Lys	Ala
		395	400	405
	Met Tyr Ala Pro	Pro Ile Arg Gly Glu	Ile Lys Cys Ser Ser	Asn
		410	415	420
45	Ile Thr Gly Leu	Leu Leu Thr Arg Asp	Gly Gly Ile Asn Thr	Ser
		425	430	435
	Asp Ala Thr Glu	Thr Phe Arg Pro Gly	Gly Gly Asp Met Arg	Asp
50		440	445	450
	Asn Trp Arg Ser	Glu Leu Tyr Lys Tyr	Lys Val Val Lys Ile	Glu
		455	460	465
55	Pro Leu Gly Val	Ala Pro Thr Lys Ala	Lys Arg Arg Val Val	Gln
		470	475	480
	Arg Glu Lys Arg	Ala Val Thr Leu Gly	Ala Met Phe Leu Gly	Phe
		485	490	495
60	Leu Gly Ala Xaa	Ser Phe		
		500 501		

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:

AP/P/99/01432

(A) LENGTH: 1461 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

5 G GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
 Val Pro Val Trp Lys Glu Ala Thr Thr Leu Phe
 1 5 10

10 TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
 Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
 15 20 25

15 AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
 30 35

20 AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
 Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
 40 45 50

25 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
 Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
 55 60

30 GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
 Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65 70 75

35 TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
 Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
 80 85 90

40 ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
 Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
 95 100

45 AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
 Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
 105 110 115

50 ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA ACA 388
 Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
 120 125

55 GAT AAG GTG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
 Asp Lys Val Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
 130 135 140

60 GAT GTA GTA CAA ATA CAT AAT AGT ACC AAC TAT ACG CTG 466
 Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
 145 150 155

65 ATA ACT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
 Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
 160 165

70 AAG GTA TCC TTT GAG CTA ATT CCC ATA CAT TAT TGT GCC 544
 Lys Val Ser Phe Glu Leu Ile Pro Ile His Tyr Cys Ala
 170 175 180

75 CCG GCT GST TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
 Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
 185 190

AP/P/99/01432

AP001282

DATE

	TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA GTA 622
	Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val 195 200 205
5	CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
	Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln 210 215 220
10	CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
	Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val 225 230
15	ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
	Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile 235 240 245
20	ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
	Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr 250 255
25	AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
	Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly 260 265 270
30	CCA GGG ACA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
	Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly 275 280 285
35	GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
	Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln 290 295
40	TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
	Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu 300 305 310
45	GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
	Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser 315 320
50	TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
	Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn 325 330 335
55	TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA AAA CTG 1051
	Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Lys Leu 340 345 350
60	TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
	Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn 355 360
65	ACC GGG AAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
	Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro 365 370 375
70	TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
	Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val 380 385
75	GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
	Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile 390 395 400

AP/P/99/01432

AGA TST TCA TCA AAT ATT ACA GGG CTA CTA TTA ACA AGA 1246
 Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
 405 410 415

5 GAT GGT GGA AGT AAC ACC GGT GAC AAC AGG ACT GAG ACC 1285
 Asp Gly Gly Ser Asn Thr Gly Asp Asn Arg Thr Glu Thr
 420 425

10 TTT AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA 1324
 Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
 430 435 440

15 AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
 Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
 445 450

20 TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTC 1402
 Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
 455 460 465

CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA CCT ATG TTC 1441
 Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
 470 475 480

25 CTT GGG TTC TTG GGA GAT AA 1461
 Leu Gly Phe Leu Gly Asp
 485 486

(2) INFORMATION FOR SEQ ID NO:6:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 486 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

35 Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
 1 5 10 15

40 Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
 20 25 30

His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val Val Leu
 35 40 45

45 Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
 50 55 60

Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75

50 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
 80 85 90

55 Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn Asn Thr
 95 100 105

Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu Ile Lys Asn Cys
 110 115 120

60 Ser Phe Asn Ile Thr Thr Ser Leu Arg Asp Lys Val Lys Lys Glu
 125 130 135

Tyr Ala Leu Phe Tyr Lys Leu Asp Val Val Gln Ile Asp Asn Ser
 140 145 150

65

AP/P/99/01432

AP001282

	Thr Asn Tyr Arg	Leu 155	Ile Ser Cys Asn	Thr 160	Ser Val Ile Thr	Gln 165
5	Ala Cys Pro Lys	Val 170	Ser Phe Glu Leu	Ile 175	Pro Ile His Tyr	Cys 180
	Ala Pro Ala Gly	Phe 185	Ala Ile Leu Lys	Cys 190	Lys Asp Lys Lys	Phe 195
10	Asn Gly Thr Gly	Pro 200	Cys Lys Asn Val	Ser 205	Thr Val Gln Cys	Thr 210
	His Gly Ile Arg	Pro 215	Val Val Ser Thr	Gln 220	Leu Leu Leu Asn	Gly 225
15	Ser Leu Ala Glu	Glu 230	Glu Ile Val Ile	Arg 235	Ser Glu Asn Ile	Thr 240
	Asp Asn Ala Lys	Thr 245	Ile Ile Val Gln	Leu 250	Asn Glu Ser Ile	Val 255
20	Ile Asn Cys Thr	Arg 260	Pro Asn Asn Asn	Thr 265	Arg Lys Ser Ile	Asn 270
	Ile Gly Pro Gly	Arg 275	Ala Phe Tyr Thr	Thr 280	Gly Asp Ile Ile	Gly 285
25	Asp Ile Arg Gln	Ala 290	His Cys Asn Leu	Ser 295	Lys Thr Gln Trp	Glu 300
30	Lys Thr Leu Arg	Gln 305	Ile Ala Ile Lys	Leu 310	Glu Glu Lys Phe	Lys 315
	Asn Lys Thr Ile	Ala 320	Phe Asn Lys Ser	Ser 325	Gly Gly Asp Pro	Glu 330
35	Ile Val Met His	Ser 335	Phe Asn Cys Gly	Gly 340	Glu Phe Phe Tyr	Cys 345
	Asn Thr Thr Lys	Leu 350	Phe Asn Ser Thr	Trp 355	Asn Leu Thr Gln	Pro 360
40	Phe Ser Asn Thr	Gly 365	Asn Arg Thr Glu	Glu 370	Leu Asn Ile Thr	Leu 375
45	Pro Cys Arg Ile	Lys 380	Gln Ile Ile Asn	Leu 385	Trp Gln Glu Val	Gly 390
	Lys Ala Met Tyr	Ala 395	Pro Pro Ile Arg	Gly 400	Gln Ile Arg Cys	Ser 405
50	Ser Asn Ile Thr	Gly 410	Leu Leu Leu Thr	Arg 415	Asp Gly Gly Ser	Asn 420
	Thr Gly Asp Asn	Arg 425	Thr Glu Thr Phe	Arg 430	Pro Gly Gly Gly	Asp 435
55	Met Arg Asp Asn	Trp 440	Arg Ser Glu Leu	Tyr 445	Lys Tyr Lys Val	Val 450
60	Arg Ile Glu Pro	Leu 455	Gly Val Ala Pro	Thr 460	Gln Ala Lys Arg	Arg 465
	Val Val Gln Arg	Glu 470	Lys Arg Ala Val	Gly 475	Ile Gly Ala Met	Phe 480

AP/P/99/01432

Leu Gly Phe Leu Gly Asp
485 486

(2) INFORMATION FOR SEQ ID NO:7:

- (1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1474 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

5 G GGA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
1 5 10

15 TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
15 20 25

20 AAT GTT TGG GCT ACA CAT CCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
30 35

25 AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
40 45 50

30 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
55 60

35 GAG GAT ATA ATC AGT TTA TCG GAT CAA AGT CTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
65 70 75

40 TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
80 85 90

45 ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
95 100

50 AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
105 110 115

55 AGA AAA AAC TGC TCT TTC AAT ATC ACC ACA ACC TTA AGA 388
Arg Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
120 125

60 GAT AAG GGG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
Asp Lys Gly Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
130 135 140

GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
145 150 155

ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
160 165

AP/P/99/01432

AP001282

	AAG GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC 544
	Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
	170 175 180
5	CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
	Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
	185 190
10	TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGG ACA GTA 622
	Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val
	195 200 205
15	CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
	Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
	210 215 220
20	CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
	Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
	225 230
25	ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
	Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
	235 240 245
30	ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
	Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
	250 255
35	AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
	Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
	260 265 270
40	CCA GGG ACA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
	Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
	275 280 285
45	GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
	Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
	290 295
50	TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
	Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
	300 305 310
55	GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
	Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
	315 320
60	TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
	Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
	325 330 335
65	TGT GGA GGG GGA TTT TTC TAC TGT AGT ACG AGA AAA CTG 1051
	Cys Gly Gly Gly Phe Phe Tyr Cys Ser Thr Arg Lys Leu
	340 345 350
70	TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
	Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
	355 360
75	ACC GGG GAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
	Thr Gly Asp Arg Thr Glu Leu Asn Ile Thr Leu Pro
	365 370 375

AP/P/99/01432

TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
 Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
 380 385

5 GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
 390 395 400

10 AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA AGG AGA 1246
 Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Arg Arg
 405 410 415

15 GAT GGT GGA AGT AAC ACC AGT GAC AAC CAG ACT GAG ACC 1285
 Asp Gly Gly Ser Asn Thr Ser Asp Asn Gln Thr Glu Thr
 420 425

20 TTT AGA CCT GGG GCA GCA GAT ATG AGG GAC AAG TGG AGA 1324
 Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Lys Trp Arg
 430 435 440

AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
 Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
 445 450

25 TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTC GTC 1402
 Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
 455 460 465

30 CAA AGA GAA AAA ACA GCA GTC GGG ATA GGA GCT ATG TTC 1441
 Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
 470 475 480

35 GTT AGG TIC TTA GGA GAT AAA GCT TCT ACA GTC 1474
 Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
 485 490 491

(2) INFORMATION FOR SEQ ID NO:8:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 491 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

40 Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
 1 5 10 15

Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
 20 25 30

50 His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val Val Leu
 35 40 45

Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
 50 55 60

55 Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75

60 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
 80 85 90

Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn Asn Thr
 95 100 105

AP/P/99/01432

APU 01282

	Asn Asn Tyr Thr	Leu 110	Gly Met Glu Arg Gly 115	Glu Arg Lys Asn Cys 120
5	Ser Phe Asn Ile	Thr 125	Thr Ser Leu Arg Asp 130	Lys Gly Lys Lys Glu 135
	Tyr Ala Leu Phe	Tyr 140	Lys Leu Asp Val 145	Gln Ile Asp Asn Ser 150
10	Thr Asn Tyr Arg	Leu 155	Ile Ser Cys Asn Thr 160	Ser Val Ile Thr Gln 165
	Ala Cys Pro Lys	Val 170	Ser Phe Glu Pro Ile 175	Pro Ile His Tyr Cys 180
15	Ala Pro Ala Gly	Phe 185	Ala Ile Leu Lys Cys 190	Lys Asp Lys Lys Phe 195
	Asn Gly Thr Gly	Pro 200	Cys Lys Asn Val Arg 205	Thr Val Gln Cys Thr 210
20	His Gly Ile Arg	Pro 215	Val Val Ser Thr Gln 220	Leu Leu Leu Asn Gly 225
	Ser Leu Ala Glu	Glu 230	Glu Ile Val Ile Arg 235	Ser Glu Asn Ile Thr 240
	Asp Asn Ala Lys	Thr 245	Ile Ile Val Gln Leu 250	Asn Glu Ser Ile Val 255
30	Ile Asn Cys Thr	Arg 260	Pro Asn Asn Asn Thr 265	Arg Lys Ser Ile Asn 270
	Ile Gly Pro Gly	Arg 275	Ala Phe Tyr Thr Thr 280	Gly Asp Ile Ile Gly 285
35	Asp Ile Arg Gln	Ala 290	His Cys Asn Leu Ser 295	Lys Thr Gln Trp Glu 300
	Lys Thr Leu Arg	Gln 305	Ile Ala Ile Lys Leu 310	Glu Glu Lys Phe Lys 315
	Asn Lys Thr Ile	Ala 320	Phe Asn Lys Ser Ser 325	Gly Gly Asp Pro Glu 330
45	Ile Val Met His	Ser 335	Phe Asn Cys Gly Gly 340	Gly Phe Phe Tyr Cys 345
	Ser Thr Arg Lys	Leu 350	Phe Asn Ser Thr Trp 355	Asn Leu Thr Gln Pro 360
50	Phe Ser Asn Thr	Gly 365	Asp Arg Thr Glu Glu 370	Leu Asn Ile Thr Leu 375
	Pro Cys Arg Ile	Lys 380	Gln Ile Ile Asn Leu 385	Trp Gln Glu Val Gly 390
	Lys Ala Met Tyr	Ala 395	Pro Pro Ile Arg Gly 400	Gln Ile Arg Cys Ser 405
60	Ser Asn Ile Thr	Gly 410	Leu Leu Leu Arg Arg 415	Asp Gly Gly Ser Asn 420
	Thr Ser Asp Asn	Gln 425	Thr Glu Thr Phe Arg 430	Pro Gly Gly Gly Asp 435

AP/P/99/01432

Met Arg Asp Lys Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val
 440 445 450
 5 Arg Ile Glu Pro Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg
 455 460 465
 Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
 470 475 480
 10 Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
 485 490 491

(2) INFORMATION FOR SEQ ID NO:9:

- (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1512 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

20 CTC GAG GTA CCT GTA TGG AAA GAA GCA ACT ACC ACT 36
 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1 5 10
 25 GTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
 Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
 15 20 25
 30 AAA CAT AAT GTT TGG GCG ACA CAC GCC TGT GTA CCC ACA 114
 Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
 30 35
 35 GAT CCC AAC CCA CAA GAA GTA GTA TTG CGA AAT GTG ACA 153
 Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
 40 45 50
 40 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60
 45 ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
 Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75
 50 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90
 55 AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
 Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
 95 100
 60 AGT ACT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
 Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
 105 110 115
 AAG GGG GAA ATG AAA AGA TGC TCT TTC AAT ATC ACC ACA 387
 Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
 120 125
 AGC ATA ACA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
 Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
 130 135 140

AP/P/99/01432

AP001282

	TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
	Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr 155
5	ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
	Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr 165
10	CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
	Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile 180
15	CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
	His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys 190
20	AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
	Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn 205
25	GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
	Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val 220
30	GAA GAG GTA ATA ATT AGA TCT GAC AAT ATC ACA GAC AAT 738
	Glu Glu Val Ile Ile Arg Ser Asp Asn Ile Thr Asp Asn 245
35	ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
	Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val 255
40	ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA AGA AAA AGT 816
	Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser 270
45	ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
	Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly 285
50	GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
	Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu 295
55	AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
	Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val 310
60	ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
	Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu 320
	AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
	Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro 335
	GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
	Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe 345

AP/P/99/01432

TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
 Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
 355 360

5 AAT GTT ACT AAA GGG TTG AAT AAC ACT CAA GGA AAT AGC 1128
 Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
 365 370 375

10 ACA GCA GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
 Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
 380 385

15 CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
 Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
 390 395 400

20 TAT GCC CCT CCC ATC ACT GGA CAA ATT AGA TGT TCA TCA 1245
 Tyr Ala Pro Ile Ser Gly Ile Ile Arg Cys Ser Ser
 405 410 415

25 AAC ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
 Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
 420 425

30 GGA GCA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
 Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
 445 450

35 AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCC 1401
 Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
 455 460 465

40 CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
 Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
 470 475 480

45 AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
 Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
 485 490

50 TTG GCA GCA TAA AGC TTC TAG AGT CGA CCT GCA 1512
 Leu Gly Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
 495 500 504

(2) INFORMATION FOR SEQ ID NO:10:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 504 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

55 Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
 1 5 10 15

60 Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu Lys His Asn Val Trp
 20 25 30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
 35 40 45

AP/P/99/01432

AP001282

	Val	Leu	Gly	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	50	55	60
5	Met	Val	Glu	Gln	Met	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	65	70	75
	Ser	Leu	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	80	85	90
10	Asn	Cys	Thr	Asp	Asp	Leu	Gly	Asn	Ala	Thr	Asn	Thr	Asn	Ser	Ser	95	100	105
	Ala	Thr	Thr	Asn	Ser	Ser	Ser	Trp	Glu	Glu	Met	Lys	Gly	Glu	Met	110	115	120
15	Lys	Arg	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Ile	Arg	Asp	Lys	Ile	125	130	135
	Lys	Lys	Glu	His	Ala	Leu	Phe	Tyr	Arg	Leu	Asp	Val	Val	Pro	Ile	140	145	150
20	Asp	Asn	Asp	Asn	Thr	Thr	Tyr	Arg	Leu	Ile	Asn	Cys	Asn	Thr	Ser	155	160	165
	Val	Ile	Thr	Gln	Ala	Cys	Pro	Lys	Val	Ser	Phe	Glu	Pro	Ile	Pro	170	175	180
	Ile	His	Phe	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	185	190	195
30	Asn	Lys	Thr	Phe	Glu	Gly	Lys	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	200	205	210
	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	215	220	225
35	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	Ile	Ile	Arg	Ser	230	235	240
	Asp	Asn	Ile	Thr	Asp	Asn	Thr	Lys	Thr	Ile	Ile	Val	Gln	Leu	Asn	245	250	255
	Glu	Ser	Val	Val	Ile	Asn	Cys	Thr	Arg	Pro	Asn	Asn	Asn	Thr	Arg	260	265	270
45	Lys	Ser	Ile	His	Ile	Gly	Pro	Gly	Ser	Ala	Phe	Phe	Ala	Thr	Gly	275	280	285
	Glu	Ile	Ile	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Leu	Ser	Arg	290	295	300
50	Thr	Gln	Trp	Asn	Asn	Thr	Leu	Gly	Lys	Ile	Val	Ile	Lys	Leu	Arg	305	310	315
	Glu	Gln	Phe	Arg	Lys	Gln	Phe	Gly	Glu	Lys	Thr	Ile	Val	Phe	Asn	320	325	330
	Arg	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Ala	Met	His	Ser	Phe	Asn	335	340	345
60	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Thr	Thr	Ala	Leu	Phe	Asn	350	355	360
	Ser	Thr	Trp	Asn	Val	Thr	Lys	Gly	Leu	Asn	Asn	Thr	Glu	Gly	Asn	365	370	375

AP/P/99/01432

Ser Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys Gln
380 385 390

5 Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro
395 400 405

Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu
410 415 420

10 Leu Leu Thr Arg Asp Gly Gly Ser Lys Asn Glu Ser Ile Thr Thr
425 430 435

Glu Val Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
440 445 450

15 Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly
455 460 465

20 Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
470 475 480

Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe Leu Gly
485 490 495

25 Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
500 504

(2) INFORMATION FOR SEQ ID NO:11:

30 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1501 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CTC GAG GTA CCT CTC TGG AAA GAA GCA ACT ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
1 5 10

40 GTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
15 20 25

45 AAA CAT AAT GTT TGG GGC ACA CAC GCC TGT GTA CCC ACA 114
Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
30 35

50 GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
40 45 50

55 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
55 60

60 ATG CAT GAA GAT ATA ATC ACT TTA TGG GAT CAA ACT CTA 231
Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
65 70 75

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

AP/P/99/01432

AP001282

	AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
	Asn Cys Thr Asp Asp 95 Leu Gly Asn Ala Thr Asn Thr Asn 100
5	AGC AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
	Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met 105 110 115
10	AAG GGG GAA ATG AAA AGG TGC TCT TTC AAT ATC ACC ACA 387
	Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr 120 125
15	AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
	Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe 130 135 140
20	TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
	Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr 145 150 155
25	ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
	Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr 160 165
30	CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
	Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile 170 175 180
35	CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
	His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys 185 190
40	AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
	Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn 195 200 205
45	GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
	Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val 210 215 220
50	GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
	Val Ser Thr Gln Leu Leu Asn Gly Ser Leu Ala Glu 225 230
55	GAA GAG GTA ATA ATT AGA TCT GGC AAT ATC ACA GAC AAT 738
	Glu Glu Val Ile Ile Arg Ser Gly Asn Ile Thr Asp Asn 235 240 245
60	ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
	Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val 250 255
65	ATT AAT TGT ACA AGA TCC AAC AAC AAT ACA AGA AAA AGT 816
	Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg Lys Ser 260 265 270
70	ATA CAT ATA GGA CCA GGG ACT GCA TTT TTT GCA ACA GGA 855
	Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly 275 280 285
75	GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
	Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu 290 295

AP/P/99/01432

ACT ACA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
 Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
 300 305 310

5 ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
 Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
 315 320

10 AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
 Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
 325 330 335

15 GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
 Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
 340 345 350

20 TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
 Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
 355 360

AAT GTT ACT AAA GGG TTC AAT AAC ACT GAA GGA AAT AGC 1128
 Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
 365 370 375

25 ACA GGS GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
 Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
 380 385

30 CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
 Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
 390 395 400

35 TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
 Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
 405 410 415

40 AAT ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT ACT 1284
 Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
 420 425

AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
 Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
 430 435 440

45 GGA GGA GAT ATG AGG GAC AAT TCG ACA ACT GAA TTA TAT 1362
 Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
 445 450

50 AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
 Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
 455 460 465

55 CCC ACC AAG GCA AAG AGA AGA GTG GTC CAG AGA GAA AAA 1440
 Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
 470 475 480

AAG GCA GTC GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
 Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
 485 490

60 TTA GCA GCA TAA AGC TTC TAG A 1501
 Leu Gly Ala Xaa Ser Phe Xaa
 495 500

AP/P/99/01432

APU 01282

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 500 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

	Leu	Glu	Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	Phe	Cys	
	1				5					10					15	
10	Ala	Ser	Asp	Ala	Lys	Ala	Tyr	Asn	Thr	Glu	Lys	His	Asn	Val	Trp	
					20					25					30	
15	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	Asn	Pro	Gln	Glu	Val	
					35					40					45	
	Val	Leu	Gly	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	
					50					55					60	
20	Met	Val	Glu	Gln	Met	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	
					65					70					75	
	Ser	Leu	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	
					80					85					90	
25	Asn	Cys	Thr	Asp	Asp	Leu	Gly	Asn	Ala	Thr	Asn	Thr	Asn	Ser	Ser	
					95					100					105	
30	Ala	Thr	Thr	Asn	Ser	Ser	Ser	Trp	Glu	Glu	Met	Lys	Gly	Glu	Met	
					110					115					120	
	Lys	Arg	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Ile	Arg	Asp	Lys	Ile	
					125					130					135	
35	Lys	Lys	Glu	His	Ala	Leu	Phe	Tyr	Arg	Leu	Asp	Val	Val	Pro	Ile	
					140					145					150	
	Asp	Asn	Asp	Asn	Thr	Thr	Tyr	Arg	Leu	Ile	Asn	Cys	Asn	Thr	Ser	
					155					160					165	
40	Val	Ile	Thr	Gln	Ala	Cys	Pro	Lys	Val	Ser	Phe	Glu	Pro	Ile	Pro	
					170					175					180	
45	Ile	His	Phe	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	
					185					190					195	
	Asn	Lys	Thr	Phe	Glu	Gly	Lys	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	
					200					205					210	
50	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	
					215					220					225	
	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	Ile	Ile	Arg	Ser	
					230					235					240	
55	Gly	Asn	Ile	Thr	Asp	Asn	Thr	Lys	Thr	Ile	Ile	Val	Gln	Leu	Asn	
					245					250					255	
60	Glu	Ser	Val	Val	Ile	Asn	Cys	Thr	Arg	Ser	Asn	Asn	Asn	Thr	Arg	
					260					265					270	
	Lys	Ser	Ile	His	Ile	Gly	Pro	Gly	Ser	Ala	Phe	Phe	Ala	Thr	Gly	
					275					280					285	

AP/P/99/01432

AP001282

	GTA	CCC	ACA	GAC	CCT	AGT	CCA	CAA	GAA	GTA	GTT	TTG	GAA	155
	Val	Pro	Thr	Asp	Pro	Ser	Pro	Gln	Glu	Val	Val	Leu	Glu	
		40					45					50		
5	AAT	GTG	ACA	GAA	AAT	TTT	AAC	ATG	TGG	AAA	AAT	AAC	ATG	194
	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	
				55					60					
10	GTA	GAA	CAA	ATG	CAT	GAG	GAT	ATA	ATT	AGT	TTA	TGG	GAT	233
	Val	Glu	Gln	Met	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	
		65				70					75			
15	CAA	AGC	TTA	AAG	CCA	TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	272
	Gln	Ser	Leu	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	
			80					85					90	
20	GTT	ACT	TTA	AAT	TGC	AGT	GAT	TAT	AGG	AAT	GCT	ACT	GAT	311
	Val	Thr	Leu	Asn	Cys	Ser	Asp	Tyr	Arg	Asn	Ala	Thr	Asp	
					95				100					
25	TAT	AAG	AAT	GCT	ACT	GAT	ACC	ACT	AGT	AGT	AAC	GAG	GGA	350
	Tyr	Lys	Asn	Ala	Thr	Asp	Thr	Thr	Ser	Ser	Asn	Glu	Gly	
		105					110					115		
30	AAG	ATG	GAG	AGA	GGA	GAA	ATA	AAA	AAC	TGC	TCT	TTC	AAT	389
	Lys	Met	Glu	Arg	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	
				120					125					
35	ATT	ACC	ACA	AGC	ATA	AAA	AAT	AAG	ATG	CAG	AAA	GAA	TAT	428
	Ile	Thr	Thr	Ser	Ile	Lys	Asn	Lys	Met	Gln	Lys	Glu	Tyr	
		130				135					140			
40	GCA	CTT	TTC	TAT	AAA	CTT	GAT	ATA	GTA	CCA	ATA	GAT	AAT	467
	Ala	Leu	Phe	Tyr	Lys	Leu	Asp	Ile	Val	Pro	Ile	Asp	Asn	
			145					150					155	
45	ACA	AGC	TAT	ACA	TTG	ATA	AGT	TGT	AAC	ACC	TCA	GTC	ATT	506
	Thr	Ser	Tyr	Thr	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	
					160					165				
50	ACA	CAG	GCC	TGT	CCA	AAG	GTA	TCC	TTT	GAA	CCA	ACT	CCC	545
	Thr	Gln	Ala	Cys	Pro	Lys	Val	Ser	Phe	Glu	Pro	Thr	Pro	
		170					175					180		
55	ATA	CAT	TAT	TGT	GCT	CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	584
	Ile	His	Tyr	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	
				185					190					
60	TGT	AAT	GAT	AAG	AAG	TTC	AGT	GGA	AAA	GGA	GAA	TGT	AAA	623
	Cys	Asn	Asp	Lys	Lys	Phe	Ser	Gly	Lys	Gly	Glu	Cys	Lys	
		195				200					205			
65	AAT	GTC	AGC	ACA	GTA	CAA	TGT	ACA	CAT	GGA	ATT	AGG	CCA	662
	Asn	Val	Ser	Thr	Val	Gln	Cys	Thr	His	Gly	Ile	Arg	Pro	
			210					215					220	
70	GTA	GTA	TCA	ACT	CAA	CTG	CTG	TTA	AAT	GGC	AGT	CTA	GCA	701
	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	
					225					230				
75	GAA	GAA	GAG	GTG	GTA	ATT	AGA	TCT	GAC	AAT	TTC	ATA	GAC	740
	Glu	Glu	Val	Val	Ile	Arg	Ser	Asp	Asn	Phe	Ile	Asp		
		235				240						245		

AP/P/99/01432

AAT ACT AAA ACC ATA ATA GTA CAG CTG AAA GAA TCT GTA 779
 Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val
 250 255

5 GAA ATT AAT TGT ATA AGA CCC AAC AAT AAT ACA AGA AAA 818
 Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys
 260 265 270

10 GGT ATA CAT ATA GGA CCA GGG AGA GCA TGG TAT GCA ACA 857
 Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
 275 280 285

15 GGA GAA ATA GTA GGA GAT ATA AGA AAG GCA TAT TGT AAC 896
 Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn
 290 295

20 ATT AGT AGA ACA AAA TGG AAT AAC ACT TTA ATA CAG ATA 935
 Ile Ser Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile
 300 305 310

GCT AAC AAA TTA AAA GAA AAA TAT AAT ACA ACA ATA AGC 974
 Ala Asn Lys Leu Lys Glu Lys Tyr Asn Thr Thr Ile Ser
 315 320

25 TTT AAT CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ACG 1013
 Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Thr
 325 330 335

30 CAT AGT TTT AAT TGT GGA GGG GAG TTT TTC TAC TGT GAT 1052
 His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asp
 340 345 350

35 TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT TTA AAT GGT 1091
 Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly
 355 360

40 ACT TGG AAT TTT ACT GCA GGG TCA AAT GAA ACT GAA GGC 1130
 Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly
 365 370 375

AAT ATC ACA CTC CCA TGG AGA ATA AAA CAA ATT ATA AAC 1169
 Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn
 380 385

45 AGG TGG CAG GAA GTA GCG AAA GCA ATG TAT GCC CCT CCC 1208
 Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro
 390 395 400

50 ATC AGT GGA CAA ATA AAA TGC TCA TCA AAC ATT ACA GGG 1247
 Ile Ser Gly Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly
 405 410 415

55 ATG ATA TTA ACA AGG GAT GGT GGT AAC GAG AAC AAT AAT 1286
 Met Ile Leu Thr Arg Asp Gly Gly Asn Glu Asn Asn Asn
 420 425

60 GAG AGC AGT ACT ACT GAG ACC TTC AGA CCG GGA GGA GGA 1325
 Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly Gly
 430 435 440

GAT ATG AGG AAC AAT TGG AGA AGT GAA TTA TAT AAA TAT 1364
 Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
 445 450

AP/P/99/01432

AP001282

AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC 1403
Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr
455 460 465

5 AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA 1442
Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
470 475 480

10 GTG GGA GCG CTA GGA GCT ATG TTC CTT GGG TTC TTA GGA 1481
Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly
485 490

GCA TAA AGC TTC TAG ACC GAC TCT AGA GGA TCC 1514
Ala Xaa Ser Phe Xaa Thr Asp Ser Arg Gly Ser
15 495 500 504

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 504 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

25 Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr
1 5 10 15
Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr Asp Thr Glu Val His
20 25 30

30 Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Ser Pro
35 40 45
Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp
50 55 60

35 Lys Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu
65 70 75
Trp Asp Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
40 80 85 90
Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys
95 100 105

45 Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly Lys Met Glu Arg
110 115 120
Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys
125 130 135

50 Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp Ile
140 145 150
Val Pro Ile Asp Asn Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr
55 155 160 165
Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr
170 175 180

60 Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
185 190 195
Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser
200 205 210

65

AP/F/99/01432

	Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln	215	220	225
5	Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg	230	235	240
	Ser Asp Asn Phe Ile Asp Asn Thr Lys Thr Ile Ile Val Gln Leu	245	250	255
10	Lys Glu Ser Val Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr	260	265	270
	Arg Lys Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr	275	280	285
15	Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn Ile Ser	290	295	300
	Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu	305	310	315
20	Lys Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser Gly	320	325	330
	Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys Gly Gly Glu	335	340	345
25	Phe Phe Tyr Cys Asp Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn	350	355	360
30	Leu Asn Gly Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu	365	370	375
	Gly Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn Arg	380	385	390
35	Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly	395	400	405
40	Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg	410	415	420
	Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr Glu Thr	425	430	435
45	Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn Trp Arg Ser Glu	440	445	450
50	Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala	455	460	465
	Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala	470	475	480
55	Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly Ala Xaa	485	490	495
60	Ser Phe Xaa Thr Asp Ser Arg Gly Ser	500	504	

(2) INFORMATION FOR SEQ ID NO:15:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1408 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single

AP/P/99/01432

AP001282

(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

5	G	GTA	CCT	GTG	TGG	AAG	GAA	GCA	ACC	ACC	ACT	CTA	TTC	37
		Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	Phe	
		1				5						10		
10		TGT	GCA	TCA	GAT	GCT	AGA	GCA	TAT	GAC	ACA	GAG	GTA	76
		Cys	Ala	Ser	Asp	Ala	Arg	Ala	Tyr	Asp	Thr	Glu	Val	His
			15						20				25	
15		AAT	GTT	TGG	GCC	ACA	CAT	GCC	TGT	GTA	CCC	ACA	GAC	115
		Asn	Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro
					30					35				
20		AGT	CCA	CAA	GAA	GTA	TTT	TTG	GGA	AAT	GTG	ACA	GAA	154
		Ser	Pro	Gln	Glu	Val	Phe	Leu	Gly	Asn	Val	Thr	Glu	Asn
			40					45					50	
25		TTT	AAT	ATG	TGG	AAA	AAT	AAC	ATG	GTA	GAA	CAA	ATG	193
		Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	Val	Glu	Gln	Met	Tyr
					55					60				
30		GAG	GAT	ATA	ATT	AGT	TTA	TGG	GAT	CAA	AGC	TTA	AAG	232
		Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	Pro
			65				70					75		
35		TGT	GTA	AAA	TTA	ACC	CCA	CTC	TGT	GTT	ACT	TTA	AAT	271
		Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys
				80					85				90	
40		AGT	GAT	TAT	AGG	AAT	GCT	ACT	GAT	TAT	AAG	AAT	GCT	310
		Ser	Asp	Tyr	Arg	Asn	Ala	Thr	Asp	Tyr	Lys	Asn	Ala	Thr
					95					100				
45		GAT	ACC	ACT	AGT	AGT	AAC	GAG	GGA	AAG	ATG	GAG	AGA	349
		Asp	Thr	Thr	Ser	Ser	Asn	Glu	Gly	Lys	Met	Glu	Arg	Gly
			105				110						115	
50		GAA	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	AGC	388
		Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Ile
					120					125				
55		AAA	AAT	AAG	ATG	CAG	AAA	GAA	TAT	GCA	CTT	TTC	TAT	427
		Lys	Asn	Lys	Met	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys
			130				135					140		
60		CTT	AAT	ATA	GTA	CCA	ATA	GAT	AAT	ACA	AGC	TAT	ACA	466
		Leu	Asn	Ile	Val	Pro	Ile	Asp	Asn	Thr	Ser	Tyr	Thr	Leu
				145				150					155	
65		ATA	AGT	TGT	AAC	ACC	TCA	GTC	ATT	ACA	CAG	GCC	TGT	505
		Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	Pro
					160					165				
70		AAG	GTA	TCC	TTT	GAA	CCA	ATT	CCC	ATA	CAT	TAT	TGT	544
		Lys	Val	Ser	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	Ala
			170					175					180	
75		CCG	GCT	GGT	TTT	GCG	ATT	CTA	AAG	TGT	AAT	GAT	AAG	583
		Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp	Lys	Lys
					185				190					

AP/P/99/01432

TTC AGT GGA AAA GGA GAA TGT AAA AAT CTC AGC ACA GTA 622
 Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val
 195 200 205

5 CAA TGT ACA CAT GGA ATT AGC CCA GTA GTA TCA ACT CAA 661
 Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
 210 215 220

10 CTG CCG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTG GTA 700
 Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val
 225 230

15 ATT AGA TGT GAC AAT TTC ACA GAC AAT ACT AAA ACC ATA 739
 Ile Arg Ser Asp Asn Phe Thr Asp Asn Thr Lys Thr Ile
 235 240 245

20 ATA GTA CAG CTG AAA GAA TCT GTA GAA ATT AAT TGT ATA 778
 Ile Val Gln Leu Lys Glu Ser Val Glu Ile Asn Cys Ile
 250 255

AGA CCC AAC AAT AAT ACA AGA AAA GGT ATA CAT ATA GGA 817
 Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Ile Gly
 260 265 270

25 CCA GGC AGA GCA TGG TAT GCA ACA GCA GAA ATA GTA GGA 856
 Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly
 275 280 285

30 GAT ATA AGA CAG GCA TAT TGT AAC ATT AGT AGA ACA AAA 895
 Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys
 290 295

35 TGG AAT AAC ACT TTA ATA CAG ATA GCT AAC AAA TTA AAA 934
 Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys
 300 305 310

40 GAA AAA TAT AAT ACA ACA ATA AGC TTT AAT CGA TCC TCA 973
 Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser
 315 320

GGA GGS GAC CCA GAA ATT GTA ACC CAT AGT TTT AAT TGT 1012
 Gly Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys
 325 330 335

45 GGA GGS GAA TTT TTC TAC TGT AAT TCA ACA CAA CTG TTT 1051
 Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe
 340 345 350

50 AAT AGT ACT TGG AAT TTA AAT GGT ACT TGG AAT TTT ACT 1090
 Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp Asn Phe Thr
 355 360

55 GCA GGG TCA AAT GAA ACT GAA GGC AAT ATC ACA CTC CCA 1129
 Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu Pro
 365 370 375

TGC AGA ATA AAA CAA ATT ATA AAC AGC TGG CAG GAA GTA 1168
 Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val
 380 385

60 GGA AAA GCA ATG TAT GCC CCT CCC ATC AGT GGA CAA ATA 1207
 Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile
 390 395 400

AP/P/99/01432

AP001282

AGA TGC TCA TCA AAC ATT ACA GGG ATG ATA TTA ACA AGG 1246
Arg Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
405 410 415

5 GAT GGT GGT AAC GAG AAC AAT AAT GAG AGC AGT ACT ACT 1285
Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr
420 425

10 GAG ACC TTC AGA CCG GGA GGA GGA GAT ATG AGG AAC AAT 1324
Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn
430 435 440

15 TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT 1363
Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile
445 450

GAG CCA TTA GGA GTA GCA CCC ACC GAC TCT AGA GGA TCC 1402
Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg Gly Ser
455 460 465

20 TCT AGA 1408
Ser Arg
469

25 (2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 469 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
1 5 10 15

35 Asp Ala Arg Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
20 25 30

His Ala Cys Val Pro Thr Asp Pro Ser Pro Gln Glu Val Phe Leu
35 40 45

40 Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
50 55 60

45 Glu Gln Met Tyr Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
65 70 75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
80 85 90

50 Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys Asn Ala Thr Asp Thr
95 100 105

Thr Ser Ser Asn Glu Gly Lys Met Glu Arg Gly Glu Ile Lys Asn
110 115 120

55 Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys
125 130 135

Glu Tyr Ala Leu Phe Tyr Lys Leu Asn Ile Val Pro Ile Asp Asn
140 145 150

60 Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
155 160 165

AP/P/99/01432

	Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys	170	175	180
5	Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe	185	190	195
	Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val Gln Cys Thr	200	205	210
10	His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly	215	220	225
	Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Thr	230	235	240
15	Asp Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val Glu	245	250	255
	Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His	260	265	270
20	Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly	275	280	285
	Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys Trp Asn	290	295	300
	Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys Glu Lys Tyr Asn	305	310	315
30	Thr Thr Ile Ser Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile	320	325	330
	Val Thr His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn	335	340	345
35	Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp	350	355	360
	Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu	365	370	375
40	Pro Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val Gly	380	385	390
45	Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser	395	400	405
	Ser Asn Ile Thr Gly Met Ile Leu Thr Arg Asp Gly Gly Asn Glu	410	415	420
50	Asn Asn Asn Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly	425	430	435
	Gly Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys	440	445	450
55	Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg	455	460	465
60	Gly Ser Ser Arg	469		

(2) INFORMATION FOR SEQ ID NO:17:
 (i) SEQUENCE CHARACTERISTICS:

AP001282

(A) LENGTH: 1499 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

	GAG	GTA	CCT	GTG	TGG	AAA	GAA	GCA	ACC	ACT	ACT	CTA	36
	Glu	Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	
	1				5					10			
10	TTT	TGT	GCA	TCA	GAT	GCT	AAA	GCA	TAT	GAC	ACA	GGG	GTG 75
	Phe	Cys	Ala	Ser	Asp	Ala	Lys	Ala	Tyr	Asp	Thr	Gly	Val
	15					20						25	
15	CAT	AAT	GTT	TGG	GCC	ACA	CAT	GCC	TGT	GTA	CCC	ACA	GAC 114
	His	Asn	Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp
					30				35				
20	CCC	AAC	CCA	CAA	GAA	ATA	GAA	TTG	GTA	AAT	GTG	ACA	GAA 153
	Pro	Asn	Pro	Gln	Glu	Ile	Glu	Leu	Val	Asn	Val	Thr	Glu
	40				45				50				
25	GAT	TTT	AAC	ATG	TGG	AAA	AAT	AAA	ATG	GTA	GAC	CAG	ATG 192
	Asp	Phe	Asn	Met	Trp	Lys	Asn	Lys	Met	Val	Asp	Gln	Met
			55						60				
30	CAT	GAG	GAT	ATA	ATC	AGT	TTA	TGG	GAT	GAA	AGC	CTA	AAG 231
	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Glu	Ser	Leu	Lys
	65				70				75				
35	CCA	TGT	GTA	AAG	TTA	ACC	CCA	CTT	TGT	GTT	ACT	CTA	AAC 270
	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn
	80				85				90				
40	TGC	AGT	GAT	GTG	AAC	AAT	TCC	ACA	AAT	CCT	AAT	GAT	ACT 309
	Cys	Ser	Asp	Val	Asn	Asn	Ser	Thr	Asn	Pro	Asn	Asp	Thr
					95				100				
45	AAT	ACT	AAT	TCC	ACT	AAT	ACT	ACT	TCC	TCT	ACT	CCT	ACG 348
	Asn	Thr	Asn	Ser	Thr	Asn	Thr	Thr	Ser	Ser	Thr	Pro	Thr
	105				110				115				
50	GCC	ACT	ACT	AGT	AGC	GAG	GAA	AAG	ATG	GAG	AAG	GGA	GAA 387
	Ala	Thr	Thr	Ser	Ser	Glu	Glu	Lys	Met	Glu	Lys	Gly	Glu
				120					125				
55	ATA	AAA	AAC	TGC	TCT	TTC	AAT	ATC	ACC	ACA	CAC	ATG	AAA 426
	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	His	Met	Lys
	130				135				140				
60	GAT	AAG	GCA	CAG	AAA	GAA	TAT	GCA	CTT	TTT	TAT	AAA	CTT 465
	Asp	Lys	Ala	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu
		145			150				155				
65	GAT	ATA	GTA	CCA	ATA	GAT	GAT	AAT	AAT	GCC	AGC	TAT	AGG 504
	Asp	Ile	Val	Pro	Ile	Asp	Asp	Asn	Asn	Ala	Ser	Tyr	Arg
				160					165				
70	TTG	ATA	AGT	TGT	AAT	ACC	TCA	GAC	ATT	ACA	CAG	GCC	TGT 543
	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Asp	Ile	Thr	Gln	Ala	Cys
	170				175				180				
75	CCA	AAG	GTG	ACC	TTT	GAG	CCA	ATT	CCC	ATA	CAT	TAT	TGT 582
	Pro	Lys	Val	Thr	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys
				185					190				

AP/P/99/01432

GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
 Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
 195 200 205

5 AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
 Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
 210 215 220

10 GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
 Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
 225 230

15 CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
 Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
 235 240 245

20 GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777
 Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
 250 255

ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
 Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
 260 265 270

25 ACA ASA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
 Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
 275 280 285

30 GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
 Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
 290 295

35 GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
 Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
 300 305 310

AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
 Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
 315 320

40 AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
 Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
 325 330 335

45 TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT TTT 1050
 Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
 340 345 350

50 AAC TGT CGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
 Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
 355 360

55 CTG TTT AAT AGT ACT TCG AAT AAT ACT GAA GGG ACA AAT 1128
 Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
 365 370 375

AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
 Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
 380 385

60 ATA AAA CAA ATT ATA AAT ATG TCG CAG GAA GTA GGA AAA 1206
 Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
 390 395 400

AP/P/99/01432

APC 01282

GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
405 410 415

5 ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
420 425

10 GGT AGG AAT GTC ACA AAC AAT ACC GAA ACC TTC AGA CCT 1323
Gly Arg Asn Val Thr Asn Asn Thr Glu Thr Phe Arg Pro
430 435 440

15 GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
445 450

20 TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
455 460 465

GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
470 475 480

25 AAA AGA GCA GCA CTA GGA GCC TTG TTC CTT GGG TTC TTA 1479
Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
485 490

30 GGA GCA TAA AAG CTT CTA GA 1499
Gly Ala Xaa Lys Leu Leu
495 499

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
35 (A) LENGTH: 499 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

40 Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
1 5 10 15
Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val His Asn Val Trp Ala
20 25 30
45 Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Glu
35 40 45
50 Leu Val Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Lys Met
50 55 60
Val Asp Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser
65 70 75
55 Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
80 85 90
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr Asn Thr
95 100 105
60 Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr Ala Thr Thr Ser
110 115 120
65 Ser Glu Glu Lys Met Glu Lys Gly Glu Ile Lys Asn Cys Ser Phe
125 130 135

AP/F/99/01432

	Asn Ile Thr Thr His Met Lys Asp Lys Ala Gln Lys Glu Tyr Ala	140	145	150
5	Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asp Asn Asn Ala	155	160	165
	Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Asp Ile Thr Gln Ala	170	175	180
10	Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys Ala	185	190	195
	Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn	200	205	210
15	Gly Thr Gly Pro Cys Ser Lys Val Ser Thr Val Gln Cys Thr His	215	220	225
	Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser	230	235	240
20	Leu Ala Glu Glu Glu Val Val Ile Arg Ser Val Asn Phe Thr Asp	245	250	255
	Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile	260	265	270
25	Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu	275	280	285
30	Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile Gly Asp	290	295	300
	Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu Lys Trp Asn Asn	305	310	315
35	Thr Leu Arg Gln Val Val Lys Lys Leu Arg Glu Gln Phe Gly Asn	320	325	330
40	Lys Thr Ile Ile Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile	335	340	345
	Val Met His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn	350	355	360
45	Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr	365	370	375
50	Asn Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg Ile	380	385	390
	Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Thr Tyr	395	400	405
55	Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys Ile Ser Asn Ile Thr	410	415	420
	Gly Leu Leu Leu Thr Arg Asp Gly Gly Arg Asn Val Thr Asn Asn	425	430	435
60	Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp	440	445	450
65	Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu	455	460	465

AP001282

Gly Ile Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
470 475 480

5 Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala
485 490 495

Xaa Lys Leu Leu
499

10 (2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1499 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
15 (D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAG GTA CCT GTA TGG AAA GAA GCA ACC ACT ACT CTA 36
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
20 1 5 10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
15 20 25

25 CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
30 35

30 CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
40 45 50

35 GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
55 60

40 CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
65 70 75

CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
80 85 90

45 TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
95 100

50 AAT ACT AAT TCC ACT AAT ACT ACT TCC TCT ACT CCT ACG 348
Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
105 110 115

55 GCC ACT ACT ACT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
120 125

60 ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
130 135 140

GAT AAG GTA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
Asp Lys Val Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
145 150 155

65

AP/P/99/01432

GAT ATA GTA CCA ATA GAT GAT AAT AAT ACC AGC TAT AGG 504
 Asp Ile Val Pro Ile Asp Asp Asn Asn Thr Ser Tyr Arg
 160 165

5 TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT 543
 Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
 170 175 180

10 CCA ATG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
 Pro Met Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
 185 190

15 GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
 Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
 195 200 205

20 AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
 Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
 210 215 220

GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
 Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
 225 230

25 CAA CTG TTG TTA AAT GCG AGT CTT GCA GAA GAA GAA GTA 738
 Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
 235 240 245

30 GTA AAT AGA TCT GTC AAT TTC ACA CAC AAT GCT AAA ATC 777
 Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
 250 255

35 ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
 Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
 260 265 270

40 ACA AGA CCC AAC AAC AAT ACA AGA AAA GCT ATA CAT CTA 855
 Thr Arg Pro Asn Asn Thr Arg Lys Gly Ile His Leu
 275 280 285

GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
 Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
 290 295

45 GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
 Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
 300 305 310

50 AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
 Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
 315 320

55 ACA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
 Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
 325 330 335

60 TCC TCA GCA GGG CAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
 Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
 340 345 350

AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
 Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
 355 360

AP/P/99/01432

AP001282

CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
365 370 375

5 AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
380 385

10 ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
390 395 400

15 GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
405 410 415

20 ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
420 425

25 GGT AGG AAT GTC ACA AAC AAT ACC GAN NCC TTC AGA CCT 1323
Gly Arg Asn Val Thr Asn Asn Thr Xaa Xaa Phe Arg Pro
430 435 440

30 GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA ACT GAA TTA 1362
Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
445 450

35 TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
455 460 465

40 GCA CCC ACC AAG GCA AAG AGA AGA GTG GTC CAC AGA GAC 1440
Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
470 475 480

45 AAA AGA GCA GCA CTA GGA GCT TTG TTC CTT GGG TTC TTA 1479
Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
485 490

50 (2) INFORMATION FOR SEQ ID NO:20:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
1 5 10 15

55 Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
20 25 30

Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Glu
35 40 45

60 Leu Val Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Lys Met
50 55 60

65 Val Asp Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser
65 70 75

AP/P/99'01432

	Leu	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	80	85	90
5	Cys	Ser	Asp	Val	Asn	Asn	Ser	Thr	Asn	Pro	Asn	Asp	Thr	Asn	Thr	95	100	105
	Asn	Ser	Thr	Asn	Thr	Thr	Ser	Ser	Thr	Pro	Thr	Ala	Thr	Thr	Ser	110	115	120
10	Ser	Glu	Glu	Lys	Met	Glu	Lys	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	125	130	135
	Asn	Ile	Thr	Thr	His	Met	Lys	Asp	Lys	Val	Gln	Lys	Glu	Tyr	Ala	140	145	150
15	Leu	Phe	Tyr	Lys	Leu	Asp	Ile	Val	Pro	Ile	Asp	Asp	Asn	Asn	Thr	155	160	165
	Ser	Tyr	Arg	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	170	175	180
20	Cys	Pro	Met	Val	Thr	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	Ala	185	190	195
	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Lys	Asp	Lys	Lys	Phe	Asn	200	205	210
25	Gly	Thr	Gly	Pro	Cys	Ser	Lys	Val	Ser	Thr	Val	Gln	Cys	Thr	His	215	220	225
30	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn	Gly	Ser	230	235	240
	Leu	Ala	Glu	Glu	Glu	Val	Val	Ile	Arg	Ser	Val	Asn	Phe	Thr	Asp	245	250	255
35	Asn	Ala	Lys	Ile	Ile	Ile	Val	Gln	Leu	Lys	Glu	Pro	Val	Ala	Ile	260	265	270
	Asn	Cys	Thr	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Lys	Gly	Ile	His	Leu	275	280	285
40	Gly	Pro	Gly	Ser	Thr	Phe	Tyr	Thr	Thr	Gly	Glu	Ile	Ile	Gly	Asp	290	295	300
45	Ile	Arg	Lys	Ala	Tyr	Cys	Lys	Ile	Ser	Lys	Glu	Lys	Trp	Asn	Asn	305	310	315
	Thr	Leu	Arg	Gln	Val	Val	Lys	Lys	Leu	Arg	Glu	Gln	Phe	Gly	Asn	320	325	330
50	Lys	Thr	Ile	Ile	Phe	Asn	Arg	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	335	340	345
	Val	Met	His	Ser	Phe	Asn	Cys	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	350	355	360
55	Thr	Thr	Gln	Leu	Phe	Asn	Ser	Thr	Trp	Asn	Asn	Thr	Glu	Gly	Thr	365	370	375
60	Asn	Ser	Thr	Glu	Gly	Asn	Ser	Thr	Ile	Thr	Leu	Pro	Cys	Arg	Ile	380	385	390
	Lys	Gln	Ile	Ile	Asn	Met	Trp	Gln	Glu	Val	Gly	Lys	Ala	Thr	Tyr	395	400	405

AP001282

Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys Ile Ser Asn Ile Thr
410 415 420

5 Gly Leu Leu Leu Thr Arg Asp Gly Gly Arg Asn Val Thr Asn Asn
425 430 435

Thr Xaa Xaa Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
440 445 450

10 Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu
455 460 465

Gly Ile Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
470 475 480

15 Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala
485 490 495

20 Xaa Lys Leu Leu
499

(2) INFORMATION FOR SEQ ID NO:21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1475 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

30 G GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
1 5 10

35 TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
15 20 25

40 AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
30 35

AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
40 45 50

45 TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
55 60

50 GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
65 70 75

55 TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
80 85 90

AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
95 100

60 ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
105 110 115

65

AP/P/99/01432

ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
 Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
 120 125

5 AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
 Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
 130 135 140

10 GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
 Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
 145 150 155

15 TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
 Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
 160 165

20 CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
 Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
 170 175 180

GCC GCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
 Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
 185 190

25 AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC ACC ACA 622
 Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
 195 200 205

30 GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
 Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
 210 215 220

35 CAA CTG TTG TTA AAT GCG AGT CTA GCA GAA GAA GAC GTA 700
 Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
 225 230

40 GTA ATC ACA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
 Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
 235 240 245

ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
 Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
 250 255

45 ACA ACA CTT GGC AAC AAT ACA AGA AAA ACT ATA AAT ATA 817
 Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
 260 265 270

50 GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
 Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
 275 280 285

55 GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
 Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
 290 295

60 CAA TCG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAA TTA 934
 Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
 300 305 310

AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
 Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
 315 320

AP/P/99/01432

AP001282

CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325 330 335

5 TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
340 345 350

10 CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
355 360

15 CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
365 370 375

20 AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
380 385

ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390 395 400

25 TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
405 410 415

30 AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
420 425

35 ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Asp Met Arg Asp Asn Trp
430 435 440

AGA AGT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
445 450

40 CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455 460 465

45 GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
470 475 480

50 TTC CTT GGG T TCTTAGGAG CATAAAGCTT CTAGA 1475
Phe Leu Gly
483

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS:
55 (A) LENGTH: 491 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

60 Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser
1 5 10 15

Asp Ala Lys Ala Tyr Asp Arg Glu Val His Asn Val Trp Ala Thr
20 25 30

65

AP/P/99/01432

	His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Val Leu	35	40	45
5	Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val	50	55	60
	Glu Gln Met His Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu	65	70	75
10	Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys	80	85	90
	Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile Thr Asn	95	100	105
15	Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met Thr Asn Cys Ser	110	115	120
	Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Gln Lys Glu Tyr	125	130	135
20	Ala Leu Leu Tyr Lys Leu Asp Val Val Pro Ile Glu Glu Asp Asp	140	145	150
	Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr	155	160	165
25	Gln Ala Cys Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr	170	175	180
30	Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys	185	190	195
	Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val Gln Cys	200	205	210
35	Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn	215	220	225
	Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Ala Asn Phe	230	235	240
40	Thr Asp Asn Ala Lys Thr Ile Ile Val His Leu Asn Glu Thr Val	245	250	255
45	Lys Ile Asn Cys Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile	260	265	270
	Asn Ile Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile	275	280	285
50	Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala Gln Trp	290	295	300
	Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu Arg Lys Gln Phe	305	310	315
55	Gly Asp Asn Thr Thr Ile Ala Phe Asn Arg Ser Ser Gly Gly Asp	320	325	330
60	Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu Phe Phe	335	340	345
	Tyr Cys Asn Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr	350	355	360

AP001282

Trp Lys Asp Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg
365 370 375

5 Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
380 385 390

Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser Ser Asn Ile
395 400 405

10 Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Asp Gly Asn
410 415 420

Asp Thr Thr Thr Asn Arg Thr Glu Ile Phe Arg Pro Gly Gly Gly
425 430 435

15 Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Arg Tyr Lys Val
440 445 450

Val Lys Ile Glu Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg
455 460 465

20 Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
470 475 480

25 Phe Leu Gly Phe Leu Gly Ala Leu Phe Leu Gly
485 490 491

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 1475 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

35 G GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
1 5 10

40 TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
15 20 25

45 AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
30 35

50 AAC CCA CAA GAA ATA GTA TTG GCA AAT GTG ACA GAA AAT 154
Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
40 45 50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
55 60

55 GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
65 70 75

60 TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
80 85 90

AP/P/99/01432

AAG CAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
 Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
 95 100

5 ACC AAT AAT AGT AGT TTC GAG GGA CTA AGA GAA CAA ATG 349
 Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
 105 110 115

10 ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
 Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
 120 125

15 AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
 Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
 130 135 140

20 GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
 Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
 145 150 155

25 TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
 Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
 160 165

30 CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
 Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
 170 175 180

35 GCC CCG CCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
 Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
 185 190

40 AAG TTC AAT GCA ACA GCA CCA TGT AAA AAT GTC AGC ACA 622
 Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
 195 200 205

45 GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
 Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
 210 215 220

50 CAA CIG TTG TTA AAT GGC AGT CTA CCA GAA GAA GAG GTA 700
 Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Val
 225 230

55 GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
 Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
 235 240 245

60 ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
 Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
 250 255

65 ACA AGA CTT GCC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
 Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
 260 265 270

70 GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
 Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
 275 280 285

75 GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT ACT AGA GCA 895
 Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
 290 295

AP/P/99/01432

AP001282

CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAG TTA 934
Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
300 305 310

5 AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
315 320

10 CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325 330 335

15 TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
340 345 350

CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
355 360

20 CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
365 370 375

25 AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
380 385

30 ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390 395 400

35 TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
405 410 415

AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
420 425

40 ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
430 435 440

45 AGA ACT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
445 450

50 CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455 460 465

55 GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
470 475 480

TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1475
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
485 490 491

60 (2) INFORMATION FOR SEQ ID NO:24:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 491 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

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AP/P/99/01432

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:24:

5	Val	Pro	Val	Trp	Lys	Glu	Ala	Asn	Thr	Thr	Leu	Phe	Cys	Ala	Ser	
	1				5					10					15	
	Asp	Ala	Lys	Ala	Tyr	Asp	Arg	Glu	Val	His	Asn	Val	Trp	Ala	Thr	
				20						25					30	
10	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	Asn	Pro	Gln	Glu	Ile	Val	Leu	
					35					40					45	
	Gly	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	Val	
					50					55					60	
15	Glu	Gln	Met	His	Glu	Asp	Ile	Ile	Asn	Leu	Trp	Asp	Gln	Ser	Leu	
					65					70					75	
	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Lys	Cys	
20					80					85					90	
	Lys	Asp	Leu	Glu	Arg	Asn	Thr	Thr	Tyr	Asn	Ser	Thr	Ile	Thr	Asn	
					95					100					105	
25	Asn	Ser	Ser	Leu	Glu	Gly	Leu	Arg	Glu	Gln	Met	Thr	Asn	Cys	Ser	
					110					115					120	
	Phe	Asn	Ile	Thr	Thr	Ser	Ile	Arg	Asp	Lys	Val	Gln	Lys	Glu	Tyr	
					125					130					135	
30	Ala	Leu	Leu	Tyr	Lys	Leu	Asp	Val	Val	Pro	Ile	Glu	Glu	Asp	Asp	
					140					145					150	
	Asn	Thr	Ser	Tyr	Arg	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr	
35					155					160					165	
	Gln	Ala	Cys	Pro	Lys	Thr	Ser	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	
					170					175					180	
40	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp	Lys	Lys	
					185					190					195	
	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Lys	Asn	Val	Ser	Thr	Val	Gln	Cys	
					200					205					210	
45	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn	
					215					220					225	
	Gly	Ser	Leu	Ala	Glu	Glu	Glu	Val	Val	Ile	Arg	Ser	Ala	Asn	Phe	
50					230					235					240	
	Thr	Asp	Asn	Ala	Lys	Thr	Ile	Ile	Val	His	Leu	Asn	Glu	Thr	Val	
					245					250					255	
55	Lys	Ile	Asn	Cys	Thr	Arg	Leu	Gly	Asn	Asn	Thr	Arg	Lys	Ser	Ile	
					260					265					270	
	Asn	Ile	Gly	Pro	Gly	Arg	Val	Leu	Tyr	Ala	Thr	Gly	Glu	Ile	Ile	
					275					280					285	
60	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	Asn	Ile	Ser	Arg	Ala	Gln	Trp	
					290					295					300	
65	Asn	Lys	Thr	Leu	Glu	Lys	Val	Val	Asp	Lys	Leu	Arg	Lys	Gln	Phe	
					305					310					315	

AP001282

Gly Asp Asn Thr Thr Ile Ala Phe Asn Arg Ser Ser Gly Gly Asp
320 325 330

5 Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu Phe Phe
335 340 345

Tyr Cys Asn Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr
350 355 360

10 Trp Lys Asp Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg
365 370 375

Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
380 385 390

15 Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser Ser Asn Ile
395 400 405

Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Asp Gly Asn
410 415 420

20 Asp Thr Thr Thr Asn Arg Thr Glu Ile Phe Arg Pro Gly Gly Gly
425 430 435

25 Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Arg Tyr Lys Val
440 445 450

Val Lys Ile Glu Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg
455 460 465

30 Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
470 475 480

Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
485 490 491

35

(2) INFORMATION FOR SEQ ID NO:25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1435 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

40

45 CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
1 5 10

50 CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
15 20 25

55 GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
30 35

GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
40 45 50

60 GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
55 60

AP/P/99/01432

ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
 Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75

5 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACC TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90

10 AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
 95 100

15 ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
 Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
 105 110 115

20 ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
 Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
 120 125

CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
 Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
 130 135 140

25 AAT ACT AGC TAT AGG TTG ATA ACT TGT AAC ACC TCA GTC 465
 Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
 145 150 155

30 ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
 Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
 160 165

35 CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT CCG ATT CTA 543
 Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
 170 175 180

40 AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
 Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
 185 190

ACA AAT CTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
 Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
 195 200 205

45 CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
 Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
 210 215 220

50 GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
 Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
 225 230

55 GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
 Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
 235 240 245

60 GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
 Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
 250 255

AAA AGT ATA CAT ATA GGA CCA GGC ACA GCA TTT TAT GCA 816
 Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
 260 265 270

AP/P/99/01432

APC 01282

	ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
	Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys 285
5	AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
	Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys 295
10	ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
	Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile 310
15	GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
	Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala 320
20	ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
	Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys 335
25	AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
	Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr 350
30	GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
	Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu 360
35	CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
	Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys 375
40	ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
	Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln 385
45	ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
	Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr 400
50	AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
	Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu 415
55	ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
	Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp 425
60	AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
	Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu 440
	CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
	Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val 450
	GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
	Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val 465
	TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
	Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa 478

AP/P/99/01432

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 478 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

5	Leu	Glu	Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	Phe	Cys	1	5	10	15
10	Ala	Ser	Asp	Ala	Lys	Ala	Tyr	Asp	Ser	Glu	Ala	His	Asn	Val	Trp	20	25	30	
15	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	Asn	Pro	Gln	Glu	Val	35	40	45	
	Glu	Leu	Glu	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	50	55	60	
20	Met	Val	Glu	Gln	Met	His	Gly	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	65	70	75	
	Ser	Leu	Lys	Pro	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	80	85	90	
25	Asn	Cys	Thr	Asp	Pro	Asn	Val	Thr	Asn	Ser	Glu	Arg	Thr	Ile	Glu	95	100	105	
30	Gly	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Asn	Ile	110	115	120	
	Arg	Asp	Arg	Phe	Gln	Lys	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu	Asp	125	130	135	
35	Val	Ile	Pro	Leu	Gly	Asn	Asp	Asn	Thr	Ser	Tyr	Arg	Leu	Ile	Ser	140	145	150	
	Cys	Asn	Thr	Ser	Val	Ile	Thr	Gln	Ala	Cys	Pro	Lys	Val	Ser	Phe	155	160	165	
40	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	170	175	180	
45	Leu	Lys	Cys	Lys	Asp	Lys	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Thr	185	190	195	
	Asn	Val	Ser	Thr	Val	Gln	Cys	Thr	His	Gly	Ile	Lys	Pro	Val	Val	200	205	210	
50	Ser	Thr	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala	Glu	Glu	Asp	Ile	215	220	225	
	Val	Ile	Arg	Ser	Ala	Asn	Leu	Thr	Asp	Asn	Ala	Lys	Asn	Ile	Ile	230	235	240	
55	Val	Gln	Leu	Asn	Glu	Ser	Val	Thr	Met	Asn	Cys	Thr	Arg	Pro	Asn	245	250	255	
60	Asn	Asn	Thr	Met	Lys	Ser	Ile	His	Ile	Gly	Pro	Gly	Arg	Ala	Phe	260	265	270	
	Tyr	Ala	Thr	Gly	Asn	Ile	Ile	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	275	280	285	

AP/P/99/01432

AP001282

	Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys Ile Ala	290	295	300
5	Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile Val Phe Asn Gln	305	310	315
	Ser Ser Gly Gly Asp Pro Glu Ile Ala Thr Leu Ser Phe Asn Cys	320	325	330
10	Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe Asn Ser	335	340	345
	Thr Trp Asn Ser Thr Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr	350	355	360
15	Ile Thr Leu Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln	365	370	375
20	Lys Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln Ile	380	385	390
	Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr Arg Asp Gly	395	400	405
25	Gly Asn Asn Asn Met Ser Lys Thr Thr Glu Thr Phe Arg Pro Gly	410	415	420
	Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr	425	430	435
30	Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Arg Ala	440	445	450
35	Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly	455	460	465
	Ala Val Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa	470	475	478
40	(2) INFORMATION FOR SEQ ID NO:27:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 1435 base pairs			
	(B) TYPE: Nucleic Acid			
	(C) STRANDEDNESS: Single			
45	(D) TOPOLOGY: Linear			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:			
50	CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT	36		
	Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr			
	1	5	10	
	CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG	75		
	Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu			
	15	20	25	
55	GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA	114		
	Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr			
	30	35		
60	GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA	153		
	Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr			
	40	45	50	

AP/P/99/01432

GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
 Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
 55 60

5 ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
 Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65 70 75

10 AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
 Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 80 85 90

15 AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
 95 100

20 ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
 Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
 105 110 115

ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
 Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
 120 125

25 GTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
 Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
 130 135 140

30 AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
 Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
 145 150 155

35 ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
 Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
 160 165

40 CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
 Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
 170 175 180

AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
 Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
 185 190

45 ACA AAT CTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
 Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
 195 200 205

50 CCA GTA GTA TCA ACT CAA CTG TTC TTA AAT GGC AGT CTA 660
 Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
 210 215 220

55 GCA GAA GAA GAC ATA GTA ATT ACA TCC GCC AAT CTC ACA 699
 Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
 225 230

GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
 Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
 235 240 245

60 GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
 Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
 250 255

AP/P/99/01432

AP001282

	AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
	Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
	260 265 270
5	ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
	Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
	275 280 285
10	AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
	Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
	290 295
15	ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
	Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
	300 305 310
20	GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
	Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
	315 320
25	ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
	Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
	325 330 335
30	AAT TCA ACA CAA CTG TTT AAT ACT ACT TGG AAT AGT ACT 1050
	Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
	340 345 350
35	GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
	Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
	355 360
40	CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
	Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
	365 370 375
45	ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
	Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
	380 385
50	ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
	Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
	390 395 400
55	AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
	Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
	405 410 415
60	ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
	Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
	420 425
65	AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
	Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
	430 435 440
70	CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
	Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
	445 450
75	GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
	Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
	455 460 465

AP/P/99/01432

TTC CIT GGG TTC TTG GCA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
470 475 478

5 (2) INFORMATION FOR SEQ ID NO:28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 478 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
1 5 10 15

15 Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu Ala His Asn Val Trp
20 25 30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
35 40 45

20 Glu Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
50 55 60

25 Met Val Glu Gln Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln
65 70 75

Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

30 Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr Ile Glu
95 100 105

Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Asn Ile
110 115 120

35 Arg Asp Arg Phe Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp
125 130 135

Val Ile Pro Leu Gly Asn Asp Asn Thr Ser Tyr Arg Leu Ile Ser
140 145 150

Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe
155 160 165

45 Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile
170 175 180

Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Thr
185 190 195

50 Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro Val Val
200 205 210

Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Asp Ile
215 220 225

Val Ile Arg Ser Ala Asn Leu Thr Asp Asn Ala Lys Asn Ile Ile
230 235 240

60 Val Gln Leu Asn Glu Ser Val Thr Met Asn Cys Thr Arg Pro Asn
245 250 255

Asn Asn Thr Met Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe
260 265 270

65

AP/P/99/01432

AP001282

	Tyr	Ala	Thr	Gly	Asn	Ile	Ile	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys	
					275					280					285	
5	Asn	Ile	Ser	Gly	Thr	Lys	Trp	Asn	Asp	Thr	Leu	Lys	Lys	Ile	Ala	
					290					295					300	
	Ile	Lys	Leu	Arg	Glu	Gln	Phe	Asn	Lys	Thr	Ile	Val	Phe	Asn	Gln	
					305					310					315	
10	Ser	Ser	Gly	Gly	Asp	Pro	Glu	Ile	Ala	Thr	Leu	Ser	Phe	Asn	Cys	
					320					325					330	
	Gly	Gly	Glu	Phe	Phe	Tyr	Cys	Asn	Ser	Thr	Gln	Leu	Phe	Asn	Ser	
					335					340					345	
15	Thr	Trp	Asn	Ser	Thr	Gly	Ser	Asn	Asn	Thr	Lys	Gly	Asn	Asp	Thr	
					350					355					360	
	Ile	Thr	Leu	Pro	Cys	Arg	Ile	Arg	Gln	Ile	Ile	Asn	Met	Trp	Gln	
20					365					370					375	
	Lys	Ile	Gly	Lys	Ala	Met	Tyr	Ala	Pro	Pro	Ile	Lys	Gly	Gln	Ile	
					380					385					390	
25	Arg	Cys	Ser	Ser	Asn	Ile	Thr	Gly	Leu	Ile	Leu	Thr	Arg	Asp	Gly	
					395					400					405	
	Gly	Asn	Asn	Asn	Met	Ser	Lys	Thr	Thr	Glu	Thr	Phe	Arg	Pro	Gly	
					410					415					420	
30	Gly	Gly	Asp	Met	Arg	Asp	Asn	Trp	Arg	Ser	Glu	Leu	Tyr	Lys	Tyr	
					425					430					435	
	Lys	Val	Val	Lys	Ile	Glu	Pro	Leu	Gly	Val	Ala	Pro	Thr	Arg	Ala	
35					440					445					450	
	Lys	Arg	Arg	Val	Val	Gln	Arg	Glu	Lys	Arg	Ala	Val	Gly	Ile	Gly	
					455					460					465	
40	Ala	Val	Phe	Leu	Gly	Phe	Leu	Gly	Ala	Xaa	Ser	Phe	Xaa			
					470					475			478			
	(2) INFORMATION FOR SEQ ID NO:29:															
	(i) SEQUENCE CHARACTERISTICS:															
45	(A) LENGTH: 511 amino acids															
	(B) TYPE: Amino Acid															
	(D) TOPOLOGY: Linear															
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:															
50	Met	Arg	Val	Lys	Gly	Ile	Arg	Arg	Asn	Tyr	Gln	His	Trp	Trp	Gly	Arg
	1				5					10					15	
	Gly	Thr	Met	Leu	Leu	Gly	Leu	Leu	Met	Ile	Cys	Ser	Ala	Thr	Glu	Lys
				20					25					30		
55	Leu	Trp	Val	Thr	Val	Tyr	Tyr	Gly	Val	Pro	Val	Trp	Lys	Glu	Ala	Thr
			35					40					45			
	Thr	Thr	Leu	Phe	Cys	Ala	Ser	Asp	Ala	Lys	Ala	Tyr	Asp	Thr	Glu	Ala
60		50					55					60				
	His	Asn	Val	Trp	Ala	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	Asn	Pro
	65					70					75				80	

AP/P/99/01432

Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp Lys
 85 90 95
 5 Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asn
 100 105 110
 Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
 115 120 125
 10 Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr Asp
 130 135 140
 Asn Asn Asn Ser Lys Ser Glu Gly Thr Ile Lys Gly Gly Glu Met Lys
 145 150 155 160
 15 Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Gly Asp Lys Met Glu Lys
 165 170 175
 Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Glu Pro Ile Asp Asn Asp
 180 185 190
 20 Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
 195 200 205
 25 Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
 210 215 220
 Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser Gly
 225 230 235 240
 30 Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile
 245 250 255
 Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
 260 265 270
 Glu Glu Val Val Ile Arg Ser Glu Asp Phe Thr Asp Asn Ala Lys Thr
 275 280 285
 40 Ile Ile Val His Leu Lys Glu Ser Val Gln Ile Asn Cys Thr Arg Pro
 290 295 300
 Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala Phe
 305 310 315 320
 45 Tyr Thr Thr Lys Asn Ile Lys Gly Thr Ile Arg Gln Ala His Cys Ile
 325 330 335
 Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser Lys
 340 345 350
 Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Pro Ser Ser
 355 360 365
 55 Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
 370 375 380
 Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Ile Trp Asn Gly
 385 390 395 400
 60 Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr Leu
 405 410 415
 Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Lys Val Gly Lys
 420 425 430

AP/P/99/014/32

APC 01282

Ala Met Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser Ser Asn
435 440 445
5 Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Glu Asp Thr Asp Thr
450 455 460
Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
465 470 475 480
10 Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro Leu
485 490 495
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu
500 505 510
15

(2) INFORMATION FOR SEQ ID NO:30

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 2800 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

25 TTCGAGCTCG CCCGACATTG ATTATTGACT AGAGTCGATC GACAGCTGTG 50
GAATGTGTGT CAGTTAGGGT GTGAAAGTC CCCAGGCTCC CCAGCAGGCA 100
GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG 150
30 TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA 200
GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG CCCCTAACTC 250
35 CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT TTTTTTTATT 300
TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG 350
AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTA GCTTATCCGG 400
40 CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTCAGGTAA 450
GTACCGCCTA TAGAGTCTAT AGGCCACCC CCTTGCTTC GTTAGAACGC 500
45 GGCTACAATT AATACATAAC CTTTGGATC GATCCTACTG AACTGACAT 550
CCACTTTTTC TTTTCTCCA CAGGTGTCCA CTCCCAGGTC CAACTGCACC 600
TCGTTTCGCG AAGCTAGCTT GGGCTGCATC GATTGAATTC CACTGCCTTC 650
50 CACCAAGCTC TGCAGGATCC CAGAGTCAGG GG TCT GTA TCT TCC TGC 697
Ser Val Ser Ser Cys
1 5
55 TGG TGG CTC CAG TTC AGG AAC AGT AAA CCC TGC TCC GAA TAT 739
Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Glu Tyr
10 15
60 TGC CTC TCA CAT CTC GTC AAT CTC CGC GAG GAC TGG GGA CCC 781
Cys Leu Ser His Leu Val Asn Leu Arg Glu Asp Trp Gly Pro
20 25 30

AP/P/99/01432

APC 01282

	TCT GAC AAG CTT CAG CGC GAA CGA CCA ACT ACC CCG ATC ATC	523
	Cys Asp Lys Leu Gln Arg Glu Arg Pro Thr Thr Pro Ile Ile	
	35 40 45	
5	AGT TAT CCT TAA GGT CTC TTT TGT GTG GTG CGT TCC GGT ATG	565
	Ser Tyr Pro * Gly Leu Phe Cys Val Val Arg Ser Gly Met	
	50 55 60	
10	GGG GGG ACT GCC GCC ACC TTG GGG GCC GTG ATT TTG TTT GTC	907
	Gly Gly Thr Ala Ala Arg Leu Gly Ala Val Ile Leu Phe Val	
	62 65 70 75	
15	GTC ATA GTG GGC CTC CAT GGG GTC CGC GGC AAA TAT GCC TTG	949
	Val Ile Val Gly Leu His Gly Val Arg Gly Lys Tyr Ala Leu	
	80 85	
20	GGG GAT GCC TCT CTC AAG ATG GCC GAC CCC AAT CGA TTT CGC	991
	Ala Asp Ala Ser Leu Lys Met Ala Asp Pro Asn Arg Phe Arg	
	90 95 100	
25	GGC AAA GAC CTT CCG GTC CTG GAC CAG CTG CTC GAG GTA CCT	1033
	Gly Lys Asp Leu Pro Val Leu Asp Gln Leu Leu Glu Val Pro	
	105 110 115	
30	GTG TGG AAA GAA GCA AAC ACC ACT CTA TTT TGT GCA TCA GAT	1075
	Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser Asp	
	120 125 130	
35	CCT AAA GCA TAT AAG ACA GAG GCA CAT AAT GTT TGG GCC ACA	1117
	Ala Lys Ala Tyr Lys Thr Glu Ala His Asn Val Trp Ala Thr	
	135 140 145	
40	CAT GCC TGT GTA CCC ACA GAC CCC AAA CCA CAA GAA ATA AAA	1159
	His Ala Cys Val Pro Thr Asp Pro Lys Pro Gln Glu Ile Lys	
	150 155	
45	TTG GAA AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC	1201
	Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn	
	160 165 170	
50	ATG GTA GAA CAG ATG CAT GAG GAT ATA ATC ACT TTA TGG GAT	1243
	Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp	
	175 180 185	
55	CAA AGC CTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT	1285
	Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val	
	190 195 200	
60	ACT TTA AAT TGC ACT GAT TTG AGG AAT AAT ACT AAT ACC AAT	1327
	Thr Leu Asn Cys Thr Asp Leu Arg Asn Asn Thr Asn Thr Asn	
	205 210 215	
65	AGT ACC TAC GGA AAA ATA ATG GAG GGA GGA GAG ATA AAA AAC	1369
	Ser Thr Tyr Gly Lys Ile Met Glu Gly Gly Glu Ile Lys Asn	
	220 225	
70	TGC TCT TTC AAT ATC ACC ACA AGC ATA AAA GAT AAG CTG AAA	1411
	Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys Asp Lys Leu Lys	
	230 235 240	
75	GAT ATG TCA CTT TTT TAT AAA CTT GAT GTA GTA CCA ATA GGT	1453
	Asp Met Ser Leu Phe Tyr Lys Leu Asp Val Val Pro Ile Gly	
	245 250 255	

AP/P/99/01432

APC 01282

	AAT AAT AGT AAT ACT ACT AGT TAT AGG TTG ATA AGT TGT AAC	1495
	Asn Asn Ser Asn Thr Thr Ser Tyr Arg Leu Ile Ser Cys Asn	
	260 265 270	
5	ACC TCA GTC ATT ACA CAA GCC TGT CCA AAG ACA TCC TTT GAG	1537
	Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Thr Ser Phe Glu	
	275 280 285	
10	CCA ATT CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT	1579
	Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile	
	290 295	
15	CTC AAG TGT AAT GAT AAT AAG TTC AAT GGA ACA GGA CCA TGT	1621
	Leu Lys Cys Asn Asp Asn Lys Phe Asn Gly Thr Gly Pro Cys	
	300 305 310	
20	CCA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA	1663
	Pro Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro	
	315 320 325	
25	GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA	1705
	Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu	
	330 335 340	
30	AAA GAG GTA GTC CTT AGA TCT GAA AAT TTC ACG GAC AAT GCT	1747
	Lys Glu Val Val Leu Arg Ser Glu Asn Phe Thr Asp Asn Ala	
	345 350 355	
35	AAA ACC ATA ATA GTA CAG CTG AAC GAA TCT GTA ATA ATT GAT	1789
	Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Ile Ile Asp	
	360 365	
40	TGT ATG AGA CCC AAC AAC AAT ACA AGA ACA AGT ATA CCT ATG	1831
	Cys Met Arg Pro Asn Asn Asn Thr Arg Thr Ser Ile Pro Met	
	370 375 380	
45	GGA CCA GGG AAA GCA TTT TAT GCA ACA GGA GAT GTA ATA GGA	1873
	Gly Pro Gly Lys Ala Phe Tyr Ala Thr Gly Asp Val Ile Gly	
	385 390 395	
50	GAT ATA AGA CGA GCA CAT TGT AAC ATT AGT AGA GCA GGA TGG	1915
	Asp Ile Arg Arg Ala His Cys Asn Ile Ser Arg Ala Gly Trp	
	400 405 410	
55	AAT ACC ACT TTA CAA CAG ATA GCT AAA AAA TTA AGA GAA AAA	1957
	Asn Thr Thr Leu Gln Gln Ile Ala Lys Lys Leu Arg Glu Lys	
	415 420 425	
60	TTT GAG AAC AAA ACA ATA GTT TTT AAT CAC TCC TCA GGA GGG	1999
	Phe Glu Asn Lys Thr Ile Val Phe Asn His Ser Ser Gly Gly	
	430 435	
65	GAC CCA GAA ATT GTA ATG CAC ACT TTT AAT TGT GGA GGG GAA	2041
	Asp Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu	
	440 445 450	
70	TTT TTC TGC TGT AAT TCA ACA CCA CTG TTT AAT AGT ACT TGG	2083
	Phe Phe Cys Cys Asn Ser Thr Pro Leu Phe Asn Ser Thr Trp	
	455 460 465	
75	AAT GAT GCA CAA CTG TTT AAT ACT ACT TGG GAT GAT ACT AAA	2125
	Asn Asp Ala Gln Leu Phe Asn Ser Thr Trp Asp Asp Thr Lys	
	470 475 480	

AP/P/99/01432

APC 01282

TGG TCA AAA GGC ACT AAC GAA AAT GAC ACA ATC ACC CTC CAT 2167
 Trp Ser Lys Gly Thr Asn Glu Asn Asp Thr Ile Thr Leu His
 485 490 495
 5 TGC AGA ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA 2209
 Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly
 500 505
 10 AAA GCA ATG TAT GCC CCT CCC ATC AAA GGA CAA ATT AGA TGT 2251
 Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln Ile Arg Cys
 510 515 520
 GAA TCA AAT ATT ACA GGG CTG CTA TTA ACA AGA GAT GGT GGT 2293
 15 Glu Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
 525 530 535
 AAC GAC ACG AGC AAG AAT AAC ACT GAG ATT TTC AGA CCT GGA 2335
 Asn Asp Thr Ser Lys Asn Asn Thr Glu Ile Phe Arg Pro Gly
 540 545 550
 GCA GCA AAT ATG AAG GAC AAT TGG AGA ACT GAA TTA TAT AAA 2377
 25 Gly Gly Asn Met Lys Asp Asn Trp Arg Ser Glu Leu Tyr Lys
 555 560 565
 TAT AAA GTA ATA AAA ATT GAA CCA TTA GGA GTA GCA CCC ATC 2419
 30 Tyr Lys Val Ile Lys Ile Glu Pro Leu Gly Val Ala Pro Ile
 570 575 579
 TAGGCAAAGA GAAGAGTGGT GCAGAGAGAA AAAAGAGCAG TGACACTAGG 2469
 35 AGCTATGTTT CTTGGGTTCT TGGGAGCAGC AGGAAGCACT ATGGGCGATA 2519
 AGCTTTAATG CGGTAGTTTA TCACAGTTAA ATTCCTAACG CAGTCAGGCA 2569
 40 CCGTGTATGA AATCTAACAA TGGCACCTGC AGAAGCTTAG AACCGAGGAA 2619
 CTTGTTTATT GCAGCTTATA ATGTTTACAA ATAAAGCAAT AGCATCACAA 2659
 ATTTACAAAA TAAAGCATTT TTTTCACTGC ATTCTAGTTG TGGTTTGTCC 2719
 45 AAACATCAAT ATGTATCTTA TCATGTCTGG ATCGGGAATT AATTCGGCGC 2769
 AGCACCATGG CCTGAAATAA CCTCTGAAAG A 2800
 50 (2) INFORMATION FOR SEQ ID NO:31
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 579 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear
 55 (x1) SEQUENCE DESCRIPTION: SEQ ID NO:31:
 Ser Val Ser Ser Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys
 1 5 10 15
 60 Ser Glu Tyr Cys Leu Ser His Leu Val Asn Leu Arg Glu Asp Trp Gly
 20 25 30
 Pro Cys Asp Lys Leu Gln Arg Glu Arg Pro Thr Thr Pro Ile Ile Ser
 35 40 45
 65

AP/P/99/01432

APC 01282

	Tyr	Pro	*	Gly	Leu	Phe	Cys	Val	Val	Arg	Ser	Gly	Met	Gly	Gly	Thr
	50						55					60				
5	Ala	Ala	Arg	Leu	Gly	Ala	Val	Ile	Leu	Phe	Val	Val	Ile	Val	Gly	Leu
	65					70					75					80
	His	Gly	Val	Arg	Gly	Lys	Tyr	Ala	Leu	Ala	Asp	Ala	Ser	Leu	Lys	Met
					85					90					95	
10	Ala	Asp	Pro	Asn	Arg	Phe	Arg	Gly	Lys	Asp	Leu	Pro	Val	Leu	Asp	Gln
				100					105					110		
	Leu	Leu	Glu	Val	Pro	Val	Trp	Lys	Glu	Ala	Asn	Thr	Thr	Leu	Phe	Cys
			115					120					125			
15	Ala	Ser	Asp	Ala	Lys	Ala	Tyr	Lys	Thr	Glu	Ala	His	Asn	Val	Trp	Ala
			130				135					140				
20	Thr	His	Ala	Cys	Val	Pro	Thr	Asp	Pro	Lys	Pro	Gln	Glu	Ile	Lys	Leu
	145					150					155					160
	Glu	Asn	Val	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	Val	Glu
					165					170					175	
25	Gln	Met	His	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	Pro
				180					185					190		
	Cys	Val	Lys	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys	Thr	Asp	Leu
			195					200					205			
30	Arg	Asn	Asn	Thr	Asn	Thr	Asn	Ser	Thr	Tyr	Gly	Lys	Ile	Met	Glu	Gly
		210					215					220				
	Gly	Glu	Ile	Lys	Asn	Cys	Ser	Phe	Asn	Ile	Thr	Thr	Ser	Ile	Lys	Asp
35		225			230					235						240
	Lys	Leu	Lys	Asp	Met	Ser	Leu	Phe	Tyr	Lys	Leu	Asp	Val	Val	Pro	Ile
				245					250						255	
40	Gly	Asn	Asn	Ser	Asn	Thr	Thr	Ser	Tyr	Arg	Leu	Ile	Ser	Cys	Asn	Thr
				260					265					270		
	Ser	Val	Ile	Thr	Gln	Ala	Cys	Pro	Lys	Thr	Ser	Phe	Glu	Pro	Ile	Pro
			275					280					285			
45	Ile	His	Tyr	Cys	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Asn	Asp
		290					295					300				
	Asn	Lys	Phe	Asn	Gly	Thr	Gly	Pro	Cys	Pro	Asn	Val	Ser	Thr	Val	Gln
50		305			310						315					320
	Cys	Thr	His	Gly	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn
				325						330					335	
55	Gly	Ser	Leu	Ala	Glu	Lys	Glu	Val	Val	Leu	Arg	Ser	Glu	Asn	Phe	Thr
			340					345						350		
	Asp	Asn	Ala	Lys	Thr	Ile	Ile	Val	Gln	Leu	Asn	Glu	Ser	Val	Ile	Ile
			355					360					365			
60	Asp	Cys	Met	Arg	Pro	Asn	Asn	Asn	Thr	Arg	Thr	Ser	Ile	Pro	Met	Gly
		370					375					380				
65	Pro	Gly	Lys	Ala	Phe	Tyr	Ala	Thr	Gly	Asp	Val	Ile	Gly	Asp	Ile	Arg
	385					390					395					400

AP/P/99/01432

AP001282

Arg Ala His Cys Asn Ile Ser Arg Ala Gly Trp Asn Thr Thr Leu Gln
405 410 415

5 Gln Ile Ala Lys Lys Leu Arg Glu Lys Phe Glu Asn Lys Thr Ile Val
420 425 430

Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr Phe
435 440 445

10 Asn Cys Gly Gly Glu Phe Phe Cys Cys Asn Ser Thr Pro Leu Phe Asn
450 455 460

Ser Thr Trp Asn Asp Ala Glu Leu Phe Asn Ser Thr Trp Asp Asp Thr
465 470 475 480

15 Lys Trp Ser Lys Gly Thr Asn Glu Asn Asp Thr Ile Thr Leu His Cys
485 490 495

20 Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
500 505 510

Tyr Ala Pro Pro Ile Lys Gly Gln Ile Arg Cys Glu Ser Asn Ile Thr
515 520 525

25 Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Thr Ser Lys Asn Asn
530 535 540

Thr Glu Ile Phe Arg Pro Gly Gly Gly Asn Met Lys Asp Asn Trp Arg
545 550 555 560

30 Ser Glu Leu Tyr Lys Tyr Lys Val Ile Lys Ile Glu Pro Leu Gly Val
565 570 575

Ala Pro Ile

(2) INFORMATION FOR SEQ ID NO:32:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1533 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(1) SEQUENCE DESCRIPTION: SEQ ID NO:32:

45 ATGGGGGGGA CTGCCGCCAG GTTGGGGGCC GTGATTTTGT TTGTCGTCAT 50
AGTGGGGCCTC CATGGGGTCC GCGGCAAATA TGCCTTGGCG GATGCCTCTC 100
TCAAGATGGC CGACCCCAAT CGATTTCGCG GCAAAGACCT TCCGGTCCTG 150
GACCAGCTGC TCGAG GTA CCT GTG TGG AAA GAA GCA ACC ACC 192
Val Pro Val Trp Lys Glu Ala Thr Thr
1 5

55 ACT CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG 234
Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu
10 15 20

60 GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAG 276
Val His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
25 30 35

AP/P/99/01432

AP001282

	CCC AAC CCA CAA GAA ATA GGA TTG GAA AAT GTA ACA GAA AAT	318
	Pro Asn Pro Gln Glu Ile Gly Leu Glu Asn Val Thr Glu Asn	
	40 45 50	
5	TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT GAG	360
	Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His Glu	
	55 60 65	
10	GAT ATA ATC AGT TTA TGG GAT CAA AGC TTA AAG CCA TGT GTA	402
	Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro Cys Val	
	70 75	
15	AAA TTA ACC CCA CTA TGT GTT ACT TTA AAT TGC ACT GAT TTG	444
	Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys Thr Asp Leu	
	80 85 90	
20	AAA AAT GCT ACT AAT ACC ACT AGT AGC AGC TGG GGA AAG ATG	486
	Lys Asn Ala Thr Asn Thr Thr Ser Ser Ser Trp Gly Lys Met	
	95 100 105	
25	GAG AGA GGA GAA ATA AAA AAC TGC TCT TTC AAT GTC ACC ACA	528
	Glu Arg Gly Glu Ile Lys Asn Cys Ser Phe Asn Val Thr Thr	
	110 115 120	
30	AGT ATA AGA GAT AAG ATG AAG AAT GAA TAT GCA CTT TTT TAT	570
	Ser Ile Arg Asp Lys Met Lys Asn Glu Tyr Ala Leu Phe Tyr	
	125 130 135	
35	AAA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACT AGC TAT	612
	Lys Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr Ser Tyr	
	140 145	
40	AGG TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT	654
	Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys	
	150 155 160	
45	CCA AAG GTG TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC	696
	Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala	
	165 170 175	
50	CCG GCT GGT TTT GCG ATT CTA AAG TGT AGA GAT AAA AAG TTC	738
	Pro Ala Gly Phe Ala Ile Leu Lys Cys Arg Asp Lys Lys Phe	
	180 185 190	
55	AAC GGA ACA GGA CCA TGT ACA AAT GTC AGC ACA GTA CAA TGT	780
	Asn Gly Thr Gly Pro Cys Thr Asn Val Ser Thr Val Gln Cys	
	195 200 205	
60	ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT CAA CTG CTG TTA	822
	Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu	
	210 215	
65	AAT GGC AGT TTA GCA GAA GAA GAA GTA GTA ATT AGA TCT GCC	864
	Asn Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Ala	
	220 225 230	
70	AAT TTC TCG GAC AAT GCT AAA ACC ATA ATA GTA CAG CTG AAC	906
	Asn Phe Ser Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Asn	
	235 240 245	

AP/P/99/01432

AP001282

	GAA TCT GTA GAA ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA Glu Ser Val Glu Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr 250 255 260	948
5	ACA AGA AGT ATA CAT ATA GGA CCA GGG AGA GCA TTT TAT GCA Arg Arg Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala 265 270 275	990
10	ACA GGA GAA ATA ATA GGA GAC ATA AGA CAA GCA CAT TGT AAC Thr Gly Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn 280 285	1032
15	CTT AGT AGC ACA AAA TGG AAT AAT ACT TTA AAA CAG ATA CTT Leu Ser Ser Thr Lys Trp Asn Asn Thr Leu Lys Gln Ile Val 290 295 300	1074
20	ACA AAA TTA AGA GAA CAT TTT AAT AAA ACA ATA GTC TTT AAT Thr Lys Leu Arg Glu His Phe Asn Lys Thr Ile Val Phe Asn 305 310 315	1116
25	CAC TCC TCA GGA GGG GAC CCA GAA ATT GTA ATC CAC AGT TTT His Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe 320 325 330	1158
	AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA CCA CTG Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Pro Leu 335 340 345	1200
30	TTT AAT AGT ACT TGG AAT TAT ACT TAT ACT TGG AAT AAT ACT Phe Asn Ser Thr Trp Asn Tyr Thr Tyr Thr Trp Asn Asn Thr 350 355	1242
35	GAA GGG TCA AAT GAC ACT GGA AGA AAT ATC ACA CTC CAA TGC Glu Gly Ser Asn Asp Thr Gly Arg Asn Ile Thr Leu Gln Cys 360 365 370	1284
40	AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys 375 380 385	1326
	GCA ATG TAT GCC CCT CCC ATA AGA GGA CAA ATT AGA TGC TCA Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser 390 395 400	1368
45	TCA AAT ATT ACA GGG CTG GTA TTA ACA AGA GAT GGT GGT AAT Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn 405 410 415	1410
50	AAC AGC GAA ACC GAG ATC TTC AGA CCT GGA GGA GGA GAT ATG Asn Ser Glu Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met 420 425	1452
55	AGG GAC AAT TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val 430 435 440	1494
60	AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC AAG GCA TAA Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Lys Ala * 445 450 455	1536

AP/P/99/01432

APC 01282

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 456 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

10	Val	Pro	Val	Trp	Lys	Glu	Ala	Thr	Thr	Thr	Leu	Phe	Cys	Ala	Ser	Asp
	1				5					10					15	
10	Ala	Lys	Ala	Tyr	Asp	Thr	Glu	Val	His	Asn	Val	Trp	Ala	Thr	His	Ala
			20						25					30		
15	Cys	Val	Pro	Thr	Asp	Pro	Asn	Pro	Gln	Glu	Ile	Gly	Leu	Glu	Asn	Val
			35					40					45			
	Thr	Glu	Asn	Phe	Asn	Met	Trp	Lys	Asn	Asn	Met	Val	Glu	Gln	Met	His
		50					55					60				
20	Glu	Asp	Ile	Ile	Ser	Leu	Trp	Asp	Gln	Ser	Leu	Lys	Pro	Cys	Val	Lys
	65					70					75					80
	Leu	Thr	Pro	Leu	Cys	Val	Thr	Leu	Asn	Cys	Thr	Asp	Leu	Lys	Asn	Ala
				85						90					95	
25	Thr	Asn	Thr	Thr	Ser	Ser	Ser	Trp	Gly	Lys	Met	Glu	Arg	Gly	Glu	Ile
				100					105					110		
30	Lys	Asn	Cys	Ser	Phe	Asn	Val	Thr	Thr	Ser	Ile	Arg	Asp	Lys	Met	Lys
			115					120					125			
	Asn	Glu	Tyr	Ala	Leu	Phe	Tyr	Lys	Leu	Asp	Val	Val	Pro	Ile	Asp	Asn
		130					135					140				
35	Asp	Asn	Thr	Ser	Tyr	Arg	Leu	Ile	Ser	Cys	Asn	Thr	Ser	Val	Ile	Thr
	145					150					155				160	
	Gln	Ala	Cys	Pro	Lys	Val	Ser	Phe	Glu	Pro	Ile	Pro	Ile	His	Tyr	Cys
					165					170					175	
40	Ala	Pro	Ala	Gly	Phe	Ala	Ile	Leu	Lys	Cys	Arg	Asp	Lys	Lys	Phe	Asn
				180					185					190		
45	Gly	Thr	Gly	Pro	Cys	Thr	Asn	Val	Ser	Thr	Val	Gln	Cys	Thr	His	Gly
			195					200					205			
	Ile	Arg	Pro	Val	Val	Ser	Thr	Gln	Leu	Leu	Leu	Asn	Gly	Ser	Leu	Ala
		210					215					220				
50	Glu	Glu	Glu	Val	Val	Ile	Arg	Ser	Ala	Asn	Phe	Ser	Asp	Asn	Ala	Lys
	225					230					235					240
	Thr	Ile	Ile	Val	Gln	Leu	Asn	Glu	Ser	Val	Glu	Ile	Asn	Cys	Thr	Arg
				245						250				255		
55	Pro	Asn	Asn	Asn	Thr	Arg	Arg	Ser	Ile	His	Ile	Gly	Pro	Gly	Arg	Ala
				260					265					270		
60	Phe	Tyr	Ala	Thr	Gly	Glu	Ile	Ile	Gly	Asp	Ile	Arg	Gln	Ala	His	Cys
			275					280					285			
	Asn	Leu	Ser	Ser	Thr	Lys	Trp	Asn	Asn	Thr	Leu	Lys	Gln	Ile	Val	Thr
		290					295					300				

AP/P/99/01432

AP001282

Lys Leu Arg Glu His Phe Asn Lys Thr Ile Val Phe Asn His Ser Ser
 305 310 315 320
 5 Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
 325 330 335
 Phe Phe Tyr Cys Asn Thr Thr Pro Leu Phe Asn Ser Thr Trp Asn Tyr
 340 345 350
 10 Thr Tyr Thr Trp Asn Asn Thr Glu Gly Ser Asn Asp Thr Gly Arg Asn
 355 360 365
 Ile Thr Leu Gln Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu
 370 375 380
 15 Val Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys
 385 390 395 400
 20 Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asn
 405 410 415
 Ser Glu Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
 420 425 430
 25 Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
 435 440 445
 Gly Val Ala Pro Thr Lys Ala *
 450 455

(2) INFORMATION FOR SEQ ID NO:34:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 37 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (x1) SEQUENCE DESCRIPTION: SEQ ID NO:34:
 40 GGGAATTCGG ATCCAGAGCA GAACACAGTG GCAATGA 37

(2) INFORMATION FOR SEQ ID NO:35:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 33 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (x1) SEQUENCE DESCRIPTION: SEQ ID NO:35:
 50 CTCGAGCTCC TGAAGACACT CAGACTCATC AAG 33

(2) INFORMATION FOR SEQ ID NO:36:
 (1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 39 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (x1) SEQUENCE DESCRIPTION: SEQ ID NO:36:
 60 GGTCTAGAGG CTTTAGCCCA TAGTCTTCC TGCTGCTCC 39

AP/P/99/01432

APC 01282

(2) INFORMATION FOR SEQ ID NO:37:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 36 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
GGGCGGATCC TCGAGGTACC TGTRTGAAA GAAGCA 36
10
(2) INFORMATION FOR SEQ ID NO:38:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 38 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:
GGTCTAGAAG CTTTATGCTC CYAAGAACCC AAGGAACA 38
20
(2) INFORMATION FOR SEQ ID NO:39:
25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7 amino acids
 (B) TYPE: Amino Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:
 Ile Gly Pro Gly Arg Ala Phe
 1 5
35 (2) INFORMATION FOR SEQ ID NO:40:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7 amino acids
 (B) TYPE: Amino Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:
 Ile Gly Pro Gly Arg Ala Trp
 1 5
45 (2) INFORMATION FOR SEQ ID NO:41:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7 amino acids
50 (B) TYPE: Amino Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:
55 Leu Gly Pro Gly Ser Thr Phe
 1 5
 (2) INFORMATION FOR SEQ ID NO:42:
 (i) SEQUENCE CHARACTERISTICS:
60 (A) LENGTH: 7 amino acids
 (B) TYPE: Amino Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:
65

AP/P/99/01432

AP001282

Ile Gly Pro Gly Arg Val Leu
1 5

5 (2) INFORMATION FOR SEQ ID NO:43:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:
Ile Gly Pro Gly Ser Ala Phe
1 5

15 (2) INFORMATION FOR SEQ ID NO:44:
(1) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:
Ile Gly Pro Gly Arg
1 5

25

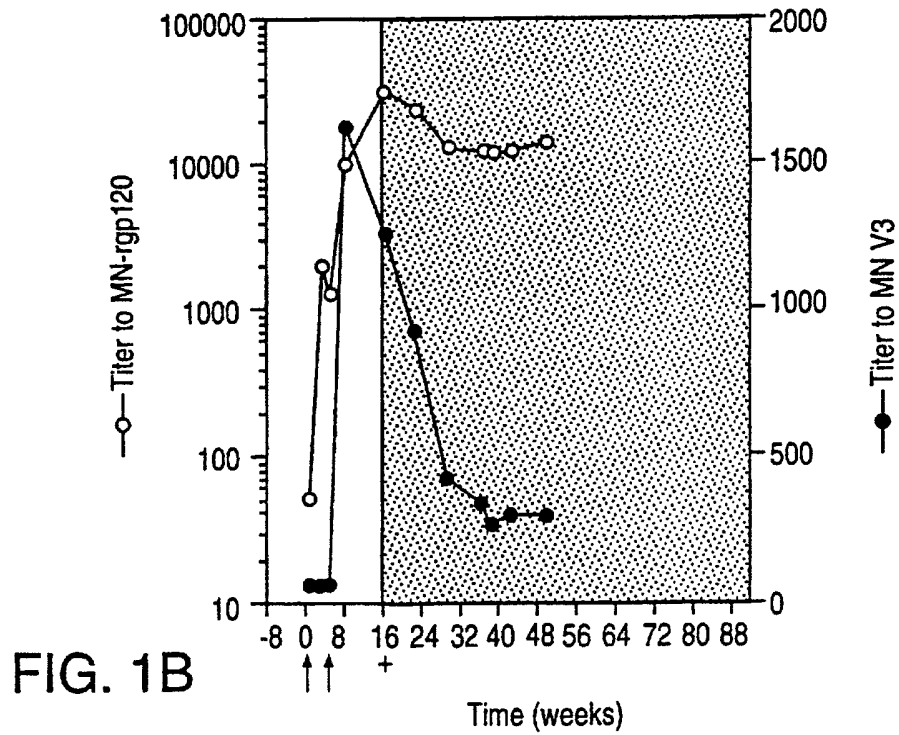
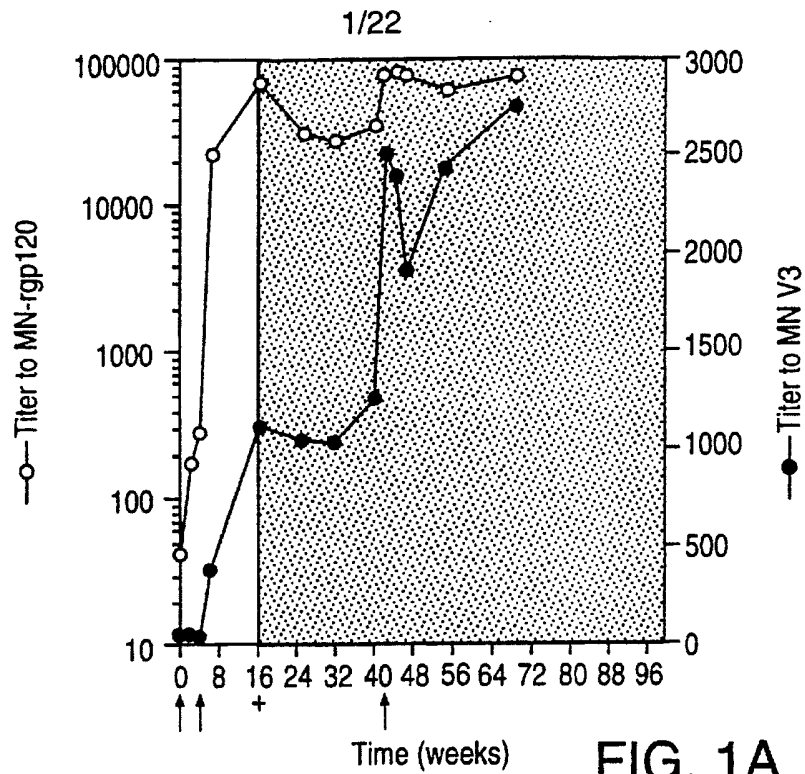
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WHAT WE CLAIM IS:

1. An isolated polypeptide comprising an HIV gp120 amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 5, 8, 10, 12, 16, 19, 23, 25, 28, 31, 33, 36, 39, and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.
2. An oligonucleotide comprising a nucleotide sequence of not more than five kilobases encoding a polypeptide comprising an HIV gp120 amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 5, 8, 10, 12, 16, 19, 23, 25, 28, 31, 33, 36, 39, and fragments thereof, wherein each of said fragments encodes at least the V2, V3 and C4 domains of gp120.
3. An oligonucleotide of not more than five kilobases comprising a nucleotide sequence selected from the group consisting of Sequence ID Nos. 1, 4, 7, 9, 11, 15, 18, 22, 24, 27, 30, 32, 35, 38, and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.
4. An immunogenic composition comprising a first polypeptide comprising the amino acid sequence of gp120 MN, or a fragment thereof, and a second polypeptide comprising a gp120 amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 5, 8, 10, 12, 16, 19, 23, 25, 28, 31, 33, 36, 39, and fragments thereof in a suitable carrier, wherein each of the said fragments comprises at least the V2, V3, and C4 domains of gp120.
5. An immunogenic composition comprising:
 - a. a first polypeptide comprising a first gp120 amino acid sequence of a fragment thereof; and
 - b. a polypeptide comprising a breakthrough isolate gp120 amino acid sequence or a fragment thereof, wherein said breakthrough isolate gp120 amino acid sequence is derived from a vaccinee vaccinated with said first polypeptide;wherein said fragment comprises at least the V2, V3, and C4 domains of gp120 and said polypeptides are in a suitable carrier.
6. The immunogenic composition of Claim 5 wherein said first HIV gp120 amino acid sequence comprises the amino acid sequence of gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID Nos. 43 and 44), or gp120 MN-GNE8 (Sequence ID No. 46).
7. A method for making an HIV vaccine comprising adding a polypeptide comprising an HIV gp120 amino acid sequence or a fragment thereof, wherein said HIV gp120 amino acid sequence is derived from a breakthrough isolate from a vaccinee to the vaccine with which the vaccinee was vaccinated.

8. The immunogenic composition of Claim 5 wherein said first gp120 amino acid sequence is from a macrophage-tropic HIV-1 strain.
9. The immunogenic composition of Claim 5 wherein said first gp120 amino acid sequence is from a T-cell-tropic HIV-1 strain.
10. The immunogenic composition of Claim 9 wherein said vaccine additionally comprises a second polypeptide comprising a second gp120 amino acid sequence or a fragment thereof from a macrophage-tropic HIV-1 strain.

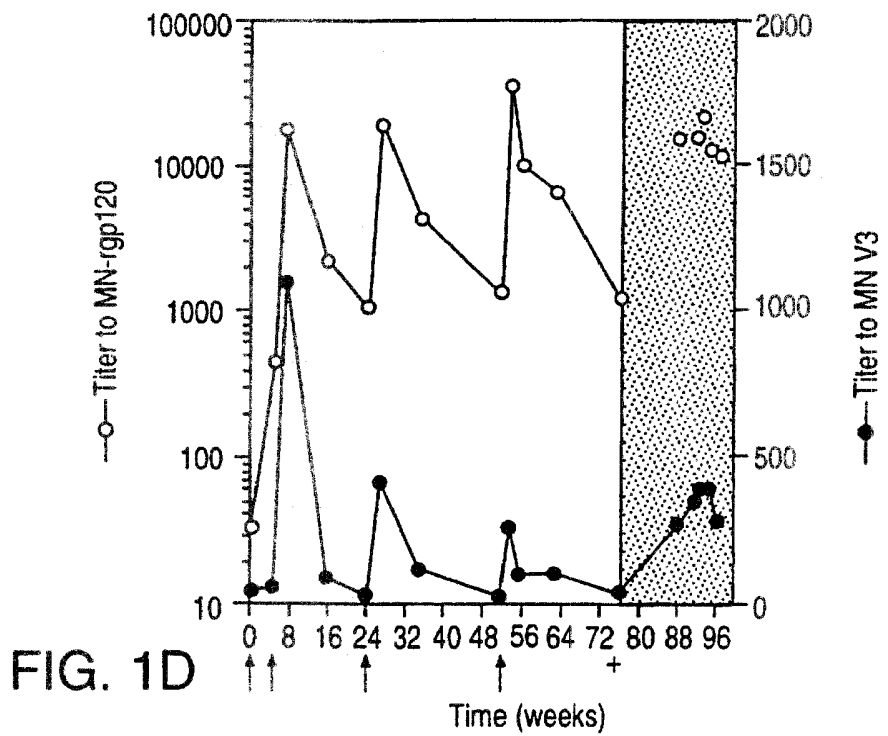
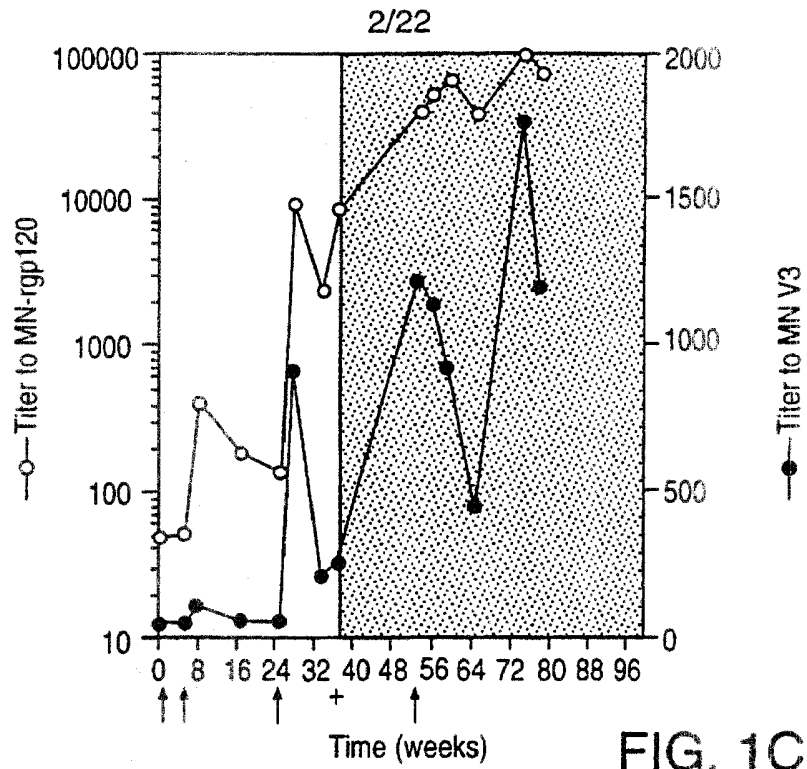
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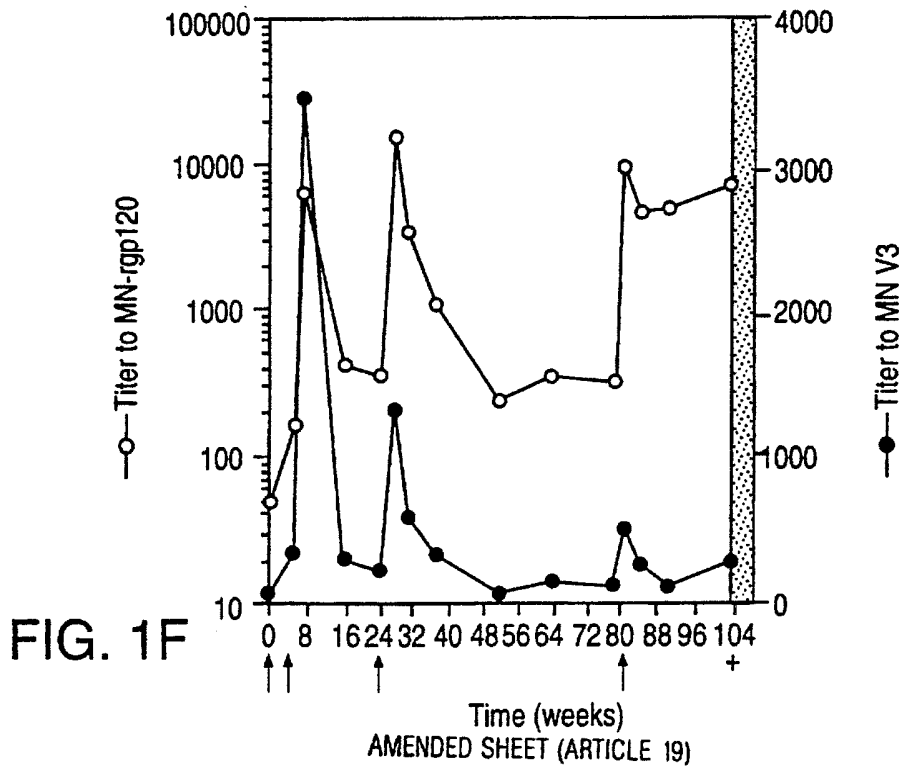
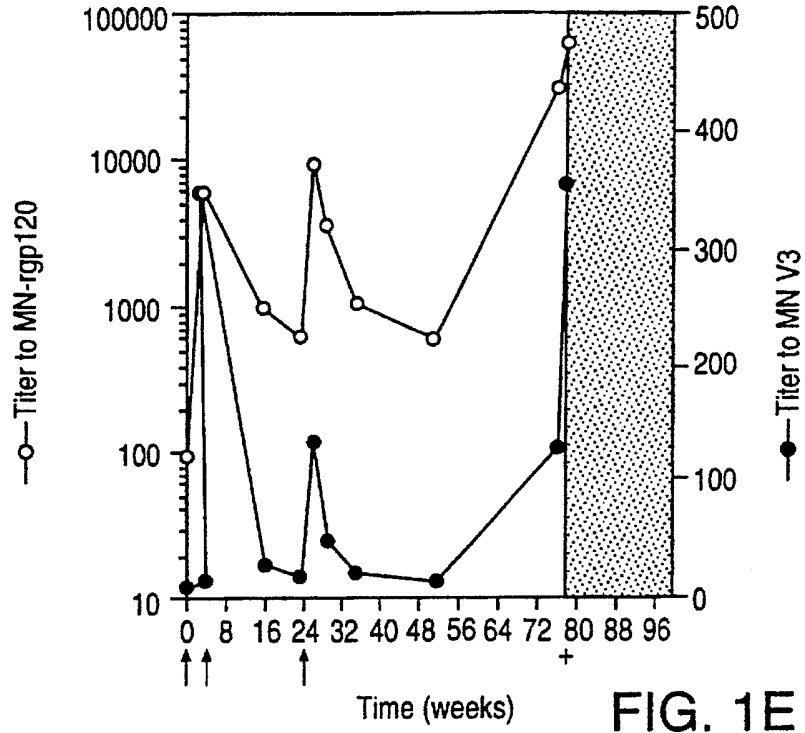
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AP/P/99/01432

AP 001282

3/22



AP/P/99/01432

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4/22

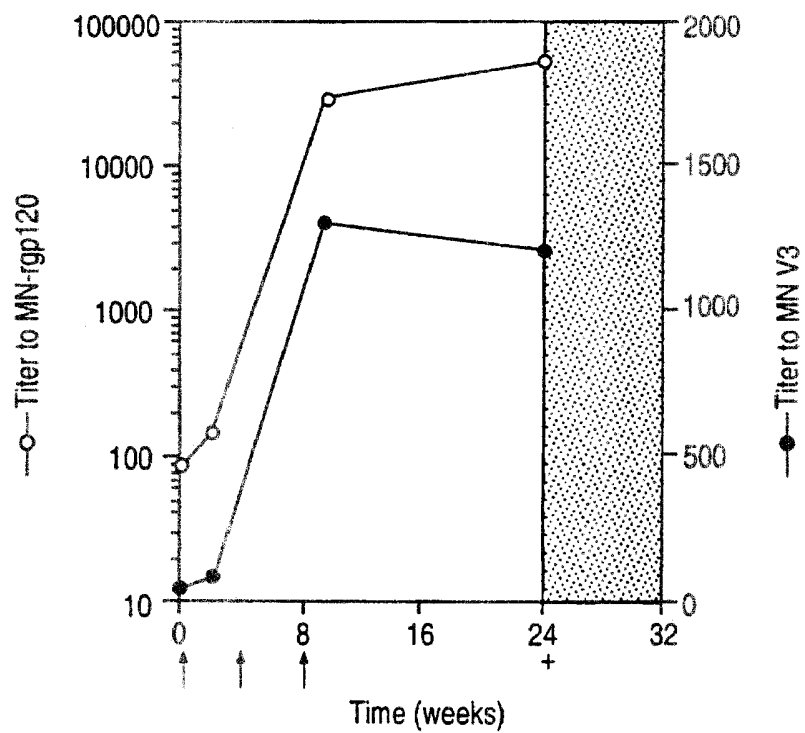


FIG. 1G

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5/22

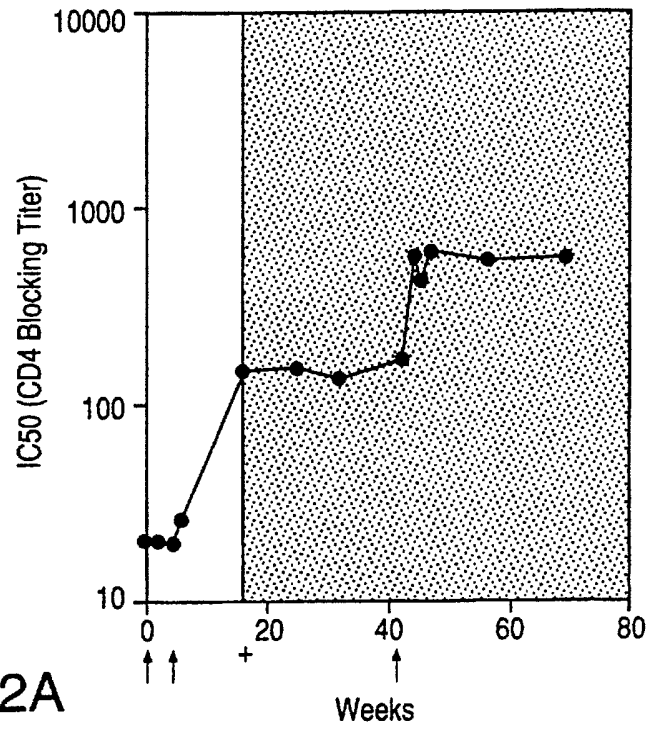


FIG. 2A

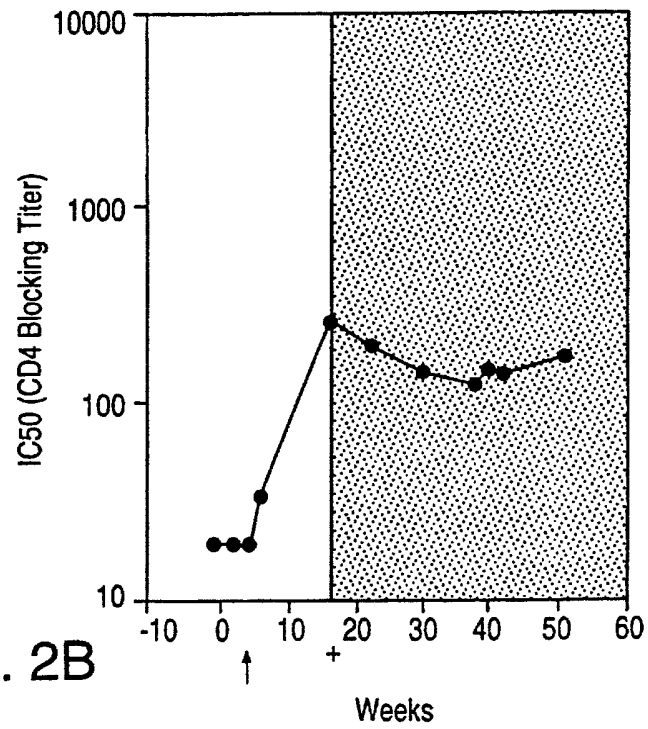


FIG. 2B

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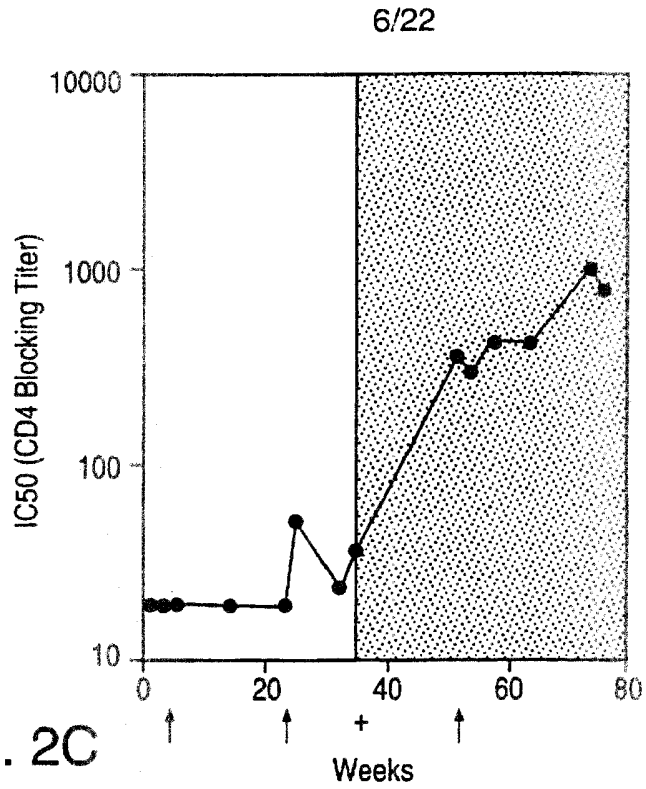


FIG. 2C

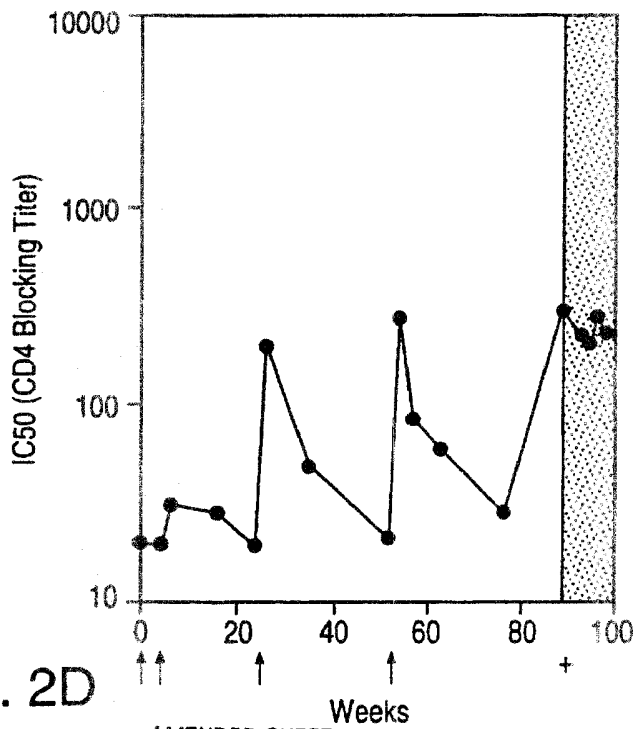
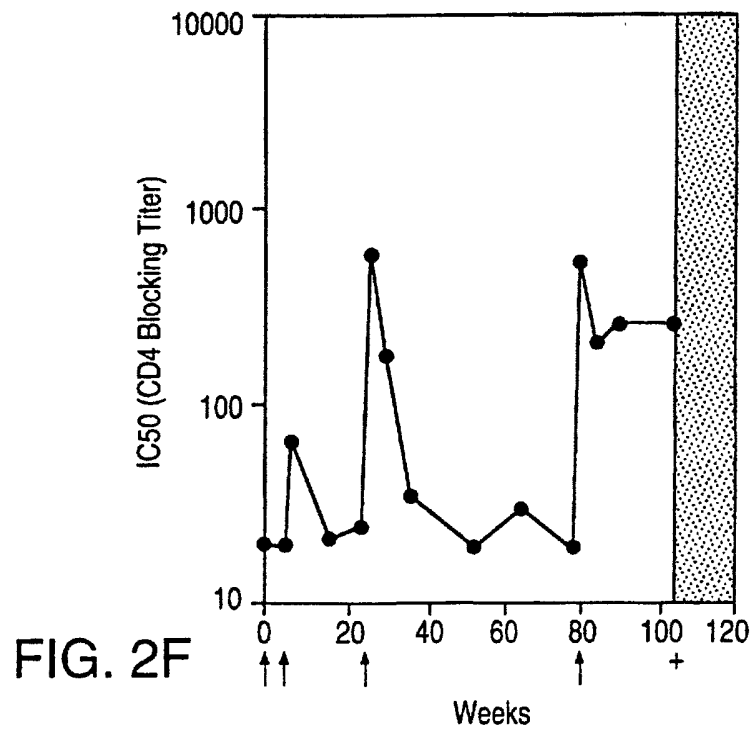
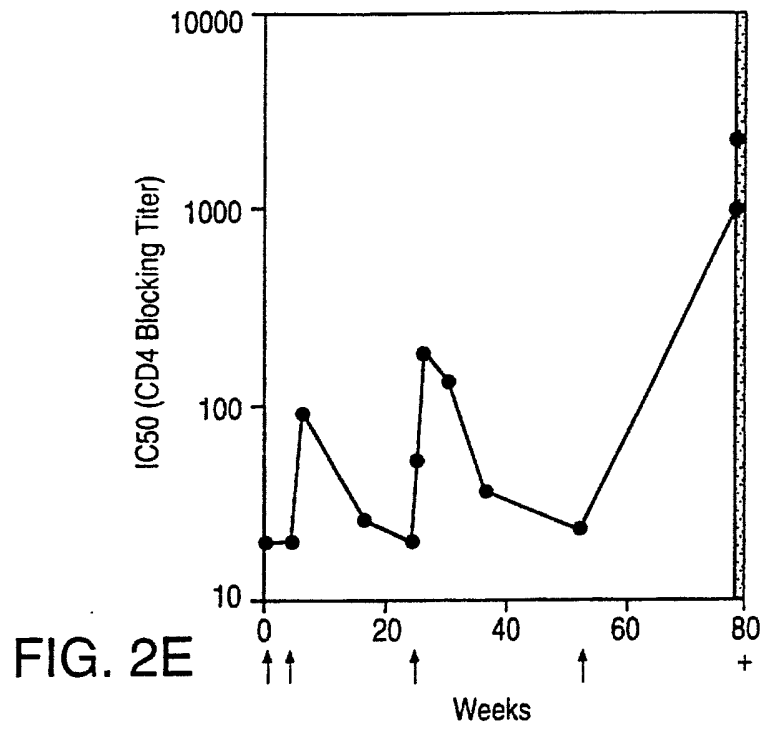


FIG. 2D

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AP/P/99/01432

7/22



AP 001282

8/22

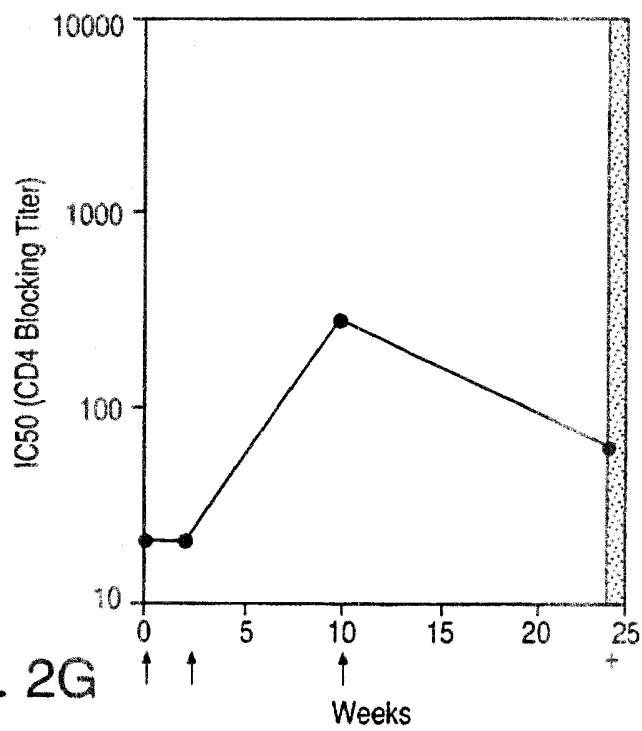


FIG. 2G

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11/22

	V1										V2									
C61	N	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C65	A	N	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C83	T	A	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
C86	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C15.2	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C15.3	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C7.2	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C7.10	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C11.5	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C11.7	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C10.5	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C10.7	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C17.1	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
C17.3	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T
MNGNE	S	S	S	S	S	S	S	S	S	S	T	T	T	T	T	T	T	T	T	T

FIG. 3C

AP/F/99/014'32

13/22

C2

C6.1	240	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	A	H	G	I	K	P	V	S	T	Q	L	L	N	G	S	L	A
C6.5	240	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	K	P	V	S	T	Q	L	L	N	G	S	L	A
C8.3	223	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C8.6	223	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C15.2	225	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C15.3	225	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C7.2	223	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C7.10	223	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C11.5	236	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C11.7	236	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C10.5	224	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C10.7	224	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C17.1	214	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
C17.3	214	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A
MNGNE	226	A	G	F	A	I	L	K	C	R	D	K	K	F	N	G	T	G	P	C	K	N	V	S	T	V	Q	C	T	H	G	I	R	P	V	S	T	Q	L	L	N	G	S	L	A

FIG. 3E

14/22

C2-

33

AP/P/99/01432

15/22

C6.1	340	I	R	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S				
C6.5	340	I	R	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S				
C8.3	323	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C8.6	323	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C15.2	325	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C15.3	325	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C7.2	323	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C7.10	323	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C11.5	336	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C11.7	336	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C10.5	324	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C10.7	324	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C17.1	314	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
C17.3	314	I	I	G	D	I	I	G	D	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S
MNGNE	326	I	K	G	T	I	R	Q	A	H	C	N	I	S	G	A	K	W	N	N	T	L	L	K	K	V	V	V	K	L	K	E	Q	F	F	K	R	K	Q	F	G	E	K	T	I	N	K	T	I	V	F	N	F	N	H	S				

FIG. 3G

AP/P/99/01432

16/22

C3										V4									
S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G
G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G	G
E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H
S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K	K
L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L
F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q
P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L
P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P

FIG. 3H

C6.1	429	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C6.5	429	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C8.3	417	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C8.6	417	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C15.2	424	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C15.3	424	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C7.2	417	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C7.10	417	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C11.5	427	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C11.7	427	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C10.5	414	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C10.7	414	C	R	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C17.1	403	C	R	I	R	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
C17.3	403	C	R	I	R	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S
MNGNE	418	C	K	I	K	Q	I	N	M	W	Q	E	I	G	K	A	M	Y	A	P	P	I	R	G	E	I	K	C	S	S	N	I	T	G	L	L	L	L	R	D	G	G	I	N	T	S

FIG. 3I

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FIG. 3A	FIG. 3B
FIG. 3C	FIG. 3D
FIG. 3E	FIG. 3F
FIG. 3G	FIG. 3H
FIG. 3I	FIG. 3J

FIG. 3

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19/22

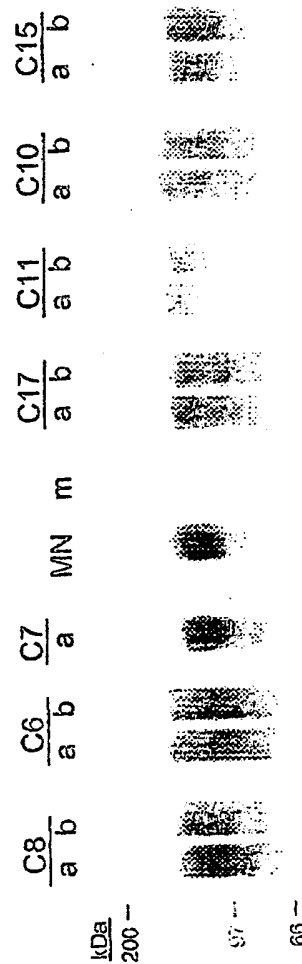


FIG. 4

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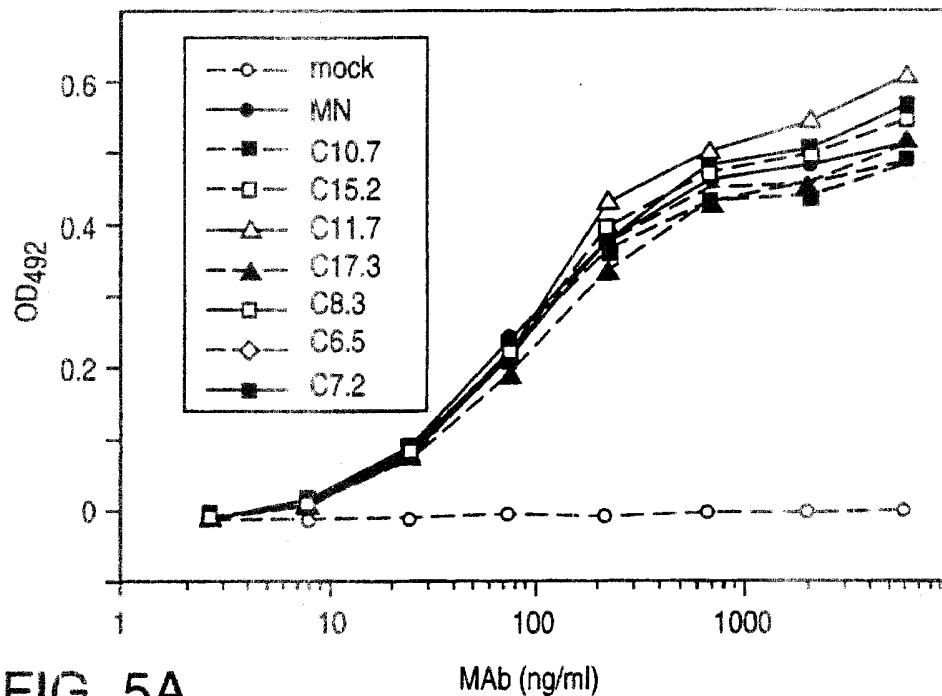


FIG. 5A

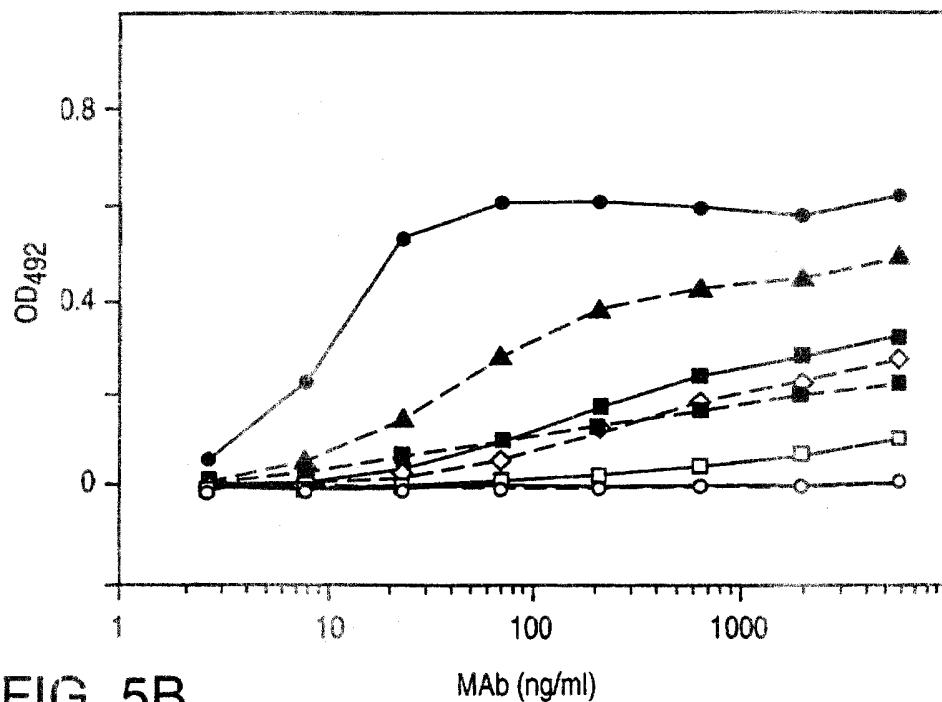


FIG. 5B

AMENDED SHEET (ARTICLE 19)

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21/22

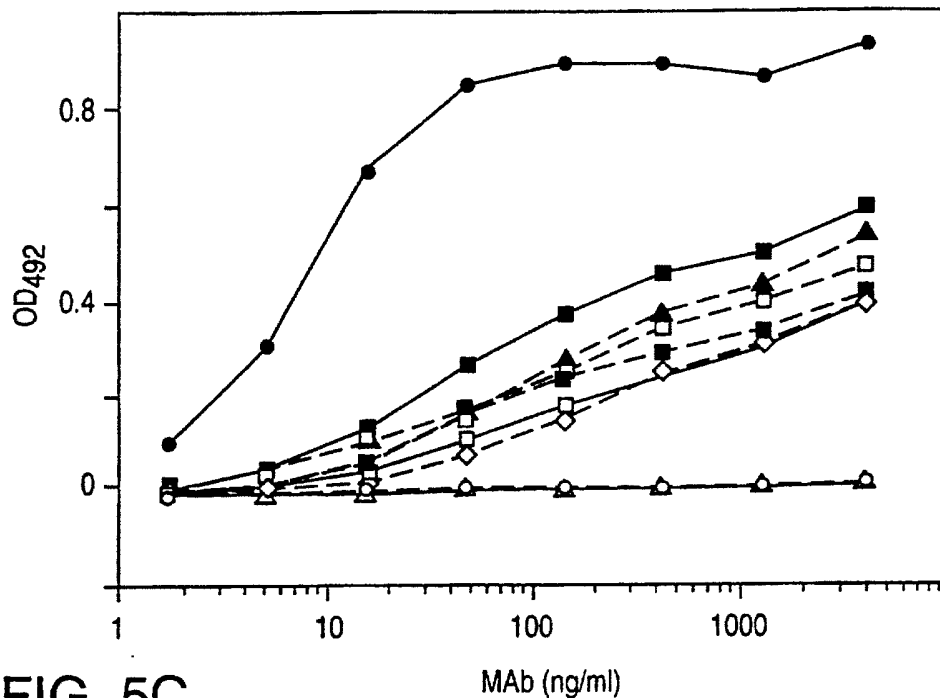


FIG. 5C

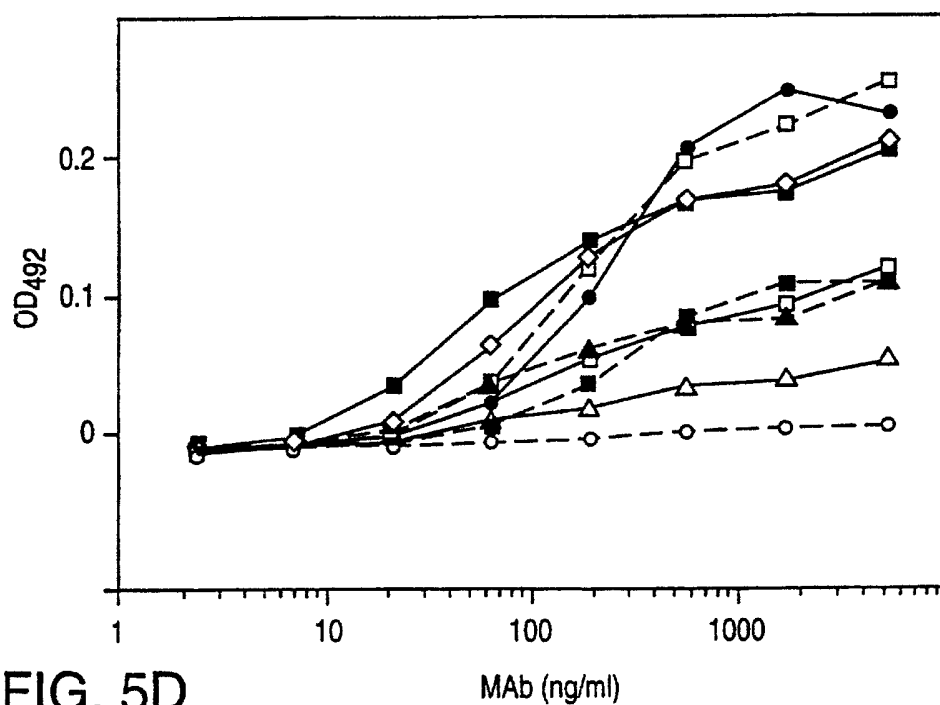


FIG. 5D

AMENDED SHEET (ARTICLE 19)

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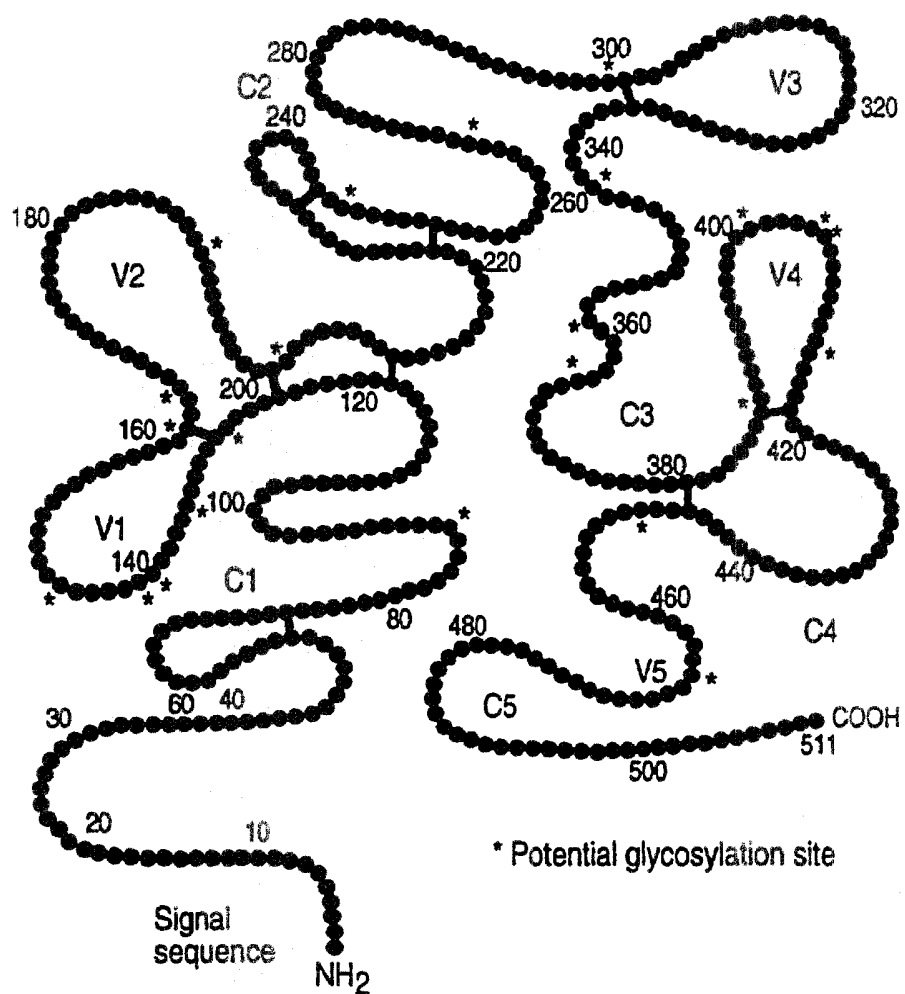


FIG. 6