



(86) **Date de dépôt PCT/PCT Filing Date:** 2006/10/17
(87) **Date publication PCT/PCT Publication Date:** 2007/04/26
(45) **Date de délivrance/Issue Date:** 2018/09/04
(85) **Entrée phase nationale/National Entry:** 2008/04/17
(86) **N° demande PCT/PCT Application No.:** US 2006/060025
(87) **N° publication PCT/PCT Publication No.:** 2007/048086
(30) **Priorités/Priorities:** 2005/10/18 (US60/727,808);
2006/10/05 (US11/539,123)

(51) **Cl.Int./Int.Cl. A61K 39/145** (2006.01),
C07K 14/11 (2006.01), **C12N 7/00** (2006.01),
C12N 7/04 (2006.01)
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(54) **Titre : VIRUS DE LA GRIPPE CANINE ET COMPOSITIONS ET METHODES D'UTILISATION ASSOCIEES**
(54) **Title: CANINE INFLUENZA VIRUS AND RELATED COMPOSITIONS AND METHODS OF USE**

(57) **Abrégé/Abstract:**

The present invention provides an isolated canine influenza virus of subtype H3N8 comprising an HA having SEQ ID NO: 4 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acids at positions 94 and 233 are identical to SEQ ID NO: 4; a composition comprising attenuated or inactivated virus; isolated or purified HA, NM, NP, MI, NSI, PA, PBI, and PB2 proteins and fragments thereof and compositions comprising same or nucleic acids, optionally as part of a vector, encoding same; and a method of inducing an immune response to canine influenza virus in an animal comprising administering to the animal an aforementioned composition.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 April 2007 (26.04.2007)

PCT

(10) International Publication Number
WO 2007/048086 A3

(51) International Patent Classification:

A61K 39/145 (2006.01) C12N 7/00 (2006.01)
C07K 14/11 (2006.01) C12N 7/04 (2006.01)

(21) International Application Number:

PCT/US2006/060025

(22) International Filing Date: 17 October 2006 (17.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/727,808 18 October 2005 (18.10.2005) US
11/539,123 5 October 2006 (05.10.2006) US

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

(88) Date of publication of the international search report:
4 October 2007

(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 29/2007 of 19 July 2007

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

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

(54) Title: CANINE INFLUENZA VIRUS AND RELATED COMPOSITIONS AND METHODS OF USE

(57) Abstract: The present invention provides an isolated canine influenza virus of subtype H3N8 comprising an HA having SEQ ID NO: 4 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acids at positions 94 and 233 are identical to SEQ ID NO: 4; a composition comprising attenuated or inactivated virus; isolated or purified HA, NM, NP, M1, NS1, PA, PB1, and PB2 proteins and fragments thereof and compositions comprising same or nucleic acids, optionally as part of a vector, encoding same; and a method of inducing an immune response to canine influenza virus in an animal comprising administering to the animal an aforementioned composition.

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CANINE INFLUENZA VIRUS AND RELATED COMPOSITIONS AND METHODS OF USE

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 60/727,808, filed October 18, 2005, and U.S. Utility Patent Application No. 11/539,123, filed October 5, 2006.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to the fields of virology, molecular biology, and immunology. In particular, the present invention relates to canine influenza virus, as well as related compositions and methods of use in inducing an immune response in animals.

BACKGROUND OF THE INVENTION

[0003] Influenza virus is an RNA virus belonging to the family Orthomyxoviridae. The viral RNA consists of eight independent segments, which easily recombine among influenza viruses to produce new subtypes.

[0004] Nucleoprotein (NP), which is the primary component of the nucleocapsid, is encoded in the fifth segment. The NP and the matrix protein are used to classify the influenza virus into group A, B or C. Since NP is an internal protein, it is not subject to the pressure of selection by a host's immune system. It binds RNA, is part of the transcriptase complex, and is involved in the nuclear-cytoplasmic transport of viral RNA (vRNA).

[0005] Neuraminidase (NM), which splits the α -keto bond that joins a terminal sialic acid and the next sugar residue, thereby allowing the release of viral progeny from infected cells, is encoded by the sixth segment. Nine subtypes (N1-N9) of this enzyme have been identified. All subtypes have two structural regions – a stalk and a head. All N8 proteins have 470 amino acids, the first eight of which are highly conserved. The following region is rich in hydrophobic amino acids and is considered to be the transmembrane domain. The next 51 amino acids make up the stalk region, and the head region begins at Cys91. The last region contains the catalytic site of the enzyme. Cysteine residues in the head and stalk region tend to be highly conserved. There are 6-8 putative N-glycosylation sites.

[0006] Hemagglutinin (HA), which is a membrane glycoprotein responsible for the adsorption of the virus into the host cell, is the main antigen to which neutralizing

antibodies are directed. Its antigenic variation is the major cause of influenza epidemics. It is encoded by the fourth segment. Sixteen different subtypes (H1-H16) have been identified. HA has a signal peptide of 16 amino acids and two polypeptides (HA1 and HA2) joined by disulfide bridges. HA1 has the amino terminal end, whereas HA2 has the carboxyl terminal end. A hydrophobic region in HA2 anchors HA to the viral membrane. Cysteine residues tend to be highly conserved. There are six putative glycosylation sites, which enable the virus to mask its antigenic sites (Skehel et al., PNAS USA 81: 1779 (1984)).

[0007] Other proteins include matrix (M or M1 and M2), nonstructural (NS or NS1 and NS2), PA, PB1, and PB2. The M1 protein is a major component of the virion that binds to the plasma membrane of infected cells by means of two hydrophobic regions at the N-terminus of the protein, whereas M2 is an ion channel and, therefore, an integral membrane protein. The NS1 protein is found in the nucleus and affects cellular RNA transport, splicing, and translation. The NS2 protein is found in the nucleus and cytoplasm and has unknown function. The PA protein is a transcriptase and may have protease activity, whereas the PB1 protein functions in transcription elongation and the PB2 protein functions in transcription cap binding.

[0008] Globally, influenza is the most economically significant respiratory disease in humans, pigs, horses and poultry (Wright et al., Orthomyxoviruses. In: *Fields Virology*. Knipe et al., eds. Lippincott Williams & Wilkins, Philadelphia, 2001. pp. 1533-1579.). Influenza virus is known for its continuous genetic and antigenic changes, which impede effective control of the virus (Wright et al. (2001), *supra*; Webster et al., Microbiol. Rev. 56: 152-179 (1992)). Of particular concern for prevention of epidemics and pandemics is the emergency of a new subtype of the virus by genetic re-assortment or inter-species transmission (Wright et al. (2001), *supra*).

[0009] Recently, influenza outbreaks have occurred in species, e.g., feline and canine, which historically do not carry influenza virus (Keawcharoen et al., Emerg. Infect. Dis. 10: 2189-2191 (2004); Crawford et al., Science 310: 398-485 (October 21, 2005; published online September 29, 2005); Dubovi et al., Isolation of equine influenza virus from racing greyhounds with fatal hemorrhagic pneumonia. In: *Proceedings of the 47th Annual Meeting of American Association of Veterinary Laboratory Diagnosticians*, Greensboro, NC, October 2005. p. 158; and Yoon et al., Emerg. Infect. Dis. 11(12): 1974-1976 (December 2005)). Therefore, the host range of influenza virus is expanding.

[0010] Outbreaks of respiratory disease in racing greyhounds caused by infection with influenza virus have occurred in Florida in 2004, in eastern and western Iowa in April 2005, and in Texas in 2005. The disease was characterized by rapid onset of fever and cough, rapid respiration, and hemorrhagic nasal discharge. The morbidity was almost 100% in both race track compounds in Iowa, although the mortality was less than 5%. While a large percentage of affected dogs recovered, many succumbed to hemorrhagic pneumonia. Therapeutic administration of broad-spectrum antibiotics reduced the severity of the disease but could not control it.

[0011] In view of the above, it is an object of the present invention to provide the influenza virus that infects canines. It is another object of the present invention to provide materials and methods for inducing an immune response to the influenza virus in canines. These and other objects and advantages, as well as additional inventive features, will become apparent from the detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

[0012] The present invention provides an isolated canine influenza virus of subtype H3N8 comprising an HA having SEQ ID NO: 4 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acids at positions 94 and 233 are identical to SEQ ID NO: 4. In particular, the present invention provides an isolated canine influenza virus of subtype H3N8 deposited with the American Type Culture Collection (Manassas, VA) on June 29, 2006, as Patent Deposit No. PTA-7694. Accordingly, the present invention also provides a composition comprising attenuated virus as well as a composition comprising inactivated virus.

[0013] The present invention also provides isolated or purified proteins. In one embodiment, the present invention provides an isolated or purified HA, which (i) has the amino acid sequence of SEQ ID NO: 4 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 4 at amino acid positions 94 and 233, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 94 or 233 of SEQ ID NO: 4.

[0014] In another embodiment, the present invention provides an isolated or purified NM, which (i) comprises the amino acid sequence of SEQ ID NO: 2 or (ii) is derived from an influenza virus and which comprises an amino acid sequence that is greater than 99%

identical to SEQ ID NO: 2, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 2 at amino acid positions 68 and 134, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 68 or 134 of SEQ ID NO: 2.

[0015] In yet another embodiment, the present invention provides an isolated or purified NP, which (i) has the amino acid sequence of SEQ ID NO: 6 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 6, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 6 at amino acid position 402, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 402 of SEQ ID NO: 6.

[0016] In still yet another embodiment, the present invention provides an isolated or purified M1, which (i) has the amino acid sequence of SEQ ID NO: 8 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 8, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 8 at amino acid position 111, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 111 of SEQ ID NO: 8.

[0017] Also provided is an isolated or purified NS1, which has the amino acid sequence of SEQ ID NO: 10.

[0018] Further provided is an isolated or purified PA protein, which (i) has the amino acid sequence of SEQ ID NO: 12 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 98% (or 99%) identical to SEQ ID NO: 12, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 12 at amino acid positions 233, 256, 327, and 561, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 233, 256, 327, and 561, of SEQ ID NO: 12.

[0019] Still further provided is an isolated or purified PB1, which (i) has the amino acid sequence of SEQ ID NO: 14 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 14, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 14 at amino acid positions 200 and 213, or a fragment of (i) or (ii), wherein the fragment comprises at least nine

contiguous amino acids, at least one of which is identical to the amino acid at position 200 or 213 of SEQ ID NO: 14.

[0020] Even still further provided is an isolated or purified PB2, which (i) has the amino acid sequence of SEQ ID NO: 16 or (ii) is derived from an influenza virus and which has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 16, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 16 at amino acid positions 107, 221, 292, and 661, or a fragment of (i) or (ii), wherein the fragment comprises at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 107, 221, 292, or 661 of SEQ ID NO: 16.

[0021] In view of the above, the present invention further provides a composition comprising an above-described protein, such as HA or NM, or a fragment thereof in an amount sufficient to induce an immune response in an animal and a biologically acceptable carrier.

[0022] Also in view of the above, the present invention provides a method of inducing an immune response to canine influenza virus in an animal. The method comprises administering to the animal the composition comprising a protein or fragment thereof.

[0023] An isolated or purified nucleic acid encoding above-described protein or fragment thereof, optionally as part of a vector, is also provided, as is a composition comprising the isolated or purified nucleic acid, which expresses the protein, such as HA or NM, or a fragment thereof, in an amount sufficient to induce an immune response in an animal and a biologically acceptable carrier.

[0024] Accordingly, the present invention also provides another method of inducing an immune response to canine influenza virus in an animal. The method comprises administering to the animal the composition comprising a nucleic acid.

BRIEF DESCRIPTION OF THE FIGURES

[0025] Fig. 1 is the partial nucleotide sequence (SEQ ID NO: 1; see also GenBank Acc. No. DQ146420) of the coding domain sequence (CDS) of the NM gene from subtype H3N8 of canine influenza virus. In accordance with convention, the sequence is presented from left to right and top to bottom.

[0026] Fig. 2 is the amino acid sequence (SEQ ID NO: 2; see also GenBank Acc. No. DQ146420) encoded by SEQ ID NO: 1. In accordance with convention the sequence is presented in single letter format from left to right and top to bottom.

[0027] Fig. 3 is the complete nucleotide sequence (SEQ ID NO: 3; see also GenBank Acc. No. DQ146419) of the CDS of the HA gene from subtype H3N8 of canine influenza virus.

[0028] Fig. 4 is the amino acid sequence (SEQ ID NO: 4; see also GenBank Acc. No. DQ146419) encoded by SEQ ID NO: 3.

[0029] Fig. 5 is the complete nucleotide sequence (SEQ ID NO: 5) of the CDS of the NP gene from subtype H3N8 of canine influenza virus.

[0030] Fig. 6 is the deduced amino acid sequence (SEQ ID NO: 6) encoded by SEQ ID NO: 5.

[0031] Fig. 7 is the complete nucleotide sequence (SEQ ID NO: 7) of the CDS of the M1 protein gene from subtype H3N8 of canine influenza virus.

[0032] Fig. 8 is the deduced amino acid sequence (SEQ ID NO: 8) encoded by SEQ ID NO: 7.

[0033] Fig. 9 is the complete nucleotide sequence (SEQ ID NO: 9) of the CDS of the NS1 protein gene from subtype H3N8 of canine influenza virus.

[0034] Fig. 10 is the deduced amino acid sequence (SEQ ID NO: 10) encoded by SEQ ID NO: 9.

[0035] Fig. 11 is the complete nucleotide sequence (SEQ ID NO: 11) of the CDS of the PA protein gene from subtype H3N8 of canine influenza virus.

[0036] Fig. 12 is the deduced amino acid sequence (SEQ ID NO: 12) encoded by SEQ ID NO: 11.

[0037] Fig. 13 is the complete nucleotide sequence (SEQ ID NO: 13) of the CDS of the PB1 protein gene from subtype H3N8 of canine influenza virus.

[0038] Fig. 14 is the deduced amino acid sequence (SEQ ID NO: 14) encoded by SEQ ID NO: 13.

[0039] Fig. 15 is the complete nucleotide sequence (SEQ ID NO: 15) of the CDS of the PB2 protein gene from subtype H3N8 of canine influenza virus.

[0040] Fig. 16 is the deduced amino acid sequence (SEQ ID NO: 16) encoded by SEQ ID NO: 15.

DETAILED DESCRIPTION OF THE INVENTION

[0041] The present invention is predicated on the discovery of a strain of influenza virus in canines. The strain was isolated from racing greyhounds in eastern and western Iowa. The strain has been classified as an H3N8 subtype, and has been designated A/canine/Iowa/13628/2005. Accordingly, the present invention provides a virus comprising an HA having SEQ ID NO: 4 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acids at positions 94 and 233 are identical to SEQ ID NO: 4. The virus can further comprise an NM comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 2, with the proviso that the amino acids at positions 68 and 134 are identical to SEQ ID NO: 2. The virus comprising the aforementioned HA, alone or in further combination with the aforementioned NM, can further comprise at least one of the following: an NP having the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 6, with the proviso that amino acid 402 is identical to that of SEQ ID NO: 6; an M1 having the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 8, with the proviso that amino acid 111 is identical to that of SEQ ID NO: 8; an NS1 having the amino acid sequence of SEQ ID NO: 10; a PA protein having the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence that is greater than 98% (or 99%) identical to SEQ ID NO: 12, with the proviso that amino acids 233, 256, 327, and 561 are identical to SEQ ID NO: 12; a PB1 having the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 14, with the proviso that amino acids 200 and 213 are identical to SEQ ID NO: 14; and/or PB2 having the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 16, with the proviso that amino acids 107, 221, 292, and 661 are identical to SEQ ID NO: 16. In particular, the present invention provides an isolated canine influenza virus of subtype H3N8 deposited with the American Type Culture Collection, 10801

University Blvd., Manassas, VA 20110-2209, U.S.A., on June 29, 2006, as Patent Deposit No. PTA-7694.

[0042] Influenza virus can be precipitated by subjecting the virus in aqueous medium to one or more insolubilizing steps brought about by the presence of up to 5% by weight of polyethylene glycol (PEG) having a molecular weight between 3,000 and 20,000 or another linear filamentary noncharged polymer in an amount equivalent to the solubilizing power of PEG, separating an insolubilized fraction from a non-insolubilized fraction, and recovering virus from one of the fractions (see, e.g., U.S. Pat. No. 3,989,818). Preferably, the temperature does not exceed 35°C, the pH is between 6 and 9, and the ionic strength of the aqueous medium is below the salting out point for the virus. The concentration of the virus in the aqueous medium prior to insolubilizing corresponds to a hemagglutination titer of at least 1 in 32. Aggregated viral particles are obtained, which are believed to provide a better antigenic effect due to the slow release of viral particles after vaccination. If, however, non-aggregated or less aggregated particles are desired, they can be dissociated using any suitable method, such as sonication.

[0043] The virus can be attenuated by passaging in a cell system until the virus has lost its ability to produce disease, while fully retaining its immunogenic character. For example, the virus can be serially passaged in a culture of cells originating from a canine species or other suitable species at a temperature of about 37 °C. At each passage, the virus is harvested from one culture and inoculated into a medium containing a fresh cell culture in accordance with methods known in the art. For example, the virus can be collected from tissue cell culture fluids and/or cells. Optionally, during harvesting, the cell culture can be sonicated to promote release of the virus. See, e.g., U.S. Pat. Nos. 5,698,433 and 6,455,298.

[0044] If desired, an influenza strain can be passaged at least once in the allantoic cavity of embryonated eggs, such as chicken eggs, in the presence of serum, to obtain serum-resistant virus (see, e.g., U.S. Pat. No. 3,953,592; Kilbourne et al., J.Exp. Med. 111: 387 (1960); Kilbourne, Science 160: 74-75 (April 1968); and Laver et al., Virology 30: 493-501 (1966)). High potency influenza vaccine with low pyrogenicity and low endotoxicity can be achieved by treating the concentrated allantoic fluid containing an attenuated virus sequentially with butyl acetate and ethyl acetate, followed by flash evaporation (see, e.g., U.S. Pat. No. 4,000,257). Such virus can be administered intranasally as a vaccine.

[0045] Once inoculated into the host, the virus multiplies to some extent so that only a small initial inoculum is required. The virus must be innocuous, and infection of susceptible contacts should be kept to a minimum.

[0046] Alternatively, the virus can be inactivated by abolishing replication and virulence. This can be done by chemical or physical means. Chemical inactivation can be carried out by treatment of the virus with an enzyme, formaldehyde, β -propiolacton or derivative thereof, ethyleneimine or derivative thereof, an organic solvent (e.g., halogenated hydrocarbon), and/or a detergent (e.g., Tween®, Triton X®, sodium desoxycholate, sulfobetain, or cetyltrimethylammonium salts). If necessary, chemically activated compositions can be neutralized. For example, if formaldehyde is used to deactivate the composition, the composition can be neutralized with thio-sulphate. If required, the pH subsequently can be returned to a value of about 7. Alternatively, the virus can be extracted with a mixture of ether and ethanol, the aqueous and organic phases can be separated, and residual ether can be removed from the viral suspension under reduced pressure (see, e.g., U.S. Pat. No. 4,431,633). Physical inactivation advantageously can be carried by subjecting the virus to energy-rich radiation, such as ultraviolet light, γ -radiation, or X-rays. Inactivated forms require a relatively high amount of inoculum and, therefore, a correspondingly large quantity of antigenic material, which has to be manufactured, tested, and distributed.

[0047] In view of the above, the present invention also provides a composition comprising an attenuated or inactivated virus. The virus should be present in an amount sufficient to induce an immune response and, desirably, should provide protection upon challenge. Generally, an adjuvant, such as Tween®, Span®, Freund's complete adjuvant, saponin, *Corynebacterium parvum* (Coparvax®), aluminium phosphate, aluminium hydroxide, or a mixture thereof, is added to the composition, particularly if the composition comprises inactivated virus. Protein hydrolysates and/or amino acids can be added to stabilize the composition (see, e.g., U.S. Pat. No. 4,537,769). Alternatively, the composition can be formulated as an oil-in-water emulsion using oils such as MarcolTM and/or ArlacelTM.

[0048] Recombinant influenza strains also can be prepared, such as from the combination of an "over-attenuated" (i.e., the number of passages for attenuation is substantially greater than what is normally required to remove pathogenicity) influenza A parent strain, e.g., A2, with a virulent influenza strain as provided herein (see, e.g., U.S. Pat. No. 3,991,179; also, see U.S. Pat. Nos. 4,009,258; 4,278,662; 4,318,903; 4,338,296; and

4,693,893). A recombinant strain preferably has the growth characteristics of the over-attenuated strain coupled with the antigenic properties, e.g., the HA and NM proteins, of the virulent strain. The selection of strains of influenza virus for vaccine formulation is described in U.S. Pat. No. 5,162,112. Recombinant strains can be formulated as compositions for inducing an immune response.

[0049] Sucrose, arginine monohydrochloride, the monosodium monohydrate of glutamic acid, and gelatin hydrolysate can be used to stabilize an influenza virus composition for storage in a refrigerator. See, e.g., U.S. Pat. App. Pub. No. 2006/0110406.

[0050] In view of the above, the present invention also provides an isolated or purified HA. The HA either has the amino acid sequence of SEQ ID NO: 4 or is derived from an influenza virus and has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 4 at amino acid positions 94 and 233. A fragment of HA comprising at least nine (such as 9, 12, 15, 18, 21 or 24) contiguous amino acids, at least one of which is identical to the amino acid at position 94 or 233 of SEQ ID NO: 4, is also provided.

[0051] An isolated or purified NM is also provided. The NM comprises the amino acid sequence of SEQ ID NO: 2 or is derived from an influenza virus and comprises an amino acid sequence that is greater than 99% identical to SEQ ID NO: 2, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 2 at amino acid positions 68 and 134. A fragment of NM comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 68 or 134 of SEQ ID NO: 2, is also provided.

[0052] Further provided is an isolated or purified NP. The NP has the amino acid sequence of SEQ ID NO: 6 or is derived from an influenza virus and has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 6, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 6 at amino acid position 402. A fragment of NP comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 402 of SEQ ID NO: 6, is also provided.

[0053] Still further provided is an isolated or purified M1. The M1 has the amino acid sequence of SEQ ID NO: 8 or is derived from an influenza virus and has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 8, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 8 at amino acid position 111. A

fragment of M1 comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 111 of SEQ ID NO: 8, is also provided.

[0054] Even still further provided is an isolated or purified NS1, which has the amino acid sequence of SEQ ID NO: 10.

[0055] An isolated or purified PA protein is also provided. The PA has the amino acid sequence of SEQ ID NO: 12 or is derived from an influenza virus and has an amino acid sequence that is greater than 98% (or 99%) identical to SEQ ID NO: 12, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 12 at amino acid positions 233, 256, 327, and 561. A fragment of PA comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 233, 256, 327, or 561 of SEQ ID NO: 12, is also provided.

[0056] An isolated or purified PB1 is provided. The PB1 has the amino acid sequence of SEQ ID NO: 14 or is derived from an influenza virus and has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 14, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 14 at amino acid positions 200 and 213. A fragment of PB1 comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 200 or 213 of SEQ ID NO: 14, is also provided.

[0057] Provided also is an isolated or purified PB2. The PB2 has the amino acid sequence of SEQ ID NO: 16 or is derived from an influenza virus and has an amino acid sequence that is greater than 99% identical to SEQ ID NO: 16, with the proviso that the amino acid sequence is identical to that of SEQ ID NO: 16 at amino acid positions 107, 221, 292, and 661. A fragment of PB2 comprising at least nine contiguous amino acids, at least one of which is identical to the amino acid at position 107, 221, 292, or 661 of SEQ ID NO: 16, is provided as well.

[0058] The above proteins and fragments thereof can be purified (coupled with chemical or physical fragmentation to generate fragments) or synthesized in accordance with methods known in the art. See, e.g., Meienhofer, *Hormonal Proteins and Peptides* 2: 46, Academic Press, NY (1973), for solid phase protein synthesis, and Schroder et al., *The Peptides*, vol. 1, Academic Press, NY (1965), for solution phase protein synthesis. Automated systems can be used to carry out such techniques in accordance with manufacturer's instructions. Therapeutic quantities can be recombinantly produced and purified.

[0059] Alternatively, proteins, in particular HA and NM, can be isolated by selective solubilization, while leaving residual subviral particles consisting of the intact lipid/protein membrane enclosing all other non-essential viral components. The difference in size/density of the solubilized proteins and the residual subviral particles allows separation based on differences in physical properties by gradient centrifugation and fractionation, sedimentation, molecular sieve chromatography, or pelleting in an ultracentrifuge. Selective solubilization of HA and NM can be achieved by treatment of the virus with a cationic detergent (see, e.g., U.S. Pat. No. 4,140,762; the '762 patent). The whole virus-containing fluid obtained from cell culture can be treated with a DNA-digesting enzyme followed by addition of a cationic detergent and isolation of surface-antigen proteins (see, e.g., U.S. Pat. No. 5,948,410). The fluid can be subjected to several ultracentrifugation steps, or the virus can be fragmented in the presence of an amphiphilic nonionic detergent followed by filtration to remove undesirable substances (see, e.g., U.S. Pat. No. 6,048,537). Alternatively, membrane filtration and chemical splitting can be used to obtain a viral protein (see, e.g., U.S. Pat. No. 4,327,182). Other procedures are described in U.S. Pat. Nos. 4,064,232 and 4,057,626. Preferably, the virus is multiplied before treatment as exemplified in the '762 patent (col. 2, ll. 10 *et seq*).

[0060] Mapping can be conducted to identify an immune response-inducing epitope of a viral protein, i.e., "epitope mapping." Such mapping involves fragmenting of a protein into overlapping peptides (such as peptides comprising 9, 12, 15, 18, 21 or 24 amino acids). The protein can be fragmented with a proteolytic enzyme. The individual peptides are then tested for their ability to bind to an antibody elicited by the native protein or to induce T-cell or B-cell activation. Alternatively, hydrophilic regions of the protein can be selected, since hydrophilic residues are often on the surface of the protein and, therefore, are accessible to the antibody. X-ray crystallographic analysis of the antigen-antibody complex also can be performed. Potential HLA anchor binding motifs, which are peptide sequences that are known to be likely to bind to MHC molecules, can be identified from the amino acid sequence of a protein. Preferably, the epitope selected is one that shares little to no sequence identity with sequences widely found in the animal to which a composition comprising or expressing a protein fragment will be administered.

[0061] An isolated or purified nucleic acid encoding an above-described protein or fragment thereof, optionally as part of a vector, is also provided. The nucleic acid encoding the HA can comprise the nucleotide sequence of SEQ ID NO: 3 or a fragment thereof encoding at least nine (9, 12, 15, 18, 21 or 24) contiguous amino acids. If desired, a trivalent vaccine based on HA can be prepared, wherein one of the HAs comprises the

amino acid sequence of SEQ ID NO: 4 (see, e.g., U.S. Pat. Nos. 5,762,939 and 6,245,532; see, e.g., U.S. Pat. No. 6,740,325 for a tetravalent vaccine). The nucleic acid encoding the NM can have the nucleotide sequence of SEQ ID NO: 1 or a fragment thereof encoding at least nine contiguous amino acids (see, e.g., U.S. Pat. No. 6,605,457 and U.S. Pat. App. Pub. No. 2003/0129197), whereas the nucleic acid encoding the NP can have the nucleotide sequence of SEQ ID NO: 5 or a fragment thereof encoding at least nine contiguous amino acids, the nucleic acid encoding the M1 protein can have the nucleotide sequence of SEQ ID NO: 7 or a fragment thereof encoding at least nine contiguous amino acids, the nucleic acid encoding the NS1 protein can have the nucleotide sequence of SEQ ID NO: 9, the nucleic acid encoding the PA can have the nucleotide sequence of SEQ ID NO: 11 or a fragment thereof encoding at least nine contiguous amino acids, the nucleic acid encoding the PB1 can have the nucleotide sequence of SEQ ID NO: 13 or a fragment thereof encoding at least nine contiguous amino acids, and the nucleic acid encoding the PB2 can have the nucleotide sequence of SEQ ID NO: 15 or a fragment thereof encoding at least nine contiguous amino acids. One of ordinary skill in the art will appreciate, however, that due to the degeneracy of the genetic code, there are numerous other nucleotide sequences that can encode such amino acid sequences.

[0062] The above nucleic acids, which can be DNA or RNA, and fragments thereof can be synthesized (see, e.g., *Oligonucleotide Synthesis*, Gait, ed., 1984). Such molecules can include non-naturally occurring nucleotides/bases that encode the desired amino acid sequence. For example, the base or sugar can be methylated. In addition, the backbone of the nucleic acid molecule can be modified, e.g., a phosphorothioate backbone, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof.

[0063] Alternatively, isolated vRNA can be subjected to reverse transcriptase to produce an RNA/DNA hybrid, from which the RNA is digested away and the residual DNA is treated to produce a dsDNA having a hairpin end, which is treated with a single-strand-specific nuclease to produce a bimolecular double-stranded copy of the vRNA (see, e.g., U.S. Pat. No. 4,357,421). See, e.g., U.S. Pat. App. Pub. No. 2006/0166321 for the use of tandem transcription cassettes for the preparation of influenza in the absence of helper virus.

[0064] The nucleic acid is optionally part of a DNA vector comprising at least one promoter, in which case each nucleotide sequence is operably linked to a promoter, which can be the same or different. In addition to promoters, other control sequences, such as terminating signals and the like, can be part of the DNA vector.

[0065] For example, the nucleic acid can be introduced into a suitable recombinant expression vector, such as those adapted for bacteria, such as *E. coli* and *Salmonella typhi*, yeast, such as *Saccharomyces cerevisiae* or *Pichia pastoris*, or filamentous fungi, such as *Aspergillus nidulans*. The bacteria, yeast, or fungi can be grown in continuous culture. The polypeptide, which is produced during culture, then can be isolated and purified. Alternatively, the nucleic acid molecule can be introduced into Poxviridae (e.g., fowlpox-based vectors), Herpesviridae (e.g., pseudorabies virus-based vectors, turkey herpes virus-based vectors, feline herpes virus-based vectors, infectious laryngotracheitis virus-based vectors, and bovine herpes virus-based vectors), Adenoviridae (e.g., bovine adenovirus (e.g., serotype 3), human adenovirus (e.g., serotype 4 or 7), and canine adenovirus (e.g., serotype 2; CAV2; see, e.g., U.S. Pat. No. 6,090,393), or an insect virus expression vector, such as recombinant baculovirus (e.g., *Autographa californica* nuclear polyhydrosis virus (AcNPV)), which, in turn, can be used to infect susceptible cultured SF9 cells, which are derived from the insect *Spodoptera frugiperda*. Other viral vectors include vaccinia (see, e.g., U.S. Pat. No. 4,722,848), adenovirus, adeno-like virus, adeno-associated virus, retrovirus, and pox (see, e.g., Hruby, Vet. Parasitol. 29: 281-282 (1988); Uiu, "AIDS Research Reviews," Dekker, Inc., 1991, 1: 403-416), which can be administered by a skin scratch or by injection, optionally as a liposomal formulation. Other vectors include Bacille-Calmette-Guerin (BCG; Stover et al., Nature 351: 456-460 (1991)), detoxified anthrax toxin vectors, and the like. Mammalian cells, such as Chinese hamster ovary (CHO) cells, and even plant cells can be used to express the polypeptide from the appropriate construct. One of ordinary skill in the art will appreciate that the choice of host cell will affect the nature of post-translational processing (e.g., glycosylation, folding, and the like), which, in turn, can impact the immunogenicity of the polypeptide, and subsequent purification techniques.

[0066] Expression can be achieved in any appropriate host cell transformed/transfected with the expression vector. Examples of suitable host cells include, but are not limited to, those described above. Thus, the present invention also provides a host cell transformed/transfected with an expression vector.

[0067] Supernatants from host/vector systems that secrete the protein or fragment thereof into culture media can be applied to a purification matrix, such as an affinity column or an ion exchange column. One or more reverse-phase HPLC steps can be employed to purify further the recombinant protein or fragment thereof.

[0068] Production of a protein or fragment thereof as a fusion protein can stabilize production. This can be accomplished by ligating polynucleotide sequences encoding two or more proteins (or fragments thereof) into an appropriate expression vector with or without a peptidic linker. Desirably, the reading frames of the polynucleotides sequences are in phase, so that a single fusion protein that retains the biological activity of each protein (or fragment thereof) is produced. A peptidic linker from 1 to about 50 amino acids can be used to separate the resultant proteins (or fragments thereof) so as to ensure that each protein (or fragment thereof) properly folds into its native secondary, tertiary, and quaternary structures (see, e.g., Maratea et al., *Gene* 49: 39-46 (1985); Murphy et al., *PNAS USA* 83: 8258-8262 (1986); U.S. Pat. No. 4,935,233; and U.S. Pat. No. 4,751,180). The ability to adopt a flexible extended conformation, the inability to adopt a secondary structure that could interact with functional amino acids on either one or both of the proteins, and the lack of hydrophobic or charged residues that might react with either one or both of the proteins are factors, which are taken into consideration in selecting a peptide linker. Linkers are not required when the ends of the proteins to be joined do not contain essential regions, such that the ends can be used to separate functional domains and prevent steric interference. Preferred peptide linker sequences contain Gly, Asn, and Ser residues. Other near neutral residues, such as Thr and Ala, also can be used.

[0069] Other additional amino acid sequence(s) can be selected to enhance the expression and/or immunogenicity of the protein or fragment thereof. For example, the protein or fragment thereof can be fused to the heavy chain of immunoglobulin G (IgG) or an antigen-presenting cell (APC) binding protein or a dendritic cell binding protein, such as IL-D, GM-CSF, IL-1, TNF, IL-4, CD40L, CTLA4, CD28, or FLT-3 ligand. Techniques, such as the use of dehydrating agents, e.g., dicyclohexylcarbodiimide (DCCI), or the creation of linkages between sulfhydryl groups, epsilon amino groups, carboxyl groups, and the like, can be used. If desired, a cleavage site can be introduced into the fusion protein to enable separation of the protein (or fragment thereof) from the non-naturally occurring sequence(s). Examples of cleavage sites include a target sequence for a proteolytic enzyme or, if methionine is not present in the protein (or fragment thereof), methionine, which, in turn, is cleaved by cyanogen bromide. Such methods are known in the art. The protein or fragment thereof can be modified by glycosylation or other derivatization (e.g., acetylation or carboxylation), also in accordance with methods known in the art.

[0070] The protein (or fragment thereof) can be expressed *in situ* from a suitable expression system. Any DNA construct, which is effective in producing the encoded

protein or fragment thereof in the desired environment, can be used to express the protein or fragment thereof as described above.

[0071] Alternatively, the nucleic acid molecule can behave as an effective expression system *in situ* when injected into an animal as “naked DNA” (see, e.g., Ulmer et al., Science 259: 1745-1749 (1993); and Cohen, Science 259: 1691-1692 (1993)). DNA delivery also can be facilitated through the use of bupivacaine, polymers, and peptides; alternatively, cationic lipid complexes, particles, or pressure (see, e.g., U.S. Pat. No. 5,922,687) can be used.

[0072] Examples of amino acid sequences that are at least about or greater than 95% identical to, such as at least about or greater than 96%, 97%, 98%, or 99% identical to, SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 include amino acid sequences that contain one or more substitutions, insertions, additions and/or deletions. Sequence identity can be determined by aligning polypeptide sequences and applying publicly available computer algorithms, such as BLASTP (Pearson et al., PNAS USA 85: 2444-2448 (1988); Pearson, Methods Enzymol. 183: 63-98 (1990); and Altschul et al., Nucl. Acids Res. 25: 3389-3402 (1997)). The software for BLASTP is available on the FTP server of the National Center for Biotechnology Information (NCBI) or NCBI, National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894. Once the polypeptide sequences are aligned, the number of identical amino acids over the aligned portions is identified, the number of identical amino acids is divided by the total number of amino acids of the polypeptide of interest, and the result is multiplied by 100 to determine the percentage sequence identity.

[0073] In this regard, one of ordinary skill in the art will appreciate that a fragment of a given amino acid sequence can be at least about or greater than 95% identical to, such as 96%, 97%, 98% or 99% identical to, the amino acid sequence. Thus, fragments are intended to be encompassed by “an amino acid sequence that is at least about or greater than 95% (or 96%, 97%, 98% or 99%) identical to SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16.” Such fragments desirably retain the immunogenicity of the full-length protein. Functional fragments can be generated by mutational analysis of the nucleic acid encoding the protein and subsequent expression of the resulting mutant protein or by chemical/enzymatic digestion of the protein, itself.

[0074] Modifications, such as substitutions, insertions, additions and/or deletions, can be introduced into the nucleic acid or the protein (or fragment thereof) in accordance with methods known in the art (see, e.g., Adelman et al., DNA 2: 183 (1983), for

oligonucleotide-directed site-specific mutagenesis). Desirably, the modification does not substantially diminish the immunogenicity of the protein fragment; rather, it is preferred that the immunogenicity remains substantially the same or increases relative to the unmodified protein.

[0075] A “conservative substitution” is one in which an amino acid is substituted for another amino acid that has similar properties, i.e., similar secondary structure and hydrophobic nature. Amino acid substitutions can be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids, such as aspartic acid and glutamic acid, can be interchanged, whereas positively charged amino acids, such as lysine and arginine, can be interchanged, and amino acids with uncharged polar head groups having similar hydrophilicity values can be interchanged. In this regard, leucine, isoleucine and valine can be interchanged, glycine and alanine can be interchanged, asparagine and glutamine can be interchanged, and serine, threonine, phenylalanine, and tyrosine can be interchanged. Other groups of amino acids that can be interchanged include: (1) ala, pro, gly, glu, asp, gln, asn, ser and thr; (2) cys, ser, tyr and thr; (3) val, ile, leu, met, ala and phe; (4) lys, arg and his; and (5) phe, tyr, trp, and his.

[0076] In view of the above, a composition comprising the isolated or purified protein/nucleic acid or fragment of either of the foregoing and a biologically acceptable carrier is also provided. The nucleic acid or fragment thereof can be part of a vector. See, for example, U.S. Pat. No. 4,029,763, which is directed to an influenza vaccine comprising, as an active ingredient, NM, and U.S. Pat. No. 4,140,762, which is directed to an influenza vaccine comprising, as active ingredients, HA and NM. U.S. Pat. No. 4,826,687 describes the addition of muramyl dipeptide to a vaccine comprising HA and NM. If desired, polypeptides corresponding substantially to amino acids 148-162, 163-166, and/or 215-239 of M1 can be added to a composition of a protein/nucleic acid or fragment thereof (see, e.g., U.S. Pat. Nos. 5,136,019; 5,616,327; and 5,741,493). Any suitable biologically acceptable carrier can be used in the composition. For example, the protein(s)/nucleic acid(s)/fragments thereof can be resuspended in a diluent, e.g., 0.9% sodium chloride solution, which is optionally buffered with, for example, a phosphate buffer. Any sucrose that remains from purification of the virus can be reduced by dialysis. Dialysis or gel chromatography can be used to remove any remaining cationic detergent. Preferably, the protein or fragment thereof is present in an amount sufficient to induce an immune response (i.e., cellular or humoral) in an animal. A frequently selected carrier for pharmaceuticals and antigens is poly(d,l-lactide-co-glycolide) (PLGA). PLGA is a biodegradable polyester,

and can be used for the controlled release of antigen (Eldridge et al., Curr. Topics Micro. Immuno. 146: 59-66 (1989); see also U.S. Pat. No. 6,090,393). The entrapment of antigens in PLGA microspheres of 1-10 μ in diameter has been shown to have a remarkable adjuvant effect when administered orally.

[0077] If desired, a preserving agent or an inactivating agent, such as formaldehyde, can be added. A conventional amount of preserving/inactivating agent is 1 part per 10,000 parts.

[0078] If desired, one or more proteins (or immunogenic fragments thereof), such as the above-described HA, can be combined with proteosomes. See, e.g., U.S. Pat. No. 6,743,900 and U.S. Pat. App. Pub. No. 2004/0156867.

[0079] Immunogenicity can be improved by inclusion of conventional immunological adjuvants, such as aluminium hydroxide (e.g., about 0.2%) or aluminium phosphate, aluminum (see, e.g., U.S. Pat. Nos. 6,372,223, 6,635,246, 6,861,244 and 7,052,701 and U.S. Pat. App. Pub. Nos. 2004/0096464 and 2006/0147468), chitosan (see, e.g., U.S. Pat. Nos. 6,136,606 and 6,534,065), alum, such as in the form of aluminum hydroxide, aluminum phosphate or aluminum oxide, mineral oils (e.g., Bayol F® and Marcol 52®), Freund's complete adjuvant, Freund's incomplete adjuvant, muramyl dipeptide, monophosphoryl lipid A, and saponins, including the Quil A component. Immunogenicity also can be improved by adding a cytokine, such as an interleukin, or by conjugating proteins or fragments thereof. Preferably, the protein or fragment thereof is conjugated with a macromolecular carrier, such as a protein (e.g., serum albumin, keyhole limpet hemocyanin, immunoglobulin, throglobulin, and ovalbumin), polysaccharide (e.g., latex-functionalized sepharose, agarose, cellulose beads, and the like), phospholipid, polymeric amino acids (e.g., polyglutamic acid, polylysine, and the like), or amino acid co-polymers (see, e.g., U.S. Pat. Nos. 5,136,019 and 5,612,037). Alternatively, the protein or fragment thereof can be encapsulated with a proteoliposome or lipid vesicle.

[0080] The composition, which can induce an immune response, can be prepared in the form of a suspension or can be lyophilized. If lyophilized, it is preferable to add one or more stabilizers. Suitable stabilizers are, for example, sucrose, phosphate, glutamate, and albumin (SPGA; Bovarnick, J. Bacteriol. 59: 509 (1950)), carbohydrates (e.g., sorbitol, mannitol, starch, dextran, and glucose), proteins (e.g., albumin and casein) or degradation products thereof, protein-containing agents (e.g., bovine serum or skim milk), and buffers (e.g., alkali metal phosphates).

[0081] Alternatively, the composition can be formulated as a controlled-release composition. The attenuated/inactivated virus or recombinant vector can be microencapsulated with polymers, such as polycarbonates, polyesters, polyurethanes, polyorthoesters, and polyamides. The particular polymer selected depends on a number of factors including reproducibility of polymer synthesis and microencapsulation, cost of materials and process, toxicological profile, requirements for variable release kinetics, and the physicochemical compatibility of the polymer and the virus/vector.

[0082] The compositions described herein can be used alone or in combination with other active ingredients/compositions. Examples include compositions, which can induce an immune response against canine distemper, infectious canine hepatitis (CAV-1 and CAV-2), rabies, parainfluenza, canine corona virus, measles, leptospirosis, and Bordetella. Polyphenols have been disclosed to inhibit influenza infection in humans (see, e.g., U.S. Pat. No. 5,173,922; the '922 patent). Accordingly, the addition of a polyphenol, such as epigallocatechin gallate, epicatechin gallate, epigallocatechin, epicatechin, free theaflavin, theaflavin monogallate A, theaflavin monogallate B, and/or theaflavin digallate may be beneficial (see the '922 patent). Inhibitors of NM are disclosed in U.S. Pat. No. 5,453,533. The use of cytokines as immunopotentiators and liposomal encapsulation are described in U.S. Pat. No. 5,919,480.

[0083] The amount of nucleic acid in the composition can vary widely. For example, the concentration can range from less than about 0.1% to as much as about 20-50% or more by weight, usually at least about 2%. The concentration of protein in the composition also can vary widely. For example, the concentration can range from less than about 0.1% to as much as about 20-50% or more by weight, usually at least about 2%. Fluid volume and viscosity are taken into consideration when determining the final concentration.

[0084] Accordingly, a method of inducing an immune response to canine influenza virus in an animal is also provided. The susceptibility of an animal to infection can be assessed using the plaque reduction neutralization test (U.S. Pat. No. 4,315,073) or the hemagglutination test. The method comprises administering to the animal an above-described composition comprising an isolated or purified protein/nucleic acid or fragment thereof. If the composition comprises a nucleic acid (or fragment thereof) as part of a vector, preferably the protein (or fragment thereof) is expressed in an amount sufficient to induce an immune response in an animal. For example, a single dose of from about 9 to about 43 international units per kg of animal body weight can be administered. For larger mammals, a single dose can comprise from about 600 to about 3,000 international units per

kg of body weight. For vaccine compositions prepared by culturing virus in the allantoic cavity of fertile eggs, harvesting the virus, and, if desired, stabilizing the harvested virus with a stabilizer, such as a peptone or sucrose, and then distribution into glass vials for subsequent freeze-drying, an effective vaccine dosage unit can contain at least 10^7 EID₅₀ (50% egg-infective dose) of virus. In the latter situation, the freeze-dried vaccine is reconstituted by addition of water or another pharmaceutically acceptable diluent prior to administration, such as in the form of a nasal spray or nasal drops. If desired, the vaccine can be administered in two successive dosages at a one-week interval.

[0085] The composition can be administered to puppies as a single dose at the age of 12 weeks, or repeatedly starting from the age of 6 weeks (e.g., at 6, 9 and 12 weeks), or weekly from 4 weeks on. The effective dosage and route of administration are determined by the nature of the composition, the nature of the expression product, LD₅₀, and, if recombinant vector is used, the expression level of the vector, as well as the breed of dog and its age, sex, weight, and condition. Dosages of expressed product can range from a few to a few hundred micrograms, e.g., 5-500 µg. Preferred dosages of virus or recombinant vector can range from about 10^3 to about 10^6 pfu. The dose for the live attenuated strain can be at least about 10^3 TCID₅₀.

[0086] The compositions can be administered parenterally (i.e., by injection (e.g., intradermal, subcutaneous, or intramuscular) or by the route of infection, such as nasally) or enterally (i.e., by oral administration). The use of a gelling agent and a muco- or bio-adhesive to enhance the immune response against an intradermally administered immunogenic composition is described in U.S. Pat. App. Pub. No. 2005/0255121. If desired, the composition for inducing an immune response can be administered through drinking water or syrup in accordance with Chu et al. (U.S. Pat. App. Pub. No. 2006/0171960, which was published on August 3, 2006). Oral administration is advantageous inasmuch as it avoids time-consuming and labor-intensive intramuscular injection, which, in turn, can create stress for the animal and discomfort. Discomfort, in turn, can affect the performance of race dogs. Alternatively, the composition comprising a recombinant vector expressing at least one immune response-inducing epitope can be applied directly to the skin for localized expression and induction of an immune response.

[0087] Efficacy of the composition, which can induce an immune response, can be demonstrated by exposing puppies to a virulent strain of canine influenza virus. Untreated dogs should develop clinical signs characteristic of canine influenza viral infection, whereas treated dogs should not.

[0088] The recombinant vectors and the products expressed from them can be used to produce antibodies, such as polyclonal antibodies (pAb) and monoclonal antibodies (mAb), in accordance with methods known in the art (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1988); Harlow and Lane, *Using Antibodies: A Laboratory Manual* (1998), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1998); Shepherd and Dean, *Monoclonal Antibodies: A Practical Approach*, Oxford University Press, U.S.A. (2000)); and Harris and Adair, *Antibody Therapeutics*, CRC Press, Inc., Boca Raton, FL (1997)). The antibodies, in particular mAbs, can be used in binding assays and diagnostic kits/tests to determine the presence/absence of an antigen of canine influenza virus or whether or not an immune response to the virus has been stimulated. The antibodies also can be used to recover material by immuno-adsorption chromatography.

[0089] Antibodies also can provide passive immunization. For example, partially purified immune sera from host animals or from hybridoma cell lines can be injected into an animal. The antibodies provide a therapeutic effect by binding to and neutralizing an infectious influenza virus.

[0090] A composition comprising an anti-idiotypic antibody having an internal image of an epitope of an above-described protein, such as a protein consisting of the amino acid sequence SEQ ID NO: 1 or SEQ ID NO: 3, is also provided.

[0091] One of ordinary skill in the art will appreciate that an anti-idiotypic antibody, which bears an internal image of an epitope, such as those described herein, can be prepared. See, e.g., Herlyn et al., *Science* 232: 100-102 (1986)). Methods of preparing monoclonal and polyclonal anti-idiotypic antibodies, which bear the internal image of the polypeptide, are described in U.S. Pat. No. 5,053,224, for example. Briefly, polyclonal anti-idiotypic antibodies can be produced by immunizing animals with monoclonal idiotypic antibodies raised against the polypeptide and screened for reactivity with the polypeptide and screening for antisera, which react with idiotypic antibodies to the polypeptide. Monoclonal antibodies (mAbs) also can be prepared from such animals using standard techniques of immortalizing the antibody-secreting cells of the animal and screening cultures with idiotypic antibodies in competition with the polypeptide. While mAbs are preferred, polyclonal antibodies (pAbs), which are prepared in a variety of mammalian systems, also can be used.

[0092] Another method for inducing an immune response to CIV in a canine is also provided. This method comprises administering to the canine an effective amount of a composition comprising an anti-idiotypic antibody as described above.

[0093] The isolated or purified nucleic acid molecules or vectors comprising them can be used to generate DNA for probes/primers, which can be used to detect the presence or absence of hybridizable DNA or to amplify DNA, such as cDNA.

[0094] Labeled proteins or fragments thereof, as well as labeled nucleic acids or fragments thereof, can be used in assays. Assay methods include fluoroimmunoassays (smith et al., Ann. Clin. Biochem. 18: 253-275 (1981)), radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), and enzyme-multiplied immunoassay technique (EMIT; see *Enzyme Immunoassay*, Maggio, ed., CRC Press, Inc., Boca Raton, FL, 1980. pp. 141-150; 234-235, and 242-243). Such methods can be used to detect the presence of the virus and to diagnose the state of infection.

[0095] The virus, itself, can be used as a vector. The use of viruses as vectors is within the skill in the art.

EXAMPLE

[0096] The following example serves to illustrate the present invention. The example is not intended to limit the scope of the invention in any way. The example describes the identification and partial characterization of a canine influenza virus.

[0097] Outbreaks of acute respiratory disease, characterized by cough, fever, rapid respiration, and hemorrhagic nasal discharge, occurred among greyhounds within two race track compounds located in eastern and western Iowa in April 2005. While a large percentage of affected dogs recovered, many succumbed to hemorrhagic pneumonia.

[0098] Lungs of affected dogs exhibited extensive red to red-black discoloration with moderate to marked palpable firmness and mild fibrinous pleuritis. Lung sections were characterized by severe hemorrhagic interstitial to bronchointerstitial pneumonia. Patchy interstitial change with alveolar septal thickening, coagulum of debris in alveoli, and associated atelectasis were evident. Focally extensive pyogranulomatous bronchointerstitial pneumonia with dilatation of airways by degenerate cells and debris was observed. Scattered vasculitis and vascular thrombi were apparent.

[0099] Microbiological testing for conventional viral and bacterial agents did not reveal any significant pathogens except *Streptococcus equi* subsp. *zooepidemicus*, which was present in lung tissues from all animals examined. Two of four lung samples tested positive for influenza virus using real-time reverse transcriptase-polymerase chain reaction (RT-PCR; Harmon et al., Development of a PCR-based differential test for H1N1 and H3N2 swine influenza viruses. In: *Proceedings of the 42nd Annual Meeting of American Association of Veterinary Laboratory Diagnosticians*. San Diego, CA. October 1999. p. 44.). Immunohistochemistry using monoclonal antibody (mAb) specific for the NP of influenza virus (Vincent et al., J. Vet. Diagn. Invest. 9: 191-195 (1997)) was also positive within viral pneumonic lesions of both lungs as was antigen-capturing ELISA (DirectgenTM Flu A, Becton/Dickinson, Sparks, MD) testing on the samples. Bronchioalveolar lavage samples from the two positive lungs tested positive for influenza virus by PCR.

[00100] Virus isolation was attempted because the detection of influenza virus in canine lungs was an unexpected observation, since only a single report of influenza virus infection in dogs existed (Dubovi et al., Isolation of equine influenza virus from racing greyhounds with fatal hemorrhagic pneumonia. In: *Proceedings of the 47th Annual Meeting of American Association of Veterinary Laboratory Diagnosticians*. Greensboro, NC. October

2004. p. 158.). A virus that was able to agglutinate rooster red blood cells was isolated in Madin-Darby canine kidney (MDCK) cells from lung and bronchioalveolar lavage fluid of one of the two animals in which influenza virus was detected by immunohistochemical (IHC) assay and PCR. The isolate was determined by PCR to be influenza virus of H3N8 subtype. The virus isolate was subtyped as H3N8 using HA-inhibition and NM-inhibition assays. The virus isolate was recognized by antisera raised against various H3 equine influenza viruses, including Miami ((A/Eq/MI/1/63-H3N8) 640-1280), AK((A/Eq/AK/29759/91-H3N8) 320-640), and Kentucky ((A/Eq/Kentucky/81-H3N8) 160-320).

[00101] Sequencing of HA and NA genes of both isolates revealed 100% and 99.8% identity, respectively, between the two isolates. Phylogenetically, the HA gene of the isolates was genetically close (96-98% nucleotide homology) to the HA gene of recent H3N8 equine influenza viruses (Macken et al., The value of a database in surveillance and vaccine selection. In: *Options for the Control of Influenza IV*. Osterhaus et al., eds. Elsevier Science, Amsterdam. 2001. pp. 103-106.). The NA gene of the isolates also showed 96-98% homology with the NA gene of recent H3N8 equine influenza viruses. Since greyhounds in two different race tracks, which are geographically remote in Iowa, simultaneously succumbed to the disease without the involvement of sick horses indicates that the influenza virus isolate is a canine-adapted strain that can perpetuate in and spread among dogs. *S. zooepidemicus*, which has been implicated in respiratory disease and septicemia-associated problems in many different animal species (Wood et al., J. Clin. Microbiol. 43: 120-126 (2005); and Gillespie et al., The General Staphylococcus and Streptococcus. In: *Hagan and Bruner's Infectious Diseases of Domestic Animals*. 7th ed. Comstock/Cornell University Press. Ithaca, NY. 1981. pp. 164-180)), probably contributed to the severity of the disease.

[00102]

[00103] The use of the terms "a," "an," "the," and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within

the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to illuminate better the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[00104] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. It should be understood that the illustrated embodiments are exemplary only, and should not be taken as limiting the scope of the invention.

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His	Ala	Val 35	Ala	Asn	Gly	Thr	Leu 40	Val	Lys	Thr	Met	Ser 45	Asp	Asp	Gln
Ile 50	Glu	Val	Thr	Asn	Ala	Thr 55	Glu	Leu	Val	Gln 60	Ser	Ile	Ser	Met	Gly
Lys 65	Ile	Cys	Asn	Lys	Ser 70	Tyr	Arg	Ile	Leu	Asp 75	Gly	Arg	Asn	Cys	Thr 80
Leu Ile Asp Ala Met Leu Gly Asp Pro His Cys Asp Ala Leu Gln Tyr															

14956497_1.TXT

85	90	95
Glu Ser Trp Asp 100	Leu Phe Ile Glu Arg Ser Ser Ala Phe 105	Ser Asn Cys 110
Tyr Pro Tyr Asp Ile Pro Asp Tyr Ala Ser Leu Arg Ser Ile Val Ala 115	120	125
Ser Ser Gly Thr Val Glu Phe Thr Ala Glu Gly Phe Thr Trp Thr Gly 130	135	140
Val Thr Gln Asn Gly Arg Ser Gly Ala Cys Lys Arg Gly Ser Ala Asp 145	150	155
Ser Phe Phe Ser Arg Leu Asn Trp Leu Thr Lys Ser Gly Ser Ser Tyr 165	170	175
Pro Thr Leu Asn Val Thr Met Pro Asn Asn Lys Asn Phe Asp Lys Leu 180	185	190
Tyr Ile Trp Gly Ile His His Pro Ser Ser Asn Gln Glu Gln Thr Lys 195	200	205
Leu Tyr Ile Gln Glu Ser Gly Arg Val Thr Val Ser Thr Lys Arg Ser 210	215	220
Gln Gln Thr Ile Ile Pro Asn Ile Glu Ser Arg Pro Leu Val Arg Gly 225	230	235
Gln Ser Gly Arg Ile Ser Ile Tyr Trp Thr Ile Val Lys Pro Gly Asp 245	250	255
Ile Leu Met Ile Asn Ser Asn Gly Asn Leu Val Ala Pro Arg Gly Tyr 260	265	270
Phe Lys Leu Asn Thr Gly Lys Ser Ser Val Met Arg Ser Asp Val Pro 275	280	285
Ile Asp Ile Cys Val Ser Glu Cys Ile Thr Pro Asn Gly Ser Ile Ser 290	295	300
Asn Asp Lys Pro Phe Gln Asn Val Asn Lys Val Thr Tyr Gly Lys Cys 305	310	315
Pro Lys Tyr Ile Arg Gln Asn Thr Leu Lys Leu Ala Thr Gly Met Arg 325	330	335
Asn Val Pro Glu Lys Gln Thr Arg Gly Ile Phe Gly Ala Ile Ala Gly 340	345	350

14956497_1.TXT

Phe Ile Glu Asn Gly Trp Glu Gly Met Val Asp Gly Trp Tyr Gly Phe
 355 360 365

Arg Tyr Gln Asn Ser Glu Gly Thr Gly Gln Ala Ala Asp Leu Lys Ser
 370 375 380

Thr Gln Ala Ala Ile Asp Gln Ile Asn Gly Lys Leu Asn Arg Val Ile
 385 390 395 400

Glu Arg Thr Asn Glu Lys Phe His Gln Ile Glu Lys Glu Phe Ser Glu
 405 410 415

Val Glu Gly Arg Ile Gln Asp Leu Glu Lys Tyr Val Glu Asp Thr Lys
 420 425 430

Ile Asp Leu Trp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu Glu Asn
 435 440 445

Gln His Thr Ile Asp Leu Thr Asp Ala Glu Met Asn Lys Leu Phe Glu
 450 455 460

Lys Thr Arg Arg Gln Leu Arg Glu Asn Ala Glu Asp Met Gly Gly Gly
 465 470 475 480

Cys Phe Lys Ile Tyr His Lys Cys Asp Asn Ala Cys Ile Glu Ser Ile
 485 490 495

Arg Thr Gly Thr Tyr Asp His Tyr Ile Tyr Arg Asp Glu Ala Leu Asn
 500 505 510

Asn Arg Phe Gln Ile Lys Gly Val Glu Leu Lys Ser Gly Tyr Lys Asp
 515 520 525

Trp Ile Leu Trp Ile Ser Phe Ala Ile Ser Cys Phe Leu Ile Cys Val
 530 535 540

Val Leu Leu Gly Phe Ile Met Trp Ala Cys Gln Lys Gly Asn Ile Arg
 545 550 555 560

Cys Asn Ile Cys Ile
 565

<210> 5
 <211> 1585
 <212> DNA
 <213> Influenza A Virus

<220>
 <221> CDS
 <222> (51)..(1544)

<400> 5

14956497_1.TXT

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Met Ala	
1	
tct caa ggc acc aaa cga tcc tat gaa cag atg gaa act gat ggg gaa	104
Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Asp Gly Glu	
5 10 15	
cgc cag aat gca act gaa atc aga gca tct gtc gga agg atg gtg gga	152
Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Arg Met Val Gly	
20 25 30	
gga atc gga cgg ttt tat gtc cag atg tgt act gag ctt aaa cta aac	200
Gly Ile Gly Arg Phe Tyr Val Gln Met Cys Thr Glu Leu Lys Leu Asn	
35 40 45 50	
gac cat gaa ggg cgg ctg att cag aac agc ata aca ata gaa agg atg	248
Asp His Glu Gly Arg Leu Ile Gln Asn Ser Ile Thr Ile Glu Arg Met	
55 60 65	
gta ctt tca gca ttc gac gaa aga aga aac aag tat ctc gag gag cat	296
Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu Glu His	
70 75 80	
ccc agt gct ggg aaa gac cct aag aaa acg gga ggc ccg ata tac aga	344
Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile Tyr Arg	
85 90 95	
aga aaa gat ggg aaa tgg atg agg gaa ctc atc ctc cat gat aaa gaa	392
Arg Lys Asp Gly Lys Trp Met Arg Glu Leu Ile Leu His Asp Lys Glu	
100 105 110	
gaa atc atg aga atc tgg cgt cag gcc aac aat ggt gaa gac gct act	440
Glu Ile Met Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp Ala Thr	
115 120 125 130	
gct ggt ctt act cat atg atg atc tgg cac tcc aat ctc aat gac acc	488
Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn Asp Thr	
135 140 145	
aca tac caa aga aca agg gct ctt gtt cgg act ggg atg gat ccc aga	536
Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp Pro Arg	
150 155 160	
atg tgc tct ctg atg caa ggc tca acc ctc cca cgg aga tct gga gcc	584
Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser Gly Ala	
165 170 175	
gct ggt gct gca gta aaa ggt gtt gga aca atg gta atg gaa ctc atc	632
Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu Leu Ile	
180 185 190	
agg atg atc aaa cgc gga ata aat gat cgg aat ttc tgg aga ggt gaa	680
Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg Gly Glu	
195 200 205 210	
aat ggt cga aga acc aga att gct tat gaa aga atg tgc aat atc ctc	728
Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn Ile Leu	
215 220 225	
aaa ggg aaa ttt cag aca gca gca caa cgg gct atg atg gac cag gtg	776
Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp Gln Val	
230 235 240	
agg gaa ggc cgc aat cct gga aac gct gag att gag gat ctc att ttc	824
Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu Ile Phe	
245 250 255	

14956497_1.TXT

ttg gca cga tca gca ctt att ttg aga gga tca gta gcc cat aaa tca	872
Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His Lys Ser	
260 265 270	
tgc cta cct gcc tgt gtt tat ggc ctt gca gta acc agt ggg tat gac	920
Cys Leu Pro Ala Cys Val Tyr Gly Leu Ala Val Thr Ser Gly Tyr Asp	
275 280 285 290	
ttt gag aag gaa gga tac tct ctg gtt gga att gat cct ttc aaa cta	968
Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe Lys Leu	
295 300 305	
ctc cag aac agt caa att ttc agt cta atc aga cca aaa gaa aac cca	1016
Leu Gln Asn Ser Gln Ile Phe Ser Leu Ile Arg Pro Lys Glu Asn Pro	
310 315 320	
gca cac aaa agc cag ttg gtg tgg atg gca tgc cat tct gca gca ttt	1064
Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala Ala Phe	
325 330 335	
gag gat ctg aga gtt tta aat ttc att aga gga acc aaa gta atc cca	1112
Glu Asp Leu Arg Val Leu Asn Phe Ile Arg Gly Thr Lys Val Ile Pro	
340 345 350	
aga gga cag tta aca acc aga gga gtt caa att gct tca aat gaa aac	1160
Arg Gly Gln Leu Thr Thr Arg Gly Val Gln Ile Ala Ser Asn Glu Asn	
355 360 365 370	
atg gag aca ata aat tct agc aca ctt gaa ctg aga agc aaa tat tgg	1208
Met Glu Thr Ile Asn Ser Ser Thr Leu Glu Leu Arg Ser Lys Tyr Trp	
375 380 385	
gca ata agg acc aga agc gga gga aac acc agt caa cag aga gca ttt	1256
Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Ser Gln Gln Arg Ala Phe	
390 395 400	
gca gga cag ata agt gtg caa cct act ttc tca gta cag aga aat ctt	1304
Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg Asn Leu	
405 410 415	
ccc ttt gag aga gca acc att atg gct gca ttc act ggt aac act gaa	1352
Pro Phe Glu Arg Ala Thr Ile Met Ala Ala Phe Thr Gly Asn Thr Glu	
420 425 430	
ggg agg act tcc gac atg aga acg gaa atc ata agg atg atg gaa aat	1400
Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met Glu Asn	
435 440 445 450	
gcc aaa tca gaa gat gtg tct ttc cag ggg cgg gga gtc ttc gag ctc	1448
Ala Lys Ser Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe Glu Leu	
455 460 465	
tcg gac gaa aag gca acg aac ccg atc gtg cct tcc ttt gac atg agc	1496
Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp Met Ser	
470 475 480	
aat gaa ggg tct tat ttc ttc gga gac aat gct gag gag ttt gac agt	1544
Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Phe Asp Ser	
485 490 495	
taaagaaaaa tacccttggt tctactaata cgagacgata t	1585

<210> 6
 <211> 498
 <212> PRT

14956497_1.TXT

<213> Influenza A Virus

<400> 6

Met Ala Ser Gln Gly Thr Lys Arg Ser Tyr Glu Gln Met Glu Thr Asp
 1 5 10 15

Gly Glu Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Arg Met
 20 25 30

Val Gly Gly Ile Gly Arg Phe Tyr Val Gln Met Cys Thr Glu Leu Lys
 35 40 45

Leu Asn Asp His Glu Gly Arg Leu Ile Gln Asn Ser Ile Thr Ile Glu
 50 55 60

Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu
 65 70 75 80

Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
 85 90 95

Tyr Arg Arg Lys Asp Gly Lys Trp Met Arg Glu Leu Ile Leu His Asp
 100 105 110

Lys Glu Glu Ile Met Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp
 115 120 125

Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
 130 135 140

Asp Thr Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
 145 150 155 160

Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser
 165 170 175

Gly Ala Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu
 180 185 190

Leu Ile Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
 195 200 205

Gly Glu Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn
 210 215 220

Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp
 225 230 235 240

Gln Val Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu
 245 250 255

14956497_1.TXT

Ile Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
 260 265 270

Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Leu Ala Val Thr Ser Gly
 275 280 285

Tyr Asp Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe
 290 295 300

Lys Leu Leu Gln Asn Ser Gln Ile Phe Ser Leu Ile Arg Pro Lys Glu
 305 310 315 320

Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala
 325 330 335

Ala Phe Glu Asp Leu Arg Val Leu Asn Phe Ile Arg Gly Thr Lys Val
 340 345 350

Ile Pro Arg Gly Gln Leu Thr Thr Arg Gly Val Gln Ile Ala Ser Asn
 355 360 365

Glu Asn Met Glu Thr Ile Asn Ser Ser Thr Leu Glu Leu Arg Ser Lys
 370 375 380

Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Ser Gln Gln Arg
 385 390 395 400

Ala Phe Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg
 405 410 415

Asn Leu Pro Phe Glu Arg Ala Thr Ile Met Ala Ala Phe Thr Gly Asn
 420 425 430

Thr Glu Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met
 435 440 445

Glu Asn Ala Lys Ser Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe
 450 455 460

Glu Leu Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp
 465 470 475 480

Met Ser Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Phe
 485 490 495

Asp Ser

<210> 7
 <211> 1056

14956497_1.TXT

<212> DNA
<213> Influenza A virus

<220>
<221> CDS
<222> (40) .. (795)

<400> 7																			
tattcgtctc	agggagcaaa	agcaggtaga	tattttaag	atg	agt	ctt	cta	acc								54			
				Met	Ser	Leu	Leu	Thr											
				1								5							
gag	gtc	gaa	acg	tac	gtt	ctc	tct	atc	gta	cca	tca	ggc	ccc	ctc	aaa	102			
Glu	Val	Glu	Thr	Tyr	Val	Leu	Ser	Ile	Val	Pro	Ser	Gly	Pro	Leu	Lys				
				10								15					20		
gcc	gag	atc	gcg	cag	aga	ctt	gaa	gat	gtc	ttt	gcg	gga	aag	aac	acc	150			
Ala	Glu	Ile	Ala	Gln	Arg	Leu	Glu	Asp	Val	Phe	Ala	Gly	Lys	Asn	Thr				
				25								30					35		
gat	ctt	gag	gca	ctc	atg	gaa	tgg	cta	aag	aca	aga	cca	atc	ctg	tca	198			
Asp	Leu	Glu	Ala	Leu	Met	Glu	Trp	Leu	Lys	Thr	Arg	Pro	Ile	Leu	Ser				
				40								45					50		
cct	ctg	act	aaa	ggg	att	tta	gga	ttt	gta	ttc	acg	ctc	acc	gtg	ccc	246			
Pro	Leu	Thr	Lys	Gly	Ile	Leu	Gly	Phe	Val	Phe	Thr	Leu	Thr	Val	Pro				
				55								60					65		
agt	gag	cga	gga	ctg	cag	cgt	aga	cgc	ttt	gtc	caa	aat	gcc	ctt	agt	294			
Ser	Glu	Arg	Gly	Leu	Gln	Arg	Arg	Arg	Phe	Val	Gln	Asn	Ala	Leu	Ser				
				70								75					80	85	
gga	aac	gga	gat	cca	aac	aac	atg	gac	aga	gca	gta	aaa	ctg	tac	agg	342			
Gly	Asn	Gly	Asp	Pro	Asn	Asn	Met	Asp	Arg	Ala	Val	Lys	Leu	Tyr	Arg				
				90								95					100		
aag	ctt	aaa	aga	gaa	ata	aca	ttc	cat	gag	gca	aaa	gag	gtg	gca	ctc	390			
Lys	Leu	Lys	Arg	Glu	Ile	Thr	Phe	His	Glu	Ala	Lys	Glu	Val	Ala	Leu				
				105								110					115		
agc	tat	tcc	act	ggt	gca	cta	gcc	agc	tgc	atg	gga	ctc	ata	tac	aac	438			
Ser	Tyr	Ser	Thr	Gly	Ala	Leu	Ala	Ser	Cys	Met	Gly	Leu	Ile	Tyr	Asn				
				120								125					130		
aga	atg	gga	act	gtt	aca	acc	gaa	gtg	gca	ttt	ggc	ctg	gta	tgc	gcc	486			
Arg	Met	Gly	Thr	Val	Thr	Thr	Glu	Val	Ala	Phe	Gly	Leu	Val	Cys	Ala				
				135								140					145		
aca	tgt	gaa	cag	att	gct	gat	tcc	cag	cat	cga	tct	cac	agg	cag	atg	534			
Thr	Cys	Glu	Gln	Ile	Ala	Asp	Ser	Gln	His	Arg	Ser	His	Arg	Gln	Met				
				150								155					160	165	
gtg	aca	aca	acc	aac	cca	tta	atc	aga	cat	gaa	aac	aga	atg	gta	tta	582			
Val	Thr	Thr	Thr	Asn	Pro	Leu	Ile	Arg	His	Glu	Asn	Arg	Met	Val	Leu				
				170								175					180		
gcc	agt	acc	acg	gct	aaa	gcc	atg	gaa	cag	atg	gca	gga	tcg	agt	gag	630			
Ala	Ser	Thr	Thr	Ala	Lys	Ala	Met	Glu	Gln	Met	Ala	Gly	Ser	Ser	Glu				
				185								190					195		
cag	gca	gca	gag	gcc	atg	gag	gtt	gct	agt	agg	gct	agg	cag	atg	gta	678			
Gln	Ala	Ala	Glu	Ala	Met	Glu	Val	Ala	Ser	Arg	Ala	Arg	Gln	Met	Val				
				200								205					210		
cag	gca	atg	aga	acc	att	ggg	acc	cac	cct	agc	tcc	agt	gcc	ggg	ttg	726			
Gln	Ala	Met	Arg	Thr	Ile	Gly	Thr	His	Pro	Ser	Ser	Ser	Ala	Gly	Leu				

14956497_1.TXT

215	220	225	
aaa gat gat ctc ctt gaa aat tta cag gcc tac cag aaa cgg atg gga			774
Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr Gln Lys Arg Met Gly			
230	235	240	245
gtg caa atg cag cga ttc aag tgatcctctc gttattgcag caagtatcat			825
Val Gln Met Gln Arg Phe Lys			
	250		
tggaatcttg cacttgatat tgtggattct tgatcgtctt ttcttcaaat tcatttatcg			885
tcgccttaaa tacgggttga aaagagggcc ttctacggaa ggagtacctg agtctatgag			945
ggaagaatat cggcaggaac agcagaatgc tgtggatggt gacgatggtc attttgtcaa			1005
catagagctg gagtaaaaaa ctaccttggt tctactaata cgagacgata t			1056

<210> 8
 <211> 252
 <212> PRT
 <213> Influenza A virus

<400> 8

Met Ser Leu Leu Thr Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro	
1 5 10 15	
Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe	
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Ala Gly Lys Asn Thr Asp Leu Glu Ala Leu Met Glu Trp Leu Lys Thr	
35 40 45	
Arg Pro Ile Leu Ser Pro Leu Thr Lys Gly Ile Leu Gly Phe Val Phe	
50 55 60	
Thr Leu Thr Val Pro Ser Glu Arg Gly Leu Gln Arg Arg Arg Phe Val	
65 70 75 80	
Gln Asn Ala Leu Ser Gly Asn Gly Asp Pro Asn Asn Met Asp Arg Ala	
85 90 95	
Val Lys Leu Tyr Arg Lys Leu Lys Arg Glu Ile Thr Phe His Glu Ala	
100 105 110	
Lys Glu Val Ala Leu Ser Tyr Ser Thr Gly Ala Leu Ala Ser Cys Met	
115 120 125	
Gly Leu Ile Tyr Asn Arg Met Gly Thr Val Thr Thr Glu Val Ala Phe	
130 135 140	
Gly Leu Val Cys Ala Thr Cys Glu Gln Ile Ala Asp Ser Gln His Arg	
145 150 155 160	
Ser His Arg Gln Met Val Thr Thr Thr Asn Pro Leu Ile Arg His Glu	

14956497_1.TXT
170

165

175

Asn Arg Met Val Leu Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met
180 185 190

Ala Gly Ser Ser Glu Gln Ala Ala Glu Ala Met Glu Val Ala Ser Arg
195 200 205

Ala Arg Gln Met Val Gln Ala Met Arg Thr Ile Gly Thr His Pro Ser
210 215 220

Ser Ser Ala Gly Leu Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr
225 230 235 240

Gln Lys Arg Met Gly Val Gln Met Gln Arg Phe Lys
245 250

<210> 9
<211> 870
<212> DNA
<213> Influenza A virus

<220>
<221> CDS
<222> (29)..(718)

<400> 9
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Met Asp Ser Asn Thr Val Ser Ser
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ttt cag gta gac tgt ttt ctt tgg cat gtc cgc aaa cga ttc gca gac 100
Phe Gln Val Asp Cys Phe Leu Trp His Val Arg Lys Arg Phe Ala Asp
10 15 20

caa gaa ctg ggt gat gcc cca ttc ctt gac cgg ctt cgc cga gac cag 148
Gln Glu Leu Gly Asp Ala Pro Phe Leu Asp Arg Leu Arg Arg Asp Gln
25 30 35 40

aag tcc cta agg gga aga ggt agc act ctt ggt ctg gac atc gaa aca 196
Lys Ser Leu Arg Gly Arg Gly Ser Thr Leu Gly Leu Asp Ile Glu Thr
45 50 55

gcc act cat gca gga aag cag ata gtg gag cag att ctg gaa aag gaa 244
Ala Thr His Ala Gly Lys Gln Ile Val Glu Gln Ile Leu Glu Lys Glu
60 65 70

tca gat gag gca ctt aaa atg acc att gcc tct gtt cct gct tca cgc 292
Ser Asp Glu Ala Leu Lys Met Thr Ile Ala Ser Val Pro Ala Ser Arg
75 80 85

tac tta act gac atg act ctt gat gag atg tca aga gac tgg ttc atg 340
Tyr Leu Thr Asp Met Thr Leu Asp Glu Met Ser Arg Asp Trp Phe Met
90 95 100

ctc atg ccc aag caa aaa gta aca ggc tcc cta tgt ata aga atg gac 388
Leu Met Pro Lys Gln Lys Val Thr Gly Ser Leu Cys Ile Arg Met Asp
105 110 115 120

caa gca atc atg gat aag aac atc ata ctt aaa gca aac ttt agt gtg 436

14956497_1.TXT

Gln Ala Ile Met Asp Lys Asn Ile Ile Leu Lys Ala Asn Phe Ser Val
 125 130 135

att ttc gaa agg ctg gaa aca cta ata cta ctt aga gcc ttc acc gaa 484
 Ile Phe Glu Arg Leu Glu Thr Leu Ile Leu Leu Arg Ala Phe Thr Glu
 140 145 150

gaa gga gca gtc gtt ggc gaa att tca cca tta cct tct ctt cca gga 532
 Glu Gly Ala Val Val Gly Glu Ile Ser Pro Leu Pro Ser Leu Pro Gly
 155 160 165

cat act aat gag gat gtc aaa aat gca att ggg gtc ctc atc gga gga 580
 His Thr Asn Glu Asp Val Lys Asn Ala Ile Gly Val Leu Ile Gly Gly
 170 175 180

ctt aaa tgg aat gat aat acg gtt aga atc tct gaa act cta cag aga 628
 Leu Lys Trp Asn Asp Asn Thr Val Arg Ile Ser Glu Thr Leu Gln Arg
 185 190 195 200

ttc gct tgg aga agc agt cat gaa aat ggg aga cct tca ttc cct tca 676
 Phe Ala Trp Arg Ser Ser His Glu Asn Gly Arg Pro Ser Phe Pro Ser
 205 210 215

aag cag aaa cga aaa atg gag aga aca att aag cca gaa att 718
 Lys Gln Lys Arg Lys Met Glu Arg Thr Ile Lys Pro Glu Ile
 220 225 230

tgaagaaata agatgggttga ttgaagaagt gcgacataga ttgaaaaata cagaaaatag 778

ttttgaacaa ataacattta tgcaagcctt acaactattg cttgaagtag aacaagagat 838

aagaactttc tcgttttcagc ttattttaatg at 870

<210> 10
 <211> 230
 <212> PRT
 <213> Influenza A virus

<400> 10

Met Asp Ser Asn Thr Val Ser Ser Phe Gln Val Asp Cys Phe Leu Trp
 1 5 10 15

His Val Arg Lys Arg Phe Ala Asp Gln Glu Leu Gly Asp Ala Pro Phe
 20 25 30

Leu Asp Arg Leu Arg Arg Asp Gln Lys Ser Leu Arg Gly Arg Gly Ser
 35 40 45

Thr Leu Gly Leu Asp Ile Glu Thr Ala Thr His Ala Gly Lys Gln Ile
 50 55 60

Val Glu Gln Ile Leu Glu Lys Glu Ser Asp Glu Ala Leu Lys Met Thr
 65 70 75 80

Ile Ala Ser Val Pro Ala Ser Arg Tyr Leu Thr Asp Met Thr Leu Asp
 85 90 95

Glu Met Ser Arg Asp Trp Phe Met Leu Met Pro Lys Gln Lys Val Thr
 100 105 110

14956497_1.TXT

Gly Ser Leu Cys Ile Arg Met Asp Gln Ala Ile Met Asp Lys Asn Ile
 115 120 125

Ile Leu Lys Ala Asn Phe Ser Val Ile Phe Glu Arg Leu Glu Thr Leu
 130 135 140

Ile Leu Leu Arg Ala Phe Thr Glu Glu Gly Ala Val Val Gly Glu Ile
 145 150 155 160

Ser Pro Leu Pro Ser Leu Pro Gly His Thr Asn Glu Asp Val Lys Asn
 165 170 175

Ala Ile Gly Val Leu Ile Gly Gly Leu Lys Trp Asn Asp Asn Thr Val
 180 185 190

Arg Ile Ser Glu Thr Leu Gln Arg Phe Ala Trp Arg Ser Ser His Glu
 195 200 205

Asn Gly Arg Pro Ser Phe Pro Ser Lys Gln Lys Arg Lys Met Glu Arg
 210 215 220

Thr Ile Lys Pro Glu Ile
 225 230

<210> 11
 <211> 2191
 <212> DNA
 <213> Influenza A virus

<220>
 <221> CDS
 <222> (4)..(2151)

<400> 11
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 Met Glu Asp Phe Val Arg Gln Cys Phe Asn Pro Met Ile Val Glu
 1 5 10 15
 ctt gcg gaa aag gca atg aaa gaa tat gga gag aac ccg aaa atc gaa 96
 Leu Ala Glu Lys Ala Met Lys Glu Tyr Gly Glu Asn Pro Lys Ile Glu
 20 25 30
 aca aac aaa ttt gca gca ata tgc act cac ttg gaa gtc tgc ttc atg 144
 Thr Asn Lys Phe Ala Ala Ile Cys Thr His Leu Glu Val Cys Phe Met
 35 40 45
 tac tcg gat ttc cac ttt ata aat gaa ctg ggt gag tca gtg gtc ata 192
 Tyr Ser Asp Phe His Phe Ile Asn Glu Leu Gly Glu Ser Val Val Ile
 50 55 60
 gag tct ggt gac cca aat gct ctt ttg aaa cac aga ttt gaa atc att 240
 Glu Ser Gly Asp Pro Asn Ala Leu Leu Lys His Arg Phe Glu Ile Ile
 65 70 75
 gag ggg aga gat cga aca atg gca tgg aca gta gta aac agc atc tgc 288
 Glu Gly Arg Asp Arg Thr Met Ala Trp Thr Val Val Asn Ser Ile Cys

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80	85	90	95													
aac Asn	acc Thr	aca Thr	aga Arg	gct Ala 100	gaa Glu	aaa Lys	cct Pro	aaa Lys	ttt Phe 105	ctt Leu	cca Pro	gat Asp	tta Leu	tac Tyr 110	gac Asp	336
tat Tyr	aag Lys	gag Glu	aac Asn 115	aga Arg	ttt Phe	gtt Val	gaa Glu	att Ile 120	ggt Gly	gtg Val	aca Thr	agg Arg	aga Arg 125	gaa Glu	gtt Val	384
cac His	ata Ile	tac Tyr 130	tac Tyr	ctg Leu	gag Glu	aaa Lys	gcc Ala 135	aac Asn	aaa Lys	ata Ile	aag Lys	tct Ser 140	gag Glu	aaa Lys	aca Thr	432
cat His	atc Ile 145	cac His	att Ile	ttc Phe	tca Ser	ttt Phe 150	aca Thr	gga Gly	gaa Glu	gaa Glu	atg Met 155	gct Ala	aca Thr	aaa Lys	gcg Ala	480
gac Asp 160	tat Tyr	act Thr	ctt Leu	gat Asp	gaa Glu 165	gag Glu	agt Ser	aga Arg	gcc Ala	agg Arg 170	atc Ile	aag Lys	acc Thr	aga Arg	cta Leu 175	528
ttc Phe	act Thr	ata Ile	aga Arg	caa Gln 180	gaa Glu	atg Met	gcc Ala	agt Ser	aga Arg 185	ggc Gly	ctc Leu	tgg Trp	gat Asp	tcc Ser 190	ttt Phe	576
cgt Arg	cag Gln	tcc Ser	gag Glu 195	aga Arg	ggc Gly	gaa Glu	gag Glu	aca Thr 200	att Ile	gaa Glu	gaa Glu	aga Arg	ttt Phe 205	gaa Glu	atc Ile	624
aca Thr	gga Gly 210	acg Thr	atg Met	cgc Arg	aag Lys	ctt Leu	gcc Ala 215	aat Asn	tac Tyr	agt Ser	ctc Leu	cca Pro 220	ccg Pro	aac Asn	ttc Phe	672
tcc Ser	agc Ser 225	ctt Leu	gaa Glu	aat Asn	ttt Phe	aga Arg 230	gtc Val	tat Tyr	ata Ile	gat Asp	gga Gly 235	ttc Phe	gaa Glu	ccg Pro	aac Asn	720
ggc Gly 240	tgc Cys	att Ile	gag Glu	agt Ser	aag Lys 245	ctt Leu	tct Ser	caa Gln	atg Met	tcc Ser 250	aaa Lys	gaa Glu	gta Val	aat Asn	gcc Ala 255	768
aaa Lys	atc Ile	gaa Glu	cca Pro	ttt Phe 260	tca Ser	aag Lys	aca Thr	aca Thr	ccc Pro 265	cga Arg	cca Pro	ctc Leu	aaa Lys	atg Met 270	cca Pro	816
ggt Gly	ggt Gly	cca Pro	ccc Pro 275	tgc Cys	cat His	cag Gln	cga Arg	tcc Ser 280	aaa Lys	ttc Phe	ttg Leu	cta Leu	atg Met 285	gat Asp	gct Ala	864
ctg Leu	aaa Lys	ctg Leu 290	agc Ser	att Ile	gag Glu	gac Asp	cca Pro 295	agt Ser	cac His	gag Glu	gga Gly	gag Glu 300	ggg Gly	ata Ile	cca Pro	912
cta Leu	tat Tyr 305	gat Asp	gca Ala	atc Ile	aaa Lys	tgc Cys 310	atg Met	aaa Lys	act Thr	ttc Phe	ttt Phe 315	gga Gly	tgg Trp	aaa Lys	gag Glu	960
ccc Pro 320	agt Ser	att Ile	gtt Val	aaa Lys	cca Pro 325	cat His	aaa Lys	aag Lys	ggt Gly	ata Ile 330	aac Asn	ccg Pro	aac Asn	tat Tyr	ctc Leu 335	1008
caa Gln	act Thr	tgg Trp	aag Lys	caa Gln 340	gta Val	tta Leu	gaa Glu	gaa Glu	ata Ile 345	caa Gln	gac Asp	ctt Leu	gag Glu	aac Asn 350	gaa Glu	1056
gaa	agg	acc	ccc	aag	acc	aag	aat	atg	aaa	aaa	aca	agc	caa	ttg	aaa	1104

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Glu	Arg	Thr	Pro	Lys	Thr	Lys	Asn	Met	Lys	Lys	Thr	Ser	Gln	Leu	Lys	
			355					360					365			
tgg	gca	cta	ggt	gaa	aat	atg	gca	cca	gag	aaa	gtg	gat	ttt	gag	gat	1152
Trp	Ala	Leu	Gly	Glu	Asn	Met	Ala	Pro	Glu	Lys	Val	Asp	Phe	Glu	Asp	
		370					375					380				
tgt	aaa	gac	atc	aat	gat	tta	aaa	caa	tat	gac	agt	gat	gag	cca	gaa	1200
Cys	Lys	Asp	Ile	Asn	Asp	Leu	Lys	Gln	Tyr	Asp	Ser	Asp	Glu	Pro	Glu	
	385					390					395					
gca	agg	tct	ctt	gca	agt	tgg	att	caa	agt	gag	ttc	aac	aag	gct	tgt	1248
Ala	Arg	Ser	Leu	Ala	Ser	Trp	Ile	Gln	Ser	Glu	Phe	Asn	Lys	Ala	Cys	
400					405					410					415	
gag	ctg	aca	gat	tca	agc	tgg	ata	gag	ctc	gat	gaa	att	ggg	gag	gat	1296
Glu	Leu	Thr	Asp	Ser	Ser	Trp	Ile	Glu	Leu	Asp	Glu	Ile	Gly	Glu	Asp	
				420					425					430		
gtc	gcc	cca	ata	gaa	tac	att	gcg	agc	atg	agg	aga	aat	tat	ttt	act	1344
Val	Ala	Pro	Ile	Glu	Tyr	Ile	Ala	Ser	Met	Arg	Arg	Asn	Tyr	Phe	Thr	
			435					440					445			
gct	gag	att	tcc	cat	tgt	aga	gca	aca	gaa	tat	ata	atg	aaa	gga	gta	1392
Ala	Glu	Ile	Ser	His	Cys	Arg	Ala	Thr	Glu	Tyr	Ile	Met	Lys	Gly	Val	
		450					455					460				
tac	atc	aac	act	gct	cta	ctc	aat	gca	tcc	tgt	gct	gcg	atg	gat	gaa	1440
Tyr	Ile	Asn	Thr	Ala	Leu	Leu	Asn	Ala	Ser	Cys	Ala	Ala	Met	Asp	Glu	
	465					470					475					
ttt	caa	tta	att	ccg	atg	ata	agt	aaa	tgc	agg	acc	aaa	gaa	ggg	aga	1488
Phe	Gln	Leu	Ile	Pro	Met	Ile	Ser	Lys	Cys	Arg	Thr	Lys	Glu	Gly	Arg	
480					485				490						495	
agg	aaa	aca	aat	tta	tat	gga	ttc	ata	ata	aag	gga	agg	tcc	cat	tta	1536
Arg	Lys	Thr	Asn	Leu	Tyr	Gly	Phe	Ile	Ile	Lys	Gly	Arg	Ser	His	Leu	
				500					505					510		
aga	aat	gat	act	gac	gtg	gtg	aac	ttt	gta	agt	atg	gaa	ttt	tct	ctc	1584
Arg	Asn	Asp	Thr	Asp	Val	Val	Asn	Phe	Val	Ser	Met	Glu	Phe	Ser	Leu	
			515					520					525			
act	gat	cca	aga	ttt	gag	cca	cac	aaa	tgg	gaa	aaa	tac	tgc	gtt	cta	1632
Thr	Asp	Pro	Arg	Phe	Glu	Pro	His	Lys	Trp	Glu	Lys	Tyr	Cys	Val	Leu	
		530					535					540				
gaa	att	gga	gac	atg	ctt	cta	aga	act	gct	gta	ggt	caa	gtg	tca	aga	1680
Glu	Ile	Gly	Asp	Met	Leu	Leu	Arg	Thr	Ala	Val	Gly	Gln	Val	Ser	Arg	
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ccc	ata	ttt	ttg	tat	gta	agg	aca	aat	gga	acc	tct	aaa	att	aaa	atg	1728
Pro	Ile	Phe	Leu	Tyr	Val	Arg	Thr	Asn	Gly	Thr	Ser	Lys	Ile	Lys	Met	
560					565					570					575	
aaa	tgg	gga	atg	gaa	atg	aga	cgc	tgc	ctc	ctt	cag	tct	ctg	caa	cag	1776
Lys	Trp	Gly	Met	Glu	Met	Arg	Arg	Cys	Leu	Leu	Gln	Ser	Leu	Gln	Gln	
				580				585						590		
att	gaa	agc	atg	atc	gaa	gct	gag	tcc	tca	gtc	aaa	gaa	aag	gac	atg	1824
Ile	Glu	Ser	Met	Ile	Glu	Ala	Glu	Ser	Ser	Val	Lys	Glu	Lys	Asp	Met	
			595					600					605			
acc	aaa	gaa	ttt	ttt	gag	aac	aaa	tca	gag	aca	tgg	cct	ata	gga	gag	1872
Thr	Lys	Glu	Phe	Phe	Glu	Asn	Lys	Ser	Glu	Thr	Trp	Pro	Ile	Gly	Glu	
		610					615					620				

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tcc Ser	ccc Pro	aaa Lys	gga Gly	gtg Val	gaa Glu	gag Glu	ggc Gly	tca Ser	atc Ile	ggg Gly	aag Lys	gtt Val	tgc Cys	agg Arg	acc Thr	1920
625					630		635									
tta Leu	tta Leu	gca Ala	aaa Lys	tct Ser	gtg Val	ttt Phe	aac Asn	agt Ser	tta Leu	tat Tyr	gca Ala	tct Ser	cca Pro	caa Gln	ctg Leu	1968
640					645				650						655	
gaa Glu	gga Gly	ttt Phe	tca Ser	gct Ala	gaa Glu	tct Ser	agg Arg	aaa Lys	tta Leu	ctt Leu	ctc Leu	att Ile	gtt Val	cag Gln	gct Ala	2016
				660					665					670		
ctt Leu	aga Arg	gat Asp	gac Asp	ctg Leu	gaa Glu	cct Pro	gga Gly	acc Thr	ttt Phe	gat Asp	att Ile	ggg Gly	ggg Gly	tta Leu	tat Tyr	2064
			675					680					685			
gaa Glu	tca Ser	att Ile	gag Glu	gag Glu	tgc Cys	ctg Leu	att Ile	aat Asn	gat Asp	ccc Pro	tgg Trp	gtt Val	ttg Leu	ctt Leu	aat Asn	2112
		690					695					700				
gca Ala	tct Ser	tgg Trp	ttc Phe	aac Asn	tcc Ser	ttc Phe	ctc Leu	aca Thr	cat His	gca Ala	ctg Leu	aag Lys	tagttgtggc			2161
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			20					25					30		
Asn	Lys	Phe	Ala	Ala	Ile	Cys	Thr	His	Leu	Glu	Val	Cys	Phe	Met	Tyr
		35					40					45			
Ser	Asp	Phe	His	Phe	Ile	Asn	Glu	Leu	Gly	Glu	Ser	Val	Val	Ile	Glu
	50					55					60				
Ser	Gly	Asp	Pro	Asn	Ala	Leu	Leu	Lys	His	Arg	Phe	Glu	Ile	Ile	Glu
65					70					75					80
Gly	Arg	Asp	Arg	Thr	Met	Ala	Trp	Thr	Val	Val	Asn	Ser	Ile	Cys	Asn
				85					90					95	
Thr	Thr	Arg	Ala	Glu	Lys	Pro	Lys	Phe	Leu	Pro	Asp	Leu	Tyr	Asp	Tyr
			100					105					110		
Lys	Glu	Asn	Arg	Phe	Val	Glu	Ile	Gly	Val	Thr	Arg	Arg	Glu	Val	His
		115					120					125			
Ile	Tyr	Tyr	Leu	Glu	Lys	Ala	Asn	Lys	Ile	Lys	Ser	Glu	Lys	Thr	His

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140

130

135

Ile His Ile Phe Ser Phe Thr Gly Glu Glu Met Ala Thr Lys Ala Asp
 145 150 155 160
 Tyr Thr Leu Asp Glu Glu Ser Arg Ala Arg Ile Lys Thr Arg Leu Phe
 165 170 175
 Thr Ile Arg Gln Glu Met Ala Ser Arg Gly Leu Trp Asp Ser Phe Arg
 180 185 190
 Gln Ser Glu Arg Gly Glu Glu Thr Ile Glu Glu Arg Phe Glu Ile Thr
 195 200 205
 Gly Thr Met Arg Lys Leu Ala Asn Tyr Ser Leu Pro Pro Asn Phe Ser
 210 215 220
 Ser Leu Glu Asn Phe Arg Val Tyr Ile Asp Gly Phe Glu Pro Asn Gly
 225 230 235 240
 Cys Ile Glu Ser Lys Leu Ser Gln Met Ser Lys Glu Val Asn Ala Lys
 245 250 255
 Ile Glu Pro Phe Ser Lys Thr Thr Pro Arg Pro Leu Lys Met Pro Gly
 260 265 270
 Gly Pro Pro Cys His Gln Arg Ser Lys Phe Leu Leu Met Asp Ala Leu
 275 280 285
 Lys Leu Ser Ile Glu Asp Pro Ser His Glu Gly Glu Gly Ile Pro Leu
 290 295 300
 Tyr Asp Ala Ile Lys Cys Met Lys Thr Phe Phe Gly Trp Lys Glu Pro
 305 310 315 320
 Ser Ile Val Lys Pro His Lys Lys Gly Ile Asn Pro Asn Tyr Leu Gln
 325 330 335
 Thr Trp Lys Gln Val Leu Glu Glu Ile Gln Asp Leu Glu Asn Glu Glu
 340 345 350
 Arg Thr Pro Lys Thr Lys Asn Met Lys Lys Thr Ser Gln Leu Lys Trp
 355 360 365
 Ala Leu Gly Glu Asn Met Ala Pro Glu Lys Val Asp Phe Glu Asp Cys
 370 375 380
 Lys Asp Ile Asn Asp Leu Lys Gln Tyr Asp Ser Asp Glu Pro Glu Ala
 385 390 395 400

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Arg Ser Leu Ala Ser Trp Ile Gln Ser Glu Phe Asn Lys Ala Cys Glu
 405 410 415
 Leu Thr Asp Ser Ser Trp Ile Glu Leu Asp Glu Ile Gly Glu Asp Val
 420 425 430
 Ala Pro Ile Glu Tyr Ile Ala Ser Met Arg Arg Asn Tyr Phe Thr Ala
 435 440 445
 Glu Ile Ser His Cys Arg Ala Thr Glu Tyr Ile Met Lys Gly Val Tyr
 450 455 460
 Ile Asn Thr Ala Leu Leu Asn Ala Ser Cys Ala Ala Met Asp Glu Phe
 465 470 475 480
 Gln Leu Ile Pro Met Ile Ser Lys Cys Arg Thr Lys Glu Gly Arg Arg
 485 490 495
 Lys Thr Asn Leu Tyr Gly Phe Ile Ile Lys Gly Arg Ser His Leu Arg
 500 505 510
 Asn Asp Thr Asp Val Val Asn Phe Val Ser Met Glu Phe Ser Leu Thr
 515 520 525
 Asp Pro Arg Phe Glu Pro His Lys Trp Glu Lys Tyr Cys Val Leu Glu
 530 535 540
 Ile Gly Asp Met Leu Leu Arg Thr Ala Val Gly Gln Val Ser Arg Pro
 545 550 555 560
 Ile Phe Leu Tyr Val Arg Thr Asn Gly Thr Ser Lys Ile Lys Met Lys
 565 570 575
 Trp Gly Met Glu Met Arg Arg Cys Leu Leu Gln Ser Leu Gln Gln Ile
 580 585 590
 Glu Ser Met Ile Glu Ala Glu Ser Ser Val Lys Glu Lys Asp Met Thr
 595 600 605
 Lys Glu Phe Phe Glu Asn Lys Ser Glu Thr Trp Pro Ile Gly Glu Ser
 610 615 620
 Pro Lys Gly Val Glu Glu Gly Ser Ile Gly Lys Val Cys Arg Thr Leu
 625 630 635 640
 Leu Ala Lys Ser Val Phe Asn Ser Leu Tyr Ala Ser Pro Gln Leu Glu
 645 650 655
 Gly Phe Ser Ala Glu Ser Arg Lys Leu Leu Leu Ile Val Gln Ala Leu
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Arg Asp Asp Leu Glu Pro Gly Thr Phe Asp Ile Gly Gly Leu Tyr Glu
675 680 685

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Lys Val Pro Ala Gln Asn Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly 15 20 25
gat cct ccc tac agt cat gga aca ggg aca gga tac acc atg gat act 147
Asp Pro Pro Tyr Ser His Gly Thr Gly Thr Gly Tyr Thr Met Asp Thr 30 35 40
gtc aac aga aca cac caa tat tca gaa aaa ggg aaa tgg aca aca aac 195
Val Asn Arg Thr His Gln Tyr Ser Glu Lys Gly Lys Trp Thr Thr Asn 45 50 55
act gag att gga gca cca caa ctt aat cca atc gat gga cca ctt cct 243
Thr Glu Ile Gly Ala Pro Gln Leu Asn Pro Ile Asp Gly Pro Leu Pro 60 65 70
gaa gac aat gaa cca agt ggg tac gcc caa aca gat tgt gta ttg gaa 291
Glu Asp Asn Glu Pro Ser Gly Tyr Ala Gln Thr Asp Cys Val Leu Glu 75 80 85 90
gca atg gct ttc ctt gaa gaa tcc cat ccc gga atc ttt gaa aat tcg 339
Ala Met Ala Phe Leu Glu Glu Ser His Pro Gly Ile Phe Glu Asn Ser 95 100 105
tgt ctt gaa acg atg gag gtg att cag cag aca aga gtg gac aaa cta 387
Cys Leu Glu Thr Met Glu Val Ile Gln Gln Thr Arg Val Asp Lys Leu 110 115 120
aca caa ggc cga caa act tat gat tgg acc ttg aat agg aat caa cct 435
Thr Gln Gly Arg Gln Thr Tyr Asp Trp Thr Leu Asn Arg Asn Gln Pro 125 130 135
gcc gca aca gca ctt gct aat acg att gaa gta ttc aga tca aat ggt 483
Ala Ala Thr Ala Leu Ala Asn Thr Ile Glu Val Phe Arg Ser Asn Gly 140 145 150
ctg act tcc aat gaa tcg ggg aga ttg atg gac ttc ctc aaa gat gtc 531
Leu Thr Ser Asn Glu Ser Gly Arg Leu Met Asp Phe Leu Lys Asp Val 155 160 165 170

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Met	Glu	Ser	Met	Asn	Lys	Glu	Glu	Met	Glu	Ile	Thr	Thr	His	Phe	Gln	
				175					180					185		
cgg	aag	aga	aga	gta	aga	gac	aac	atg	aca	aag	aga	atg	ata	aca	cag	627
Arg	Lys	Arg	Arg	Val	Arg	Asp	Asn	Met	Thr	Lys	Arg	Met	Ile	Thr	Gln	
			190					195					200			
aga	acc	ata	ggg	aag	aaa	aaa	caa	cga	tta	agc	aga	aag	agc	tat	cta	675
Arg	Thr	Ile	Gly	Lys	Lys	Lys	Gln	Arg	Leu	Ser	Arg	Lys	Ser	Tyr	Leu	
		205					210					215				
atc	aga	aca	tta	acc	cta	aac	aca	atg	acc	aag	gac	gct	gaa	aga	ggg	723
Ile	Arg	Thr	Leu	Thr	Leu	Asn	Thr	Met	Thr	Lys	Asp	Ala	Glu	Arg	Gly	
	220					225					230					
aaa	ttg	aaa	cga	cga	gca	atc	gct	acc	cca	ggg	atg	cag	ata	aga	gga	771
Lys	Leu	Lys	Arg	Arg	Ala	Ile	Ala	Thr	Pro	Gly	Met	Gln	Ile	Arg	Gly	
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ttt	gta	tat	ttt	gtt	gaa	aca	cta	gct	cga	aga	ata	tgt	gaa	aag	ctt	819
Phe	Val	Tyr	Phe	Val	Glu	Thr	Leu	Ala	Arg	Arg	Ile	Cys	Glu	Lys	Leu	
				255					260					265		
gaa	caa	tca	gga	ttg	cca	gtt	ggc	ggt	aat	gag	aaa	aag	gcc	aaa	ctg	867
Glu	Gln	Ser	Gly	Leu	Pro	Val	Gly	Gly	Asn	Glu	Lys	Lys	Ala	Lys	Leu	
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gct	aat	gtc	gtc	aga	aaa	atg	atg	act	aat	tcc	caa	gac	act	gaa	ctc	915
Ala	Asn	Val	Val	Arg	Lys	Met	Met	Thr	Asn	Ser	Gln	Asp	Thr	Glu	Leu	
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tcc	ttc	acc	atc	act	ggg	gac	aat	acc	aaa	tgg	aat	gaa	aat	cag	aac	963
Ser	Phe	Thr	Ile	Thr	Gly	Asp	Asn	Thr	Lys	Trp	Asn	Glu	Asn	Gln	Asn	
	300				305						310					
cca	cgc	ata	ttc	ctg	gca	atg	atc	aca	tac	ata	act	aga	aat	cag	cca	1011
Pro	Arg	Ile	Phe	Leu	Ala	Met	Ile	Thr	Tyr	Ile	Thr	Arg	Asn	Gln	Pro	
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gaa	tgg	ttc	aga	aat	gtt	cta	agc	att	gca	ccg	att	atg	ttc	tca	aat	1059
Glu	Trp	Phe	Arg	Asn	Val	Leu	Ser	Ile	Ala	Pro	Ile	Met	Phe	Ser	Asn	
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aaa	atg	gca	aga	ctg	ggg	aaa	gga	tat	atg	ttt	gaa	agc	aaa	agt	atg	1107
Lys	Met	Ala	Arg	Leu	Gly	Lys	Gly	Tyr	Met	Phe	Glu	Ser	Lys	Ser	Met	
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Lys	Leu	Arg	Thr	Gln	Ile	Pro	Ala	Glu	Met	Leu	Ala	Ser	Ile	Asp	Leu	
		365					370					375				
aaa	tat	ttc	aat	gat	tca	aca	aaa	aag	aaa	att	gaa	aag	ata	cga	cca	1203
Lys	Tyr	Phe	Asn	Asp	Ser	Thr	Lys	Lys	Lys	Ile	Glu	Lys	Ile	Arg	Pro	
	380					385					390					
ctc	ctg	gtt	gac	ggg	act	gct	tca	ctg	agt	cct	ggc	atg	atg	atg	gga	1251
Leu	Leu	Val	Asp	Gly	Thr	Ala	Ser	Leu	Ser	Pro	Gly	Met	Met	Met	Gly	
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atg	ttc	aac	atg	ttg	agc	act	gtg	ctg	ggt	gta	tcc	ata	tta	aac	ctg	1299
Met	Phe	Asn	Met	Leu	Ser	Thr	Val	Leu	Gly	Val	Ser	Ile	Leu	Asn	Leu	
				415					420					425		
ggc	cag	agg	aaa	tat	aca	aag	acc	aca	tac	tgg	tgg	gat	ggt	ctg	caa	1347
Gly	Gln	Arg	Lys	Tyr	Thr	Lys	Thr	Thr	Tyr	Trp	Trp	Asp	Gly	Leu	Gln	

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atc aac atg agc aaa aag aag tcc tac ata aat aga act gga aca ttc Ile Asn Met Ser Lys Lys Lys Ser Tyr Ile Asn Arg Thr Gly Thr Phe 475 480 490			1491
gaa ttc aca agc ttt ttc tac cgg tat ggt ttt gta gcc aat ttc agc Glu Phe Thr Ser Phe Phe Tyr Arg Tyr Gly Phe Val Ala Asn Phe Ser 495 500 505			1539
atg gaa cta ccc agt ttt ggg gtt tcc gga ata aat gaa tct gca gac Met Glu Leu Pro Ser Phe Gly Val Ser Gly Ile Asn Glu Ser Ala Asp 510 515 520			1587
atg agc att gga gtg aca gtc atc aaa aac aac atg ata aat aat gat Met Ser Ile Gly Val Thr Val Ile Lys Asn Asn Met Ile Asn Asn Asp 525 530 535			1635
ctc ggt cct gcc acg gca caa atg gya ctc caa ctc ttc att aag gat Leu Gly Pro Ala Thr Ala Gln Met Xaa Leu Gln Leu Phe Ile Lys Asp 540 545 550			1683
tat cgg tac aca tac cgg tgc cat aga ggt gat acc cag ata caa acc Tyr Arg Tyr Thr Tyr Arg Cys His Arg Gly Asp Thr Gln Ile Gln Thr 555 560 565 570			1731
aga aga tct ttt gag ttg aag aaa ctg tgg gaa cag act cga tca aag Arg Arg Ser Phe Glu Leu Lys Lys Leu Trp Glu Gln Thr Arg Ser Lys 575 580 585			1779
act ggt cta ctg gta tca gat ggg ggt cca aac cta tat aac atc aga Thr Gly Leu Leu Val Ser Asp Gly Gly Pro Asn Leu Tyr Asn Ile Arg 590 595 600			1827
aac cta cac atc ccg gaa gtc tgt tta aaa tgg gag cta atg gat gaa Asn Leu His Ile Pro Glu Val Cys Leu Lys Trp Glu Leu Met Asp Glu 605 610 615			1875
gat tat aag ggg agg cta tgc aat cca ttg aat cct ttc gtt agt cac Asp Tyr Lys Gly Arg Leu Cys Asn Pro Leu Asn Pro Phe Val Ser His 620 625 630			1923
aaa gaa att gaa tca gtc aac agt gca gta gta atg cct gcg cat ggc Lys Glu Ile Glu Ser Val Asn Ser Ala Val Val Met Pro Ala His Gly 635 640 645 650			1971
cct gcc aaa agc atg gag tat gat gct gtt gca aca aca cat tct tgg Pro Ala Lys Ser Met Glu Tyr Asp Ala Val Ala Thr Thr His Ser Trp 655 660 665			2019
atc ccc aag agg aac cgg tcc ata ttg aac aca agc caa agg gga ata Ile Pro Lys Arg Asn Arg Ser Ile Leu Asn Thr Ser Gln Arg Gly Ile 670 675 680			2067
cta gaa gat gag cag atg tat cag aaa tgc tgc aac ctg ttt gaa aaa Leu Glu Asp Glu Gln Met Tyr Gln Lys Cys Cys Asn Leu Phe Glu Lys 685 690 695			2115
ttc ttc ccc agc agc tca tac aga aga cca gtc gga att tct agt atg			2163

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Phe Phe Pro Ser Ser Ser Tyr Arg Arg Pro Val Gly Ile Ser Ser Met
 700 705 710
 gtt gag gcc atg gta tcc agg gcc cgc att gat gca cga att gac ttc 2211
 Val Glu Ala Met Val Ser Arg Ala Arg Ile Asp Ala Arg Ile Asp Phe
 715 720 725 730
 gaa tct gga cgg ata aag aag gat gag ttc gct gag atc atg aag atc 2259
 Glu Ser Gly Arg Ile Lys Lys Asp Glu Phe Ala Glu Ile Met Lys Ile
 735 740 745
 tgt tcc acc att gaa gag ctc aga cgg caa aaa tagtgaa 2299
 Cys Ser Thr Ile Glu Glu Leu Arg Arg Gln Lys
 750 755

<210> 14
 <211> 757
 <212> PRT
 <213> Influenza A virus

<220>
 <221> misc_feature
 <222> (547)..(547)
 <223> The 'Xaa' at location 547 stands for Ala, or Val.

<400> 14

Met Asp Val Asn Pro Thr Leu Leu Phe Leu Lys Val Pro Ala Gln Asn
1 5 10 15

Ala Ile Ser Thr Thr Phe Pro Tyr Thr Gly Asp Pro Pro Tyr Ser His
20 25 30

Gly Thr Gly Thr Gly Tyr Thr Met Asp Thr Val Asn Arg Thr His Gln
35 40 45

Tyr Ser Glu Lys Gly Lys Trp Thr Thr Asn Thr Glu Ile Gly Ala Pro
50 55 60

Gln Leu Asn Pro Ile Asp Gly Pro Leu Pro Glu Asp Asn Glu Pro Ser
65 70 75 80

Gly Tyr Ala Gln Thr Asp Cys Val Leu Glu Ala Met Ala Phe Leu Glu
85 90 95

Glu Ser His Pro Gly Ile Phe Glu Asn Ser Cys Leu Glu Thr Met Glu
100 105 110

Val Ile Gln Gln Thr Arg Val Asp Lys Leu Thr Gln Gly Arg Gln Thr
115 120 125

Tyr Asp Trp Thr Leu Asn Arg Asn Gln Pro Ala Ala Thr Ala Leu Ala
130 135 140

Asn Thr Ile Glu Val Phe Arg Ser Asn Gly Leu Thr Ser Asn Glu Ser
145 150 155 160

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Gly Arg Leu Met Asp Phe Leu Lys Asp Val Met Glu Ser Met Asn Lys
 165 170 175
 Glu Glu Met Glu Ile Thr Thr His Phe Gln Arg Lys Arg Arg Val Arg
 180 185 190
 Asp Asn Met Thr Lys Arg Met Ile Thr Gln Arg Thr Ile Gly Lys Lys
 195 200 205
 Lys Gln Arg Leu Ser Arg Lys Ser Tyr Leu Ile Arg Thr Leu Thr Leu
 210 215 220
 Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala
 225 230 235 240
 Ile Ala Thr Pro Gly Met Gln Ile Arg Gly Phe Val Tyr Phe Val Glu
 245 250 255
 Thr Leu Ala Arg Arg Ile Cys Glu Lys Leu Glu Gln Ser Gly Leu Pro
 260 265 270
 Val Gly Gly Asn Glu Lys Lys Ala Lys Leu Ala Asn Val Val Arg Lys
 275 280 285
 Met Met Thr Asn Ser Gln Asp Thr Glu Leu Ser Phe Thr Ile Thr Gly
 290 295 300
 Asp Asn Thr Lys Trp Asn Glu Asn Gln Asn Pro Arg Ile Phe Leu Ala
 305 310 315 320
 Met Ile Thr Tyr Ile Thr Arg Asn Gln Pro Glu Trp Phe Arg Asn Val
 325 330 335
 Leu Ser Ile Ala Pro Ile Met Phe Ser Asn Lys Met Ala Arg Leu Gly
 340 345 350
 Lys Gly Tyr Met Phe Glu Ser Lys Ser Met Lys Leu Arg Thr Gln Ile
 355 360 365
 Pro Ala Glu Met Leu Ala Ser Ile Asp Leu Lys Tyr Phe Asn Asp Ser
 370 375 380
 Thr Lys Lys Lys Ile Glu Lys Ile Arg Pro Leu Leu Val Asp Gly Thr
 385 390 395 400
 Ala Ser Leu Ser Pro Gly Met Met Met Gly Met Phe Asn Met Leu Ser
 405 410 415
 Thr Val Leu Gly Val Ser Ile Leu Asn Leu Gly Gln Arg Lys Tyr Thr
 420 425 430

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Lys Thr Thr Tyr Trp Trp Asp Gly Leu Gln Ser Ser Asp Asp Phe Ala
435 440 445

Leu Ile Val Asn Ala Pro Asn His Glu Gly Ile Gln Ala Gly Val Asp
450 455 460

Arg Phe Tyr Arg Thr Cys Lys Leu Val Gly Ile Asn Met Ser Lys Lys
465 470 475 480

Lys Ser Tyr Ile Asn Arg Thr Gly Thr Phe Glu Phe Thr Ser Phe Phe
485 490 495

Tyr Arg Tyr Gly Phe Val Ala Asn Phe Ser Met Glu Leu Pro Ser Phe
500 505 510

Gly Val Ser Gly Ile Asn Glu Ser Ala Asp Met Ser Ile Gly Val Thr
515 520 525

Val Ile Lys Asn Asn Met Ile Asn Asn Asp Leu Gly Pro Ala Thr Ala
530 535 540

Gln Met Xaa Leu Gln Leu Phe Ile Lys Asp Tyr Arg Tyr Thr Tyr Arg
545 550 555 560

Cys His Arg Gly Asp Thr Gln Ile Gln Thr Arg Arg Ser Phe Glu Leu
565 570 575

Lys Lys Leu Trp Glu Gln Thr Arg Ser Lys Thr Gly Leu Leu Val Ser
580 585 590

Asp Gly Gly Pro Asn Leu Tyr Asn Ile Arg Asn Leu His Ile Pro Glu
595 600 605

Val Cys Leu Lys Trp Glu Leu Met Asp Glu Asp Tyr Lys Gly Arg Leu
610 615 620

Cys Asn Pro Leu Asn Pro Phe Val Ser His Lys Glu Ile Glu Ser Val
625 630 635 640

Asn Ser Ala Val Val Met Pro Ala His Gly Pro Ala Lys Ser Met Glu
645 650 655

Tyr Asp Ala Val Ala Thr Thr His Ser Trp Ile Pro Lys Arg Asn Arg
660 665 670

Ser Ile Leu Asn Thr Ser Gln Arg Gly Ile Leu Glu Asp Glu Gln Met
675 680 685

Tyr Gln Lys Cys Cys Asn Leu Phe Glu Lys Phe Phe Pro Ser Ser Ser

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700

690

695

Tyr Arg Arg Pro Val Gly Ile Ser Ser Met Val Glu Ala Met Val Ser
705 710 715 720

Arg Ala Arg Ile Asp Ala Arg Ile Asp Phe Glu Ser Gly Arg Ile Lys
725 730 735

Lys Asp Glu Phe Ala Glu Ile Met Lys Ile Cys Ser Thr Ile Glu Glu
740 745 750

Leu Arg Arg Gln Lys
755

<210> 15
<211> 2370
<212> DNA
<213> Influenza A virus

<220>
<221> CDS
<222> (42)..(2318)

<400> 15
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Met Glu Arg Ile Lys
1 5

gaa ctg aga gat ctg atg tta caa tcc cgc acc cgc gag ata cta aca 104
Glu Leu Arg Asp Leu Met Leu Gln Ser Arg Thr Arg Glu Ile Leu Thr
10 15 20

aaa act act gtg gac cac atg gcc ata atc aag aaa tac aca tca gga 152
Lys Thr Thr Val Asp His Met Ala Ile Ile Lys Lys Tyr Thr Ser Gly
25 30 35

aga caa gag aag aac cct gca ctt agg atg aaa tgg atg atg gca atg 200
Arg Gln Glu Lys Asn Pro Ala Leu Arg Met Lys Trp Met Met Ala Met
40 45 50

aaa tac cca att aca gca gat aag agg ata atg gag atg att cct gag 248
Lys Tyr Pro Ile Thr Ala Asp Lys Arg Ile Met Glu Met Ile Pro Glu
55 60 65

aga aat gaa cag gga caa acc ctt tgg agc aaa acg aac gat gct ggc 296
Arg Asn Glu Gln Gly Gln Thr Leu Trp Ser Lys Thr Asn Asp Ala Gly
70 75 80 85

tca gac cgc gta atg gta tca cct ctg gca gtg aca tgg tgg aat agg 344
Ser Asp Arg Val Met Val Ser Pro Leu Ala Val Thr Trp Trp Asn Arg
90 95 100

aat gga cca aca acg aac aca att cat tat ccg aaa gtc tac aaa act 392
Asn Gly Pro Thr Thr Asn Thr Ile His Tyr Pro Lys Val Tyr Lys Thr
105 110 115

tat ttt gaa aag gtt gaa aga ttg aaa cac gga acc ttt ggc ccc gtt 440
Tyr Phe Glu Lys Val Glu Arg Leu Lys His Gly Thr Phe Gly Pro Val
120 125 130

cat ttt agg aat caa gtc aag ata aga cga aga gtt gat gta aac cct 488

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His	Phe	Arg	Asn	Gln	Val	Lys	Ile	Arg	Arg	Arg	Val	Asp	Val	Asn	Pro	
	135					140					145					
ggt	cac	gcg	gac	ctc	agt	gct	aaa	gaa	gca	caa	gat	gtg	atc	atg	gaa	536
Gly	His	Ala	Asp	Leu	Ser	Ala	Lys	Glu	Ala	Gln	Asp	Val	Ile	Met	Glu	
150					155					160					165	
ggt	ggt	ttc	cca	aat	gaa	gtg	gga	gcc	aga	att	cta	aca	tca	gaa	tca	584
Val	Val	Phe	Pro	Asn	Glu	Val	Gly	Ala	Arg	Ile	Leu	Thr	Ser	Glu	Ser	
				170					175					180		
caa	cta	aca	ata	acc	aaa	gag	aaa	aag	gaa	gaa	ctt	cag	gac	tgc	aaa	632
Gln	Leu	Thr	Ile	Thr	Lys	Glu	Lys	Lys	Glu	Glu	Leu	Gln	Asp	Cys	Lys	
			185					190					195			
att	gct	ccc	ttg	atg	gta	gca	tac	atg	cta	gaa	aga	gag	ttg	gtc	cga	680
Ile	Ala	Pro	Leu	Met	Val	Ala	Tyr	Met	Leu	Glu	Arg	Glu	Leu	Val	Arg	
		200					205					210				
aaa	aca	agg	ttc	ctc	cca	gta	gta	ggc	gga	aca	agc	agt	gta	tac	att	728
Lys	Thr	Arg	Phe	Leu	Pro	Val	Val	Gly	Gly	Thr	Ser	Ser	Val	Tyr	Ile	
	215					220					225					
gaa	gtg	ttg	cat	ctg	act	cag	gga	aca	tgc	tgg	gag	caa	atg	tac	acc	776
Glu	Val	Leu	His	Leu	Thr	Gln	Gly	Thr	Cys	Trp	Glu	Gln	Met	Tyr	Thr	
230					235					240					245	
cca	gga	gga	gaa	ggt	aga	aac	gat	gat	att	gat	caa	agt	tta	att	att	824
Pro	Gly	Gly	Glu	Val	Arg	Asn	Asp	Asp	Ile	Asp	Gln	Ser	Leu	Ile	Ile	
				250					255					260		
gca	gcc	cgg	aac	ata	gtg	aga	aga	gca	aca	gta	tca	gca	gat	cca	cta	872
Ala	Ala	Arg	Asn	Ile	Val	Arg	Arg	Ala	Thr	Val	Ser	Ala	Asp	Pro	Leu	
			265					270					275			
gca	tcc	cta	ctg	gaa	atg	tgc	cac	agt	aca	cag	att	ggt	gga	aca	agg	920
Ala	Ser	Leu	Leu	Glu	Met	Cys	His	Ser	Thr	Gln	Ile	Gly	Gly	Thr	Arg	
		280					285					290				
atg	gta	gac	atc	ctt	aag	cag	aac	cca	aca	gag	gaa	caa	gct	gtg	gat	968
Met	Val	Asp	Ile	Leu	Lys	Gln	Asn	Pro	Thr	Glu	Glu	Gln	Ala	Val	Asp	
	295					300					305					
ata	tgc	aaa	gca	gca	atg	gga	ttg	aga	att	agc	tca	tca	ttc	agc	ttt	1016
Ile	Cys	Lys	Ala	Ala	Met	Gly	Leu	Arg	Ile	Ser	Ser	Ser	Phe	Ser	Phe	
310					315					320					325	
ggt	gga	ttc	acc	ttc	aaa	agg	aca	agt	gga	tca	tca	gtc	aag	aga	gaa	1064
Gly	Gly	Phe	Thr	Phe	Lys	Arg	Thr	Ser	Gly	Ser	Ser	Val	Lys	Arg	Glu	
				330					335					340		
gaa	gaa	atg	ctt	acg	ggc	aac	ctt	caa	aca	ttg	aaa	ata	aga	gtg	cat	1112
Glu	Glu	Met	Leu	Thr	Gly	Asn	Leu	Gln	Thr	Leu	Lys	Ile	Arg	Val	His	
			345					350					355			
gag	ggc	tat	gaa	gaa	ttc	aca	atg	gtc	gga	aga	aga	gca	aca	gcc	att	1160
Glu	Gly	Tyr	Glu	Glu	Phe	Thr	Met	Val	Gly	Arg	Arg	Ala	Thr	Ala	Ile	
		360					365					370				
atc	aga	aag	gca	acc	aga	aga	ttg	att	caa	ttg	ata	gta	agt	ggg	aga	1208
Ile	Arg	Lys	Ala	Thr	Arg	Arg	Leu	Ile	Gln	Leu	Ile	Val	Ser	Gly	Arg	
	375					380					385					
gat	gaa	caa	tca	att	gct	gaa	gca	ata	att	gta	gcc	atg	gtg	ttt	tcg	1256
Asp	Glu	Gln	Ser	Ile	Ala	Glu	Ala	Ile	Ile	Val	Ala	Met	Val	Phe	Ser	
390					395					400					405	

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caa gaa gat tgc atg ata aaa gca gtt cga ggc gat ttg aac ttt gtt Gln Glu Asp Cys Met Ile Lys Ala Val Arg Gly Asp Leu Asn Phe Val 410 415 420	1304
aat aga gca aat cag cgt ttg aac ccc atg cat caa ctc ttg agg cat Asn Arg Ala Asn Gln Arg Leu Asn Pro Met His Gln Leu Arg His 425 430 435	1352
ttc caa aaa gat gca aaa gtg ctt ttc caa aat tgg gga att gaa ccc Phe Gln Lys Asp Ala Lys Val Leu Phe Gln Asn Trp Gly Ile Glu Pro 440 445 450	1400
atc gac aat gta atg ggg atg att gga ata ttg cct gac atg acc cca Ile Asp Asn Val Met Gly Met Ile Gly Ile Leu Pro Asp Met Thr Pro 455 460 465	1448
agc acc gag atg tca ttg aga gga gtg aga gtc agc aaa atg gga gtg Ser Thr Glu Met Ser Leu Arg Gly Val Arg Val Ser Lys Met Gly Val 470 475 480 485	1496
gat gag tac tcc agc act gag aga gtg gtg gtg agc att gac cgt ttt Asp Glu Tyr Ser Ser Thr Glu Arg Val Val Val Ser Ile Asp Arg Phe 490 495 500	1544
tta aga gtt cgg gat caa agg gga aac ata cta ctg tcc cct gaa gaa Leu Arg Val Arg Asp Gln Arg Gly Asn Ile Leu Leu Ser Pro Glu Glu 505 510 515	1592
gtc agt gaa aca caa gga acg gaa aag ctg aca ata att tat tcg tca Val Ser Glu Thr Gln Gly Thr Glu Lys Leu Thr Ile Ile Tyr Ser Ser 520 525 530	1640
tca atg atg tgg gag att aat ggt ccc gaa tca gtg ttg gtc aat act Ser Met Met Trp Glu Ile Asn Gly Pro Glu Ser Val Leu Val Asn Thr 535 540 545	1688
tat caa tgg atc atc aga aac tgg gaa att gta aaa att cag tgg tca Tyr Gln Trp Ile Ile Arg Asn Trp Glu Ile Val Lys Ile Gln Trp Ser 550 555 560 565	1736
cag gac ccc aca atg tta tac aat aag ata gaa ttt gaa cca ttc caa Gln Asp Pro Thr Met Leu Tyr Asn Lys Ile Glu Phe Glu Pro Phe Gln 570 575 580	1784
tcc ctg gtc cct agg gcc acc aga agc caa tac agc ggt ttc gta aga Ser Leu Val Pro Arg Ala Thr Arg Ser Gln Tyr Ser Gly Phe Val Arg 585 590 595	1832
acc ctg ttt cag caa atg cga gat gta ctt gga aca ttt gat act gct Thr Leu Phe Gln Gln Met Arg Asp Val Leu Gly Thr Phe Asp Thr Ala 600 605 610	1880
caa ata ata aaa ctc ctc cct ttt gcc gct gct cct ccg gaa cag agt Gln Ile Ile Lys Leu Leu Pro Phe Ala Ala Ala Pro Pro Glu Gln Ser 615 620 625	1928
agg atg cag ttc tct tct ttg act gtt aat gta aga ggt tcg gga atg Arg Met Gln Phe Ser Ser Leu Thr Val Asn Val Arg Gly Ser Gly Met 630 635 640 645	1976
agg ata ctt gta aga ggc aat tcc ccg gtg ttc aac tac aat aaa gtc Arg Ile Leu Val Arg Gly Asn Ser Pro Val Phe Asn Tyr Asn Lys Val 650 655 660	2024
act aaa agg ctc aca gtc ctc gga aag gat gca ggt gcg ctt act gag Thr Lys Arg Leu Thr Val Leu Gly Lys Asp Ala Gly Ala Leu Thr Glu 665 670 675	2072

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gac cca gat gaa ggt acg gct gga gta gaa tct gct gtt cta aga ggg 2120
 Asp Pro Asp Glu Gly Thr Ala Gly Val Glu Ser Ala Val Leu Arg Gly
 680 685 690
 ttt ctc att tta ggt aaa gaa aac aag aga tat ggc cca gca cta agc 2168
 Phe Leu Ile Leu Gly Lys Glu Asn Lys Arg Tyr Gly Pro Ala Leu Ser
 695 700 705
 atc aat gaa ctt agc aaa ctt gca aaa ggg gag aaa gcc aat gta cta 2216
 Ile Asn Glu Leu Ser Lys Leu Ala Lys Gly Glu Lys Ala Asn Val Leu
 710 715 720 725
 att ggg caa ggg gac gta gtg ttg gta atg aaa cgg aaa cgt gac tct 2264
 Ile Gly Gln Gly Asp Val Val Leu Val Met Lys Arg Lys Arg Asp Ser
 730 735 740
 agc ata ctt act gac agc cag aca gcg acc aaa agg att cgg atg gcc 2312
 Ser Ile Leu Thr Asp Ser Gln Thr Ala Thr Lys Arg Ile Arg Met Ala
 745 750 755
 atc aat tagtggttgaa ttgttttaaaa acgaccttgt ttctactaat acgagaccat at 2370
 Ile Asn

<210> 16
 <211> 759
 <212> PRT
 <213> Influenza A virus

<400> 16

Met Glu Arg Ile Lys Glu Leu Arg Asp Leu Met Leu Gln Ser Arg Thr
1 5 10 15

Arg Glu Ile Leu Thr Lys Thr Thr Val Asp His Met Ala Ile Ile Lys
20 25 30

Lys Tyr Thr Ser Gly Arg Gln Glu Lys Asn Pro Ala Leu Arg Met Lys
35 40 45

Trp Met Met Ala Met Lys Tyr Pro Ile Thr Ala Asp Lys Arg Ile Met
50 55 60

Glu Met Ile Pro Glu Arg Asn Glu Gln Gly Gln Thr Leu Trp Ser Lys
65 70 75 80

Thr Asn Asp Ala Gly Ser Asp Arg Val Met Val Ser Pro Leu Ala Val
85 90 95

Thr Trp Trp Asn Arg Asn Gly Pro Thr Thr Asn Thr Ile His Tyr Pro
100 105 110

Lys Val Tyr Lys Thr Tyr Phe Glu Lys Val Glu Arg Leu Lys His Gly
115 120 125

Thr Phe Gly Pro Val His Phe Arg Asn Gln Val Lys Ile Arg Arg Arg
130 135 140

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Val Asp Val Asn Pro Gly His Ala Asp Leu Ser Ala Lys Glu Ala Gln
 145 150 155 160
 Asp Val Ile Met Glu Val Val Phe Pro Asn Glu Val Gly Ala Arg Ile
 165 170 175
 Leu Thr Ser Glu Ser Gln Leu Thr Ile Thr Lys Glu Lys Lys Glu Glu
 180 185 190
 Leu Gln Asp Cys Lys Ile Ala Pro Leu Met Val Ala Tyr Met Leu Glu
 195 200 205
 Arg Glu Leu Val Arg Lys Thr Arg Phe Leu Pro Val Val Gly Gly Thr
 210 215 220
 Ser Ser Val Tyr Ile Glu Val Leu His Leu Thr Gln Gly Thr Cys Trp
 225 230 235 240
 Glu Gln Met Tyr Thr Pro Gly Gly Glu Val Arg Asn Asp Asp Ile Asp
 245 250 255
 Gln Ser Leu Ile Ile Ala Ala Arg Asn Ile Val Arg Arg Ala Thr Val
 260 265 270
 Ser Ala Asp Pro Leu Ala Ser Leu Leu Glu Met Cys His Ser Thr Gln
 275 280 285
 Ile Gly Gly Thr Arg Met Val Asp Ile Leu Lys Gln Asn Pro Thr Glu
 290 295 300
 Glu Gln Ala Val Asp Ile Cys Lys Ala Ala Met Gly Leu Arg Ile Ser
 305 310 315 320
 Ser Ser Phe Ser Phe Gly Gly Phe Thr Phe Lys Arg Thr Ser Gly Ser
 325 330 335
 Ser Val Lys Arg Glu Glu Glu Met Leu Thr Gly Asn Leu Gln Thr Leu
 340 345 350
 Lys Ile Arg Val His Glu Gly Tyr Glu Glu Phe Thr Met Val Gly Arg
 355 360 365
 Arg Ala Thr Ala Ile Ile Arg Lys Ala Thr Arg Arg Leu Ile Gln Leu
 370 375 380
 Ile Val Ser Gly Arg Asp Glu Gln Ser Ile Ala Glu Ala Ile Ile Val
 385 390 395 400
 Ala Met Val Phe Ser Gln Glu Asp Cys Met Ile Lys Ala Val Arg Gly

405

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410

415

Asp Leu Asn Phe Val Asn Arg Ala Asn Gln Arg Leu Asn Pro Met His
420 425 430

Gln Leu Leu Arg His Phe Gln Lys Asp Ala Lys Val Leu Phe Gln Asn
435 440 445

Trp Gly Ile Glu Pro Ile Asp Asn Val Met Gly Met Ile Gly Ile Leu
450 455 460

Pro Asp Met Thr Pro Ser Thr Glu Met Ser Leu Arg Gly Val Arg Val
465 470 475 480

Ser Lys Met Gly Val Asp Glu Tyr Ser Ser Thr Glu Arg Val Val Val
485 490 495

Ser Ile Asp Arg Phe Leu Arg Val Arg Asp Gln Arg Gly Asn Ile Leu
500 505 510

Leu Ser Pro Glu Glu Val Ser Glu Thr Gln Gly Thr Glu Lys Leu Thr
515 520 525

Ile Ile Tyr Ser Ser Ser Met Met Trp Glu Ile Asn Gly Pro Glu Ser
530 535 540

Val Leu Val Asn Thr Tyr Gln Trp Ile Ile Arg Asn Trp Glu Ile Val
545 550 555 560

Lys Ile Gln Trp Ser Gln Asp Pro Thr Met Leu Tyr Asn Lys Ile Glu
565 570 575

Phe Glu Pro Phe Gln Ser Leu Val Pro Arg Ala Thr Arg Ser Gln Tyr
580 585 590

Ser Gly Phe Val Arg Thr Leu Phe Gln Gln Met Arg Asp Val Leu Gly
595 600 605

Thr Phe Asp Thr Ala Gln Ile Ile Lys Leu Leu Pro Phe Ala Ala Ala
610 615 620

Pro Pro Glu Gln Ser Arg Met Gln Phe Ser Ser Leu Thr Val Asn Val
625 630 635 640

Arg Gly Ser Gly Met Arg Ile Leu Val Arg Gly Asn Ser Pro Val Phe
645 650 655

Asn Tyr Asn Lys Val Thr Lys Arg Leu Thr Val Leu Gly Lys Asp Ala
660 665 670

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Gly Ala Leu Thr Glu Asp Pro Asp Glu Gly Thr Ala Gly Val Glu Ser
 675 680 685

Ala Val Leu Arg Gly Phe Leu Ile Leu Gly Lys Glu Asn Lys Arg Tyr
 690 695 700

Gly Pro Ala Leu Ser Ile Asn Glu Leu Ser Lys Leu Ala Lys Gly Glu
 705 710 715 720

Lys Ala Asn Val Leu Ile Gly Gln Gly Asp Val Val Leu Val Met Lys
 725 730 735

Arg Lys Arg Asp Ser Ser Ile Leu Thr Asp Ser Gln Thr Ala Thr Lys
 740 745 750

Arg Ile Arg Met Ala Ile Asn
 755

WHAT IS CLAIMED:

1. An isolated canine influenza virus of subtype H3N8 comprising (i) a hemagglutinin having the amino acid sequence of SEQ ID NO: 4 or (ii) a hemagglutinin having an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, with the proviso that the hemagglutinin is identical to that of SEQ ID NO: 4 at corresponding amino acid position 94 or 233.

2. An isolated canine influenza virus of claim 1 which further comprises a neuraminidase comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 2, with the proviso that the amino acids at positions 68 and 134 are identical to SEQ ID NO: 2.

3. An isolated canine influenza virus which comprises a neuraminidase comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 2, with the proviso that the amino acids at positions 68 and 134 are identical to SEQ ID NO: 2, and at least one of the following: a nucleoprotein having the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 6, with the proviso that amino acid 402 is identical to that of SEQ ID NO: 6; a matrix 1 protein having the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 8, with the proviso that amino acid 111 is identical to that of SEQ ID NO: 8; a nonstructural protein 1 having the amino acid sequence of SEQ ID NO: 10; a P A protein having the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence that is greater than 98% identical to SEQ ID NO: 12, with the proviso that amino acids 233, 256, 327, and 561 are identical to SEQ ID NO: 12; a PB 1 having the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 14, with the proviso that amino acids 200 and 213 are identical to SEQ ID NO: 14; and/or PB2 having the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 16, with the proviso that amino acids 107,221,292, and 661 are identical to SEQ ID NO: 16.

4. The isolated canine influenza virus of claim 1 or claim 2, which further comprises at least one of the following: a nucleoprotein having the amino acid sequence of SEQ ID NO: 6 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 6, with the proviso that amino acid 402 is identical to that of SEQ ID NO: 6; a matrix 1 protein having the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 8, with the proviso that amino acid 111 is identical to that of SEQ ID NO: 8; a nonstructural protein 1 having the amino acid sequence of SEQ ID NO: 10; a P A protein having the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence that is greater than 98% identical to SEQ ID NO: 12, with the proviso that amino acids 233, 256, 327, and 561 are identical to SEQ ID NO: 12; a PB 1 having the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 14, with the proviso that amino acids 200 and 213 are identical to SEQ ID NO: 14; and/or PB2 having the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence that is greater than 99% identical to SEQ ID NO: 16, with the proviso that amino acids 107, 221, 292, and 661 are identical to SEQ ID NO: 16.

5. The isolated canine influenza virus of any one of claims 1-4, which is attenuated.

6. The isolated canine influenza virus of any one of claims 1-5, which is inactivated.

7. A composition comprising the isolated canine influenza virus of any one of claims 1-6 in an amount sufficient to induce an immune response and a biologically acceptable carrier.

8. The composition of claim 7, wherein the composition is formulated as a controlled-release composition.

9. An isolated canine influenza virus of subtype H3N8 deposited with the American Type Culture Collection as Patent Deposit No. PTA-7694.

10. An isolated or purified hemagglutinin, which (i) has the amino acid sequence of SEQ ID NO: 4 or (ii) has an amino acid sequence that is greater than 99% identical to SEQ ID

NO: 4, with the proviso that the isolated or purified hemagglutinin is identical to that of SEQ ID NO: 4 at corresponding amino acid position 94 or 233.

11. A composition comprising the isolated or purified hemagglutinin of claim 10 and a biologically acceptable carrier wherein the isolated or purified hemagglutinin is present in an amount sufficient to induce an immune response in an animal.

12. The use of the composition of claim 11 for the preparation of a medicament for the treatment of canine influenza virus in an animal.

13. The use of the composition of claim 11 for inducing an immune response to canine influenza virus in an animal.

14. An isolated or purified nucleic acid encoding the hemagglutinin of claim 10.

15. The isolated or purified nucleic acid of claim 14, wherein the nucleic acid encoding the hemagglutinin has the nucleotide sequence of SEQ ID NO: 3.

16. The use of the influenza virus of any one of claims 1-6 or claim 9 for inducing an immune response in an animal against an influenza virus capable of infecting a canid animal.

17. The use of the isolated canine influenza virus of any one of claims 1-6 or claim 9 for the manufacture of a medicament for treating a canid animal suffering from infection by canine influenza virus.

18. The use of any one of claims 16 or 17 wherein the canid animal is a dog.

19. The use of any one of claims 16-18 wherein the isolated canine influenza virus is inactivated.

20. The use of any one of claims 16-18 wherein the isolated canine influenza virus is attenuated.
21. The use of any one of claims 16-20, wherein the canine influenza virus comprises 10^3 to 10^6 pfu per dose.
22. The use of claim 20, wherein the attenuated strain comprises at least 10^3 TCID₅₀ per dose.
23. The use of claim 17, wherein the medicament is formulated as a controlled-release composition.

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NM

AGTTTAAAATGAATCCAAATCAAAAAGATAATAGCAATTGGATTTGCATCATTGGG
GATATTAATCATTAAATGTCATTCTCCATGTAAGTCAGCATTATAGTAACAGTACTG
GTCCTCAATAACAATAGAACAGATCTGAACTGCAAAGGGACGATCATAAGAGAA
TACAATGAAACAGTAAGAGTAGAAAAACTTACTCAATGGTATAATACCAGTACA
ATTAAGTACATAGAGAGACCTTCAAATGAATACTACATGAATAACACTGAACCA
CTTTGTGAGGGCCCAAGGCTTTGCACCATTTTCCAAAGATAATGGAATACGAATTG
GGTCGAGAGGGCCATGTTTTTGTGATAAGAGAACCTTTTGTATCATGTTTCGCCCTC
AGAATGTAGAACCTTTTTCCTCACACAGGGCTCATTACTCAATGACAAACATTCT
AACGGCACAATAAAGGATCGAAGCCCGTATAGGACTTTGATGAGTGTCAAAATA
GGGCAATCACCCAATGTATATCAAGCTAGGTTTGAATCGGTGGCATGGTCAGCA
ACAGCATGCCATGATGGAAAAAAATGGATGACAGTTGGAGTCACAGGGCCCGAC
AATCAAGCAATTGCAGTAGTGAAGTATGGAGGTGTTCCGGTTGATACTATTAATT
CATGGGCAGGGGATATTTTAAGAACCCAAGAATCATCATGCACCTGCATTAAAG
GAGACTGTTATTGGGTAATGACTGATGGACCGGCAAATAGGCAAGCTAAATATA
GGATATTCAAAGCAAAAAGATGGAAGAGTAATTGGACAAACTGATATAAGTTTCA
ATGGGGGACACATAGAGGAGTGTTCTTGTTACCCCAATGAAGGGGAAGGTGGAAT
GCATATGCAGGGGACAATTGGACTGGAACAAATAGACCAATTCTGGTAATATCTTC
TGATCTATCGTACACAGTTGGATATTTGTGTGCTGGCATTCCCCTGACACTCCTA
GGGGAGAGGATAGTCAATTCACAGGCTCATGTACAAGTCCTTTGGGAAATAAAG
GATACGGTGTAAGAGGCTTCGGGTTTCGACAAGGAACTGACGTATGGGCCGGAA
GGACAATTAGTAGGACTTCAAGATCAGGATTCGAAATAATAAAAAATCAGGAATG
GTTGGACACAGAACAGTAAGGACCAAATCAGGAGGCAAGTGATTATCGATGACC
CAAATTGGTCAGGATATAGCGGTTCTTTCACATTGCCGGTTGAACTGACAAAAAA
GGGATGTTTGGTCCCCTGTTTCTGGGTTGAAATGATTAGAGGTAAACCTGAAGAA
ACAACAATATGGACCTCTAGCAGCTCCATTGTGATGTGTGGAGTAGATCATAAAA
TTGCCAGTTGGTCATGGCACGATGGAGCTATTCTTCCCTTTGACATCGATAAGAT
GTAATTTACGAAAAAAACTCCTTGTTTCTACTA (SEQ ID NO: 1)

FIG. 1

2/14NM - Amino

MNPNQKILAIGFASLGILINVLHVVSIIIVTVLVLNNNRDTLNCKGTIIREYNETVRVEK
LTQWYNTSTIKYIERPSNEYMYMNNTEPLCEAQGFAPFSKDNGIRIGSRGHV FVIREPFV
SCSPSECR TFFLTQGSLLNDKHSNGTIKDRSPYRTLMSVKIGQSPNVYQARFESVAWS
ATACHDGKKWMTVGVTGPDNQAIAVVNYGGVPVDTINSWAGDILRTQESSCTCIKG
DCYWVMTDGPANRQAKYRIFKAKDGRVIGQTDISFNGGHIEECSCYPNEGKVEICR
DNWTGTNRPILVISSDLSYTVGYLCAGIPTDTPRGEDSQFTGSCTSPLGNKGYGVKGF
GFRQGTDVWAGRTISRTSRSGFEIKIRNGWTQNSKDQIRRQVIIDDPNWSGYSGSFTL
PVELTKKGCLVPCFWVEMIRGKPEETTIWTSSSSIVMCGVDHKIASWSWHDGAILPF
DIDKM (SEQ ID NO: 2)

FIG. 2

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HA:

AGCAAAAGCAGGGGATATTTCTGTCAATCATGAAGACAACCATTATTTTAATACT
ACTGACCCATTGGGCCTACAGTCAAAACCCAATCAGTGGCAATAACACAGCCAC
ACTGTGTCTGGGACACCATGCAGTAGCAAATGGAACATTGGTAAAAACAATGAG
TGATGATCAAATTGAGGTGACAAATGCTACAGAATTAGTTCAGAGCATTTCATG
GGGAAAATATGCAACAAATCATATAGAATTCTAGATGGAAGAAATTGCACATTA
ATAGATGCAATGCTAGGAGACCCCCACTGTGACGCCCTTCAGTATGAGAGTTGG
GACCTCTTTATAGAAAGAAGCAGCGCTTTCAGCAATTGCTACCCATATGACATCC
CTGACTATGCATCGCTCCGATCCATTGTAGCATCCTCAGGAACAGTTGAATTCAC
AGCAGAGGGATTACATGGACAGGTGTAACCTCAAAACGGAAGAAGTGGAGCCTG
CaaAAGGGGATCAGCCGATAGTTTCTTTAGCCGACTGAATTGGCTAACAATAATCT
GGAAGCTCTTACCCACATTGAATGTGACAATGCCTAACAATAAAAATTTTCGACA
AGCTATACATCTGGGGGGATTTCATCACCCGAGCTCAAATCAAGAGCAGACAAAAT
TGTACATCCAAGAATCAGGACGAGTAACAGTCTCAACAAAAAGAAGTCAACAAA
CAATAATCCCTAACATCGAATCTAGACCGTTGGTCAGAGGTCAATCAGGCAGGA
TAAGCATATACTGGACCATTGTAAAACCTGGAGATATCCTAATGATAAACAGTA
ATGGCAACTTAGTTGCACCGCGGGGATATTTTAAATTGAACACAGGGAAAAGCT
CTGTAATGAGATCCGATGTACCCATAGACATTTGTGTGTCTGAATGTATTACACC
AAATGGAAGCATCTCCAACGACAAGCCATTCCAAAATGTGAACAAAGTTACATA
TGGAAAATGCCCAAGTATATCAGGCAAAACACTTTAAAGCTGGCCACTGGGAT
GAGGAATGTACCAGAAAAGCAAACCAGAGGAATCTTTGGAGCAATAGCGGGATT
CATCGAAAACGGCTGGGAAGGAATGGTTGATGGGTGGTATGGGTTCCGATATCA
AACTCTGAAGGAACAGGGCAAGCTGCAGATCTAAAGAGCACTCAAGCAGCCAT
TGACCAGATTAATGGAAAGTTAAACAGAGTGATTGAAAGAACCAATGAGAAATT
CCATCAAATAGAGAAGGAATTCTCAGAAGTAGAAGGAAGAATTCAGGACTTGGA
GAAATATGTAGAAGACACCAAAATAGACCTATGGTCCTACAATGCAGAATTGCT
GGTGGCTCTAGAAAATCAACATACAATTGACTTAACAGATGCAGAAATGAATAA
ATTATTTGAGAAGACTAGACGCCAGTTAAGAGAAAACGCAGAAGACATGGGAGG
TGGATGTTTCAAGATTTACCACAAATGTGATAATGCATGCATTGAATCAATAAGA
ACTGGGACATATGACCATTACATATACAGAGATGAAGCATTAACAACCGATTT
CAGATCAAAGGTGTAGAGTTGAAATCAGGCTACAAAGATTGGATACTGTGGATT
TCATTCGCCATATCATGCTTCTTAATTTGCGTTGTTCTATTGGGTTTCATTATGTGG
GCTTGCCAAAAAGGCAACATCAGATGCAACATTTGCATTTGAGTAAACTGATAGT
TAAAAACACCCTTGTTTCTACT (SEQ ID NO:3)

FIG. 3

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HA - Amino

MKTTIILLTHWAYSQNPISGNNTATLCLGHHAVANGTLVKTMSDDQIEVTNATEL
VQSISMGKICNKSYRILDGRNCTLIDAMLGDPHCDALQYESWDLFIERSSAFSNCYPY
DIPDYASLR SIVASSGTVEFTAEGFTWTGVTQNGRSGACKRG SADSFFSRLNWLTKS
GSSYPTLNV TMPNNKNFDKLYIWGIIHPSSNQEQT KLYIQESGRVT VSTKRSQQTIIP
NIESRPLVRGQSGRISIYWTIVKPGDILMINSNGNLVAPRGYFKLNTGKSSVMRSDVPI
DICVSECTPNGSISNDKPFQNVNKV TYGKCPKYIRQNTLKLATGMRNVPEKQTRGIF
GAIAGFIENGWEGMVDGWYGFRYQNSEGTGQAADLKSTQA AIDQINGKLN RV IERT
NEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDAEMN
KLFETRRLRENAEDMGGGCFKIYHKCDNACIESIRTGT YDHYTYRDEALNNRFQI
KGVELKSGYKDWILWISFAISCFLICV VLLGFIMWACQKGNIRCNICI (SEQ ID NO: 4)

FIG. 4

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NP

CAGGGAGCAAAAGCAGGGTAGATAATCACTCACTGAGTGACATCAAAGTCATGG
CGTCTCAAGGCACCAAACGATCCTATGAACAGATGGAAACTGATGGGGGAACGCC
AGAATGCAACTGAAATCAGAGCATCTGTTCGGAAGGATGGTGGGAGGAATCGGAC
GGTTTTATGTCCAGATGTGTACTGAGCTTAAACTAAACGACCATGAAGGGCGGCT
GATTCAGAACAGCATAACAATAGAAAGGATGGTACTTTCAGCATTTCGACGAAAG
AAGAAACAAGTATCTCGAGGAGCATCCCAGTGCTGGGAAAGACCCTAAGAAAAC
GGGAGGCCCGATATACAGAAGAAAAGATGGGAAATGGATGAGGGAACTCATCC
TCCATGATAAAGAAGAAATCATGAGAATCTGGCGTCAGGCCAACAATGGTGAAG
ACGCTACTGCTGGTCTTACTCATATGATGATCTGGCACTCCAATCTCAATGACAC
CACATACCAAAGAACAAGGGCTCTTGTTTCGGACTGGGATGGATCCCAGAATGTG
CTCTCTGATGCAAGGCTCAACCCTCCCACGGAGATCTGGAGCCGCTGGTGCTGCA
GTAAAAGGTGTTGGAACAATGGTAATGGAACATCATCAGGATGATCAAACGCGGA
ATAAATGATCGGAATTTCTGGAGAGGTGAAAATGGTCGAAGAACCAGAATTGCT
TATGAAAGAATGTGCAATATCCTCAAAGGGGAAATTTTCAGACAGCAGCACAAACGG
GCTATGATGGACCAGGTGAGGGAAGGCCGCAATCCTGGAAACGCTGAGATTGAG
GATCTCATTTTTCTTGGCACGATCAGCACTTATTTTGAGAGGATCAGTAGCCCATA
AATCATGCCTACCTGCCTGTGTTTATGGCCTTGCAAGTAACCAGTGGGTATGACTTT
GAGAAGGAAGGATACTCTCTGGTTGGAATTGATCCTTTCAAACACTCCAGAACA
GTCAAATTTTCAGTCTAATCAGACCAAAAAGAAAACCCAGCACACAAAAGCCAGT
TGGTGTGGATGGCATGCCATTCTGCAGCATTTGAGGATCTGAGAGTTTTTAAATTT
CATTAGAGGAACCAAAGTAATCCCAAGAGGACAGTTAACAACCAGAGGAGTTCA
AATTGCTTCAAATGAAAACATGGAGACAATAAATTCTAGCACACTTGAACCTGAG
AAGCAAATATTGGGCAATAAGGACCAGAAGCGGAGGAAACACCAGTCAACAGA
GAGCATTTTGCAGGACAGATAAGTGTGCAACCTACTTTCTCAGTACAGAGAAATCT
TCCCTTTGAGAGAGCAACCATTATGGCTGCATTCACTGGTAACACTGAAGGGAGG
ACTTCCGACATGAGAACGGAAATCATAAGGATGATGGAAAATGCCAAATCAGAA
GATGTGTCTTTCCAGGGGGCGGGGAGTCTTCGAGCTCTCGGACGAAAAGGCAACG
AACCCGATCGTGCCTTCCTTTGACATGAGCAATGAAGGGTCTTATTTCTTCGGAG
ACAATGCTGAGGAGTTTGACAGTTAAAGAAAATACCCTTGTTTCTACTAATACG
AGACGATAT (SEQ ID NO: 5)

FIG. 5

6/14NP - Amino

MASQGTKRSYEQMETDGERQNATEIRASVGRMVGGIGRFYVQMCTELKLNDHEGR
LIQNSITIERMVLSAFDERRNKYLEEHPSAGKDPKKTGGPIYRRKDGKWMRELILHD
KEEIMRIWRQANNGEDATAGLTHMMIWHSNLNDTTYQRTALVRTGMDPRMCSL
MQGSTLPRRSGAAGAAVKGVGTMVMELIRMIKRGINDRNFWRGENGRRTRIAYER
MCNILKGKFQTAAQRAMMDQVREGRNPGNAEIEDLIFLARSALILRGSVAHKSCLPA
CVYGLAVTSGYDFEKEGYSLVGIDPFKLLQNSQIFSLIRPKENPAHKSQLVWMACHS
AAFEDLRVLNFIRGTKVIPRGQLTTRGVQIASNENMETINSSTLELRSKYWAIRTRSG
GNTSQQRAFAAGQISVQPTFSVQRNLPFERATIMAAFTGNTEGRTSDMRTEIRMMEN
AKSEDVSFQGRGVFELSDEKATNPVPSFDMSNEGSYFFGDNAEEFDS (SEQ ID NO:
6)

FIG. 6

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M1

TATTCGTCTCAGGGAGCAAAAGCAGGTAGATATTTAAAGATGAGTCTTCTAACCG
AGGTCGAAACGTACGTTCTCTCTATCGTACCATCAGGCCCCCTCAAAGCCGAGAT
CGCGCAGAGACTTGAAGATGTCTTTGCGGGAAAGAACACCGATCTTGAGGCACT
CATGGAATGGCTAAAGACAAGACCAATCCTGTCACCTCTGACTAAAGGGATTTTA
GGATTTGTATTACGCTCACCGTGCCAGTGAGCGAGGACTGCAGCGTAGACGCT
TTGTCCAAAATGCCCTTAGTGGAACGGGAGATCCAAACAACATGGACAGAGCAG
TAAAACTGTACAGGAAGCTTAAAAGAGAAATAACATTCCATGAGGCAAAAGAGG
TGGCACTCAGCTATTCCACTGGTGCCTAGCCAGCTGCATGGGACTCATATACAA
CAGAATGGGAACGTGTTACAACCGAAGTGGCATTGTCCTGGTATGCGCCACATGT
GAACAGATTGCTGATTCCCAGCATCGATCTCACAGGCAGATGGTGACAACAACC
AACCCATTAATCAGACATGAAAACAGAATGGTATTAGCCAGTACCACGGCTAAA
GCCATGGAACAGATGGCAGGATCGAGTGAGCAGGCAGCAGAGGCCATGGAGGT
TGCTAGTAGGGCTAGGCAGATGGTACAGGCAATGAGAACCATTGGGACCCACCC
TAGCTCCAGTGCCGGTTTGAAAGATGATCTCCTTGAAAATTTACAGGCCTACCAG
AAACGGATGGGAGTGCAAATGCAGCGATTCAAGTGATCCTCTCGTTATTGCAGC
AAGTATCATTGGAATCTTGCACTTGATATTGTGGATTCTTGATCGTCTTTTCTTCA
AATTCATTTATCGTCGCCTTAAATACGGGTTGAAAAGAGGGCCTTCTACGGAAGG
AGTACCTGAGTCTATGAGGGAAGAATATCGGCAGGAACAGCAGAATGCTGTGGA
TGTTGACGATGGTCATTTTGTCAACATAGAGCTGGAGTAAAAAACTACCTTGTTT
CTACTAATACGAGACGATAT (SEQ ID NO: 7)

FIG. 7

M1 - Amino

MSLLTEVETYVLSIVPSGPLKAEIAQRLEDVFAGKNTDLEALMEWLKTRPILSPLTKG
ILGFVFTLTVPSEGLQRRRFVQNALSGNGDPNNMDRAVKLYRKLKREITFHEAKEV
ALSYSTGALASCMGLIYNRMGTVTTEVAFGLVCATCEQIADSQHRSHRQMVTITNP
LIRHENRMVLASTTAKAMEQMAGSSEQAAEAMEVASRARQMVQAMRTIGTHPSSS
AGLKDDLENLQAYQKRMGVQMQRFK (SEQ ID NO: 8)

FIG. 8

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GGAGCAAAAGCAGGGTGACAAAAACATAATGGATTCCAACACTGTGTCAAGCTT
TCAGGTAGACTGTTTTCTTTGGCATGTCCGCAAACGATTCGCAGACCAAGAAGCTG
GGTGATGCCCCATTCCTTGACCGGCTTCGCCGAGACCAGAAGTCCCTAAGGGGA
AGAGGTAGCACTCTTGGTCTGGACATCGAAACAGCCACTCATGCAGGAAAGCAG
ATAGTGGAGCAGATTCTGGAAAAGGAATCAGATGAGGCACTTAAAATGACCATT
GCCTCTGTTCTGCTTCACGCTACTTAACTGACATGACTCTTGATGAGATGTCAAG
AGACTGGTTCATGCTCATGCCCAAGCAAAAAGTAACAGGCTCCCTATGTATAAG
AATGGACCAAGCAATCATGGATAAGAACATCATACTTAAAGCAAACCTTTAGTGT
GATTTTCGAAAGGCTGGAAACACTAATACTACTTAGAGCCTTCACCGAAGAAGG
AGCAGTCGTTGGCGAAATTTACCATTTACCTTCTCTTCCAGGACATACTAATGAG
GATGTCAAAAATGCAATTGGGGTCCTCATCGGAGGACTTAAATGGAATGATAAT
ACGGTTAGAATCTCTGAAACTCTACAGAGATTCGCTTGGAGAAGCAGTCATGAA
AATGGGAGACCTTCATTCCCTTCAAAGCAGAAACGAAAAATGGAGAGAACAATT
AAGCCAGAAATTTGAAGAAATAAGATGGTTGATTGAAGAAGTGCGACATAGATT
GAAAAATACAGAAAATAGTTTTGAACAAATAACATTTATGCAAGCCTTACAAC
ATTGCTTGAAGTAGAACAAGAGATAAGAACTTTCTCGTTTCAGCTTATTTAATGA
T (SEQ ID NO: 9)

FIG. 9

NS1 - Amino

MDSNTVSSFQVDCFLWHVRKRFAHQELGDAPFLDRLRRDQKSLRGRGSTLGLDIET
ATHAGKQIVEQILEKESDEALKMTIASVPASRYLTDMTLDEMSRDWFMLMPKQKVT
GSLCIRMDQAIMDKNIILKANFSVIFERLETLILLRAFTEEGAVVGEISPLPSLPGHTNE
DVKNAIGVLIGGLKWNDNTVRISETLQRFAWRSSHENGRPSFSPSKQKRKMERTIKPEI
(SEQ ID NO: 10)

FIG. 10

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PA

TAAATGGAAGACTTTGTGCGACAGTGCTTCAATCCAATGATCGTCGAGCTTGCGG
AAAAGGCAATGAAAGAATATGGAGAGAACCCGAAAATCGAAACAAACAAATTT
GCAGCAATATGCACTCACTTGGAAGTCTGCTTCATGTACTCGGATTTCCACTTTAT
AAATGAACTGGGTGAGTCAGTGGTCATAGAGTCTGGTGACCCAAATGCTCTTTTG
AAACACAGATTTGAAATCATTGAGGGGAGAGATCGAACAATGGCATGGACAGTA
GTAAACAGCATCTGCAACACCACAAGAGCTGAAAAACCTAAATTTCTTCCAGATT
TATACGACTATAAGGAGAACAGATTTGTTGAAATTGGTGTGACAAGGAGAGAAG
TTCACATATACTACCTGGAGAAAGCCAACAAAATAAAGTCTGAGAAAACACATA
TCCACATTTTCTCATTTACAGGAGAAGAAATGGCTACAAAAGCGGACTATACTCT
TGATGAAGAGAGTAGAGCCAGGATCAAGACCAGACTATTCCTATAAGACAAGA
AATGGCCAGTAGAGGCCTCTGGGATTCCCTTCGTCAGTCCGAGAGAGGGCGAAGA
GACAATTGAAGAAAGATTTGAAATCACAGGAACGATGCGCAAGCTTGCCAATTA
CAGTCTCCCACCGAAGTTCTCCAGCCTTGAAAATTTTAGAGTCTATATAGATGGA
TTCGAACCGAACGGCTGCATTGAGAGTAAGCTTTCTCAAATGTCCAAAGAAGTA
AATGCCAAAATCGAACCATTTTCAAAGACAACACCCCGACCACTCAAATGCCA
GGTGGTCCACCCTGCCATCAGCGATCCAAATTCTTGCTAATGGATGCTCTGAAACT
GAGCATTGAGGACCCAAGTCACGAGGGGAGAGGGGATACCACTATATGATGCAAT
CAAATGCATGAAAACCTTTCTTTGGATGGAAAGAGCCCAGTATTGTTAAACCACAT
AAAAAGGGTATAAACCCGAAGTATCTCCAAACTTGGAAGCAAGTATTAGAAGAA
ATACAAGACCTTGAGAACGAAGAAAGGACCCCAAGACCAAGAATATGAAAAA
AACAAGCCAATTGAAATGGGCACTAGGTGAAAATATGGCACCAGAGAAAGTGG
ATTTTGAGGATTGTAAAGACATCAATGATTTAAACAATATGACAGTGATGAGCC
AGAAGCAAGGTCTCTTGCAAGTTGGATTCAAAGTGAGTTCAACAAGGCTTGTGA
GCTGACAGATTCAAGCTGGATAGAGCTCGATGAAATTGGGGAGGATGTGCGCCCC
AATAGAATACATTGCGAGCATGAGGAGAAATTATTTTACTGCTGAGATTTCCCAT
TGTAGAGCAACAGAATATATAATGAAAGGAGTATACATCAACACTGCTCTACTC
AATGCATCCTGTGCTGCGATGGATGAATTTCAATTAATTCCGATGATAAGTAAAT
GCAGGACCAAGAAGGGAGAAGGAAAACAAATTTATATGGATTCATAATAAAG
GGAAGGTCCCATTTAAGAAATGATACTGACGTGGTGAACCTTTGTAAGTATGGAAT
TTTCTCTCACTGATCCAAGATTTGAGCCACACAAATGGGAAAAATACTGCGTTCT
AGAAATTGGAGACATGCTTCTAAGAACTGCTGTAGGTCAAGTGTCAAGACCCAT
ATTTTTGTATGTAAGGACAAATGGAACCTCTAAAATTAATAATGAAATGGGGAAT
GGAAATGAGACGCTGCCTCCTTCAGTCTCTGCAACAGATTGAAAGCATGATCGA
AGCTGAGTCCTCAGTCAAAGAAAAGGACATGACCAAGAATTTTTTGAGAACAA
ATCAGAGACATGGCCTATAGGAGAGTCCCCCAAGGAGTGGAAGAGGGGCTCAAT
CGGGAAGGTTTGCAGGACCTTATTAGCAAAATCTGTGTTTAACAGTTTATATGCA
TCTCCACAACCTGGAAGGATTTTCAGCTGAATCTAGGAAATTACTTCTCATTGTTC
AGGCTCTTAGAGATGACCTGGAACCTGGAACCTTTGATATTGGGGGGTTATATGA
ATCAATTGAGGAGTGCCTGATTAATGATCCCTGGGTTTTGCTTAATGCATCTTGGT
TCAACTCCTTCCTCACACATGCACTGAAGTAGTTGTGGCAATGCTACTATTTGTTA
TCCATACTGTCCA (SEQ ID NO: 11)

FIG. 11

10/14PA - Amino

MEDFVRQCFNPMIVELAEKAMKEYGENPKIETNKFAAICTHLEVCFMYSDFHFINEL
GESVVIESGDPNALLKHRFEIIEGRDRTMAWTVVNSICNTTRAETPKFLPDLYDYKEN
RFVEIGVTRREVHIYYLEKANKIKSEKTHIHIFSFTGEEMATKADYTLDEESRARIKTR
LFTIRQEMASRGLWDSFRQSERGEETIEERFEITGTMRKLANYSLPPNFSSLENFRVYI
DGFEPNGCIESKLSQMSKEVNAKIEPFSKTTTPRPLKMPGGPPCHQRSKFLMDALKLS
IEDPSHEGEGIPLYDAIKCMKTFFGWKEPSIVKPHKKGINPNYLQTWKQVLEEIQDLE
NEERTPKTKNMKKTSQLKWALGENMAPEKVDFEDCKDINDLKQYDSDEPEARSLAS
WIQSEFNKACELTDSSWIELDEIGEDVAPIEYIASMRRNYFTAESHCRATEYIMKGVY
INTALLNASCAAMDEFQLIPMISKCRTKEGRRKTNLYGFIKGRSHLRNDTDVVNFVS
MEFSLTDPRFEPHKWEKYCVLEIGDMLLRRTAVGQVSRPIFLYVRTNGTSKIKMKWG
MEMRRCLLQSLQQIESMIEAESSVKEKDMTKEFFENKSETWPIGESPKGVEEGSIGKV
CRTLLAKSVFNSLYASPQLEGFSAESRKLLLVQALRDDLEPGTFDIGGLYESIEECLIN
DPWVLLNASWFNSFLTHALK (SEQ ID NO: 12)

FIG. 12

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PB1

GAAAGCAGGCAAACCATTTGAATGGATGTCAATCCGACTCTACTTTTCTTAAAGG
TGCCAGCGCAAAATGCTATAAGCACAACATTCCCTTATACTGGAGATCCTCCCTA
CAGTCATGGAACAGGGACAGGATACACCATGGATACTGTCAACAGAACACACCA
ATATTCAGAAAAAGGGAAATGGACAACAAACACTGAGATTGGAGCACCACAACCT
TAATCCAATCGATGGACCACTTCCTGAAGACAATGAACCAAGTGGGTACGCCCCA
AACAGATTGTGTATTGGAAGCAATGGCTTTCCTTGAAGAATCCCATCCCGGAATC
TTTGAAAATTCGTGTCTTGAAACGATGGAGGTGATTTCAGCAGACAAGAGTGGAC
AACTAACACAAGGCCGACAACTTATGATTGGACCTTGAATAGGAATCAACCT
GCCGCAACAGCACTTGCTAATACGATTGAAGTATTCAGATCAAATGGTCTGACTT
CCAATGAATCGGGGAGATTGATGGACTTCCTCAAAGATGTCATGGAGTCCATGA
ACAAGGAGGAAATGGAAATAACAACACACTTCCAACGGAAGAGAAGAGTAAGA
GACAACATGACAAAGAGAATGATAACACAGAGAACCATAGGGGAAGAAAAACA
ACGATTAAGCAGAAAGAGCTATCTAATCAGAACATTAACCCTAAACACAATGAC
CAAGGACGCTGAAAGAGGGGAAATTGAAACGACGAGCAATCGCTACCCCAGGGA
TGCAGATAAGAGGATTTGTATATTTTGTGTTGAAACACTAGCTCGAAGAATATGTGA
AAAGCTTGAACAATCAGGATTGCCAGTTGGCGGTAATGAGAAAAAGGCCAAACT
GGCTAATGTCGTCAGAAAAATGATGACTAATTCCAAGCACTGAACTCTCCTTC
ACCATCACTGGGGACAATACCAAATGGAATGAAAATCAGAACCCACGCATATTC
CTGGCAATGATCACATACTAGAAATCAGCCAGAATGGTTCAGAAATGTT
CTAAGCATTGCACCGATTATGTTCTCAAATAAAATGGCAAGACTGGGGAAAGGA
TATATGTTTGAAAGCAAAAGTATGAAATTGAGAACTCAAATACCAGCAGAAATG
CTAGCAAGCATTGACCTAAAATATTTCAATGATTCAACAAAAAAGAAAATTGAA
AAGATACGACCACTCCTGGTTGACGGGACTGCTTCACTGAGTCCTGGCATGATGA
TGGGAATGTTCAACATGTTGAGCACTGTGCTGGGTGTATCCATATTAAACCTGGG
CCAGAGGAAATATACAAAGACCACATACTGGTGGGGATGGTCTGCAATCATCCGA
TGACTTTGCTTTGATAGTGAATGCGCCTAATCATGAAGGAATACAAGCTGGAGTA
GACAGATTCTATAGAACTTGCAAACCTGGTCGGGGATCAACATGAGCAAAAAGAAG
TCCTACATAAATAGAACTGGAACATTCGAATTCACAAGCTTTTTTCTACCGGTATG
GTTTTGTAGCCAATTTTCAGCATGGAACCTACCCAGTTTTTGGGGTTTCCGGAATAAA
TGAATCTGCAGACATGAGCATTGGAGTGACAGTCATCAAAAACAACATGATAAA
TAATGATCTCGGTCCTGCCACGGCACAAATGGYACTCCAACCTCTTCATTAAGGAT
TATCGGTACACATACCGGTGCCATAGAGGTGATACCCAGATACAAACCAGAAGA
TCTTTTGAGTTGAAGAACTGTGGGAACAGACTCGATCAAAGACTGGTCTACTGG
TATCAGATGGGGGTCCAAACCTATATAACATCAGAAACCTACACATCCCGGAAG
TCTGTTTAAAATGGGAGCTAATGGATGAAGATTATAAGGGGAGGCTATGCAATC
CATTGAATCCTTTCGTTAGTCACAAAGAAATTGAATCAGTCAACAGTGCAGTAGT
AATGCCTGCGCATGGCCCTGCCAAAAGCATGGAGTATGATGCTGTGCAACAACA
CATTCTTGGATCCCCAAGAGGAACCGGTCCATATTGAACACAAGCCAAAGGGGA
ATACTAGAAGATGAGCAGATGTATCAGAAATGCTGCAACCTGTTTGAAAAATTCT
TCCCCAGCAGCTCATACAGAAGACCAGTCGGAATTTCTAGTATGGTTGAGGCCAT
GGTATCCAGGGCCCGCATTGATGCACGAATTGACTTCGAATCTGGACGGATAAA
GAAGGATGAGTTCGCTGAGATCATGAAGATCTGTTCCACCATTGAAGAGCTCAG
ACGGCAAAAATAGTGAA (SEQ ID NO: 13)

FIG. 13

12/14PB1 - Amino

MDVNPTLLFLKVPAQNAISTTFPYTGDPPYSHGTGTGYTMDTVNRT HQYSEK GKWT
TNTEIGAPQLNPIDGPLPEDNEPSGYAQ TDCVLEAMAFLEESH PGIFENSCLETMEVIQ
QTRVDKLTQGRQTYDWTLNRNQPAATALANTIEVFRSNG LTSNESGRLMDFLKDV
MESMNKEEMEITTHFQRKRRVRDNMTKRMITQRTIGKKKQRLSRKSYLIRTLTLNT
MTKDAERGKLRRAIATPGMQIRGFVYFVETLARRICEKLEQSGLPVGGNEKKAKL
ANVVRKMMTNSQDTELSFTITGDNTKWNENQNPRIFLAMITYITRNQPEWFRNVLSI
APIMFSNKMARLGKGYMFESKSMKLRTQIPAEMLASIDLKYFNDSTKKKIEKIRPLL
DGTASLSPGMMMGMFNMLSTVLGV SILNLGQRKYTKTTYWWDGLQSSDDFALIVN
APNHEGIQAGVDRFYRTCKLVGINMSKKKSYINRTGTFFETSFFYRYGFVANFSMELP
SFGVSGINESADMSIGVTVIKNNMINNDLGPATAQMXLQLFIKDYRYTYRCHRGDTQ
IQTRRSFELKKLWEQTRSKTGLLVSDGGPNLYNIRNLHIPEVCLKWELMDDEDYKGRL
CNPLNPFVSHKEIESVNSAVVMPAHGPAKSMEYDAVATTHSWIPKRNR SILNTSQRGI
LEDEQMYQKCCNLFEKFFPSSSYRRPVGISSMVEAMVSRARIDARIDFESGRIKKDEF
AEIMKICSTIEELRRQK (SEQ ID NO: 14)

FIG. 14

13/14

PB2

TATTGGTCTCAGGGAGCGAAAGCAGGTCAAATATATTCAATATGGAGAGAATAA
AAGAACTGAGAGATCTGATGTTACAATCCCGCACCCGCGAGATACTAACAAAAA
CTACTGTGGACCACATGGCCATAATCAAGAAATACACATCAGGAAGACAAGAGA
AGAACCCTGCACTTAGGATGAAATGGATGATGGCAATGAAATACCCAATTACAG
CAGATAAGAGGATAATGGAGATGATTCCTGAGAGAAATGAACAGGGGACAAACC
CTTTGGAGCAAAACGAACGATGCTGGCTCAGACCGCGTAATGGTATCACCTCTGG
CAGTGACATGGTGGAATAGGAATGGACCAACAACGAACACAATTTCATTATCCGA
AAGTCTACAAAACCTTATTTTGAAGAGGTTGAAAGATTGAAACACGGAACCTTTG
GCCCCGTTTCATTTTAGGAATCAAGTCAAGATAAGACGAAGAGTTGATGTAAACC
CTGGTCACGCGGACCTCAGTGCTAAAGAAGCACAAGATGTGATCATGGAAGTTG
TTTTCCCAAATGAAGTGGGAGCCAGAATTCTAACATCAGAATCACAATAACAAT
AACCAAAGAGAAAAAGGAAGAACTTCAGGACTGCAAAATTGCTCCCTTGATGGT
AGCATACATGCTAGAAAGAGAGTTGGTCCGAAAAACAAGGTTCTCCAGTAGT
AGGCGGAACAAGCAGTGTATACATTGAAGTGTTCATCTGACTCAGGGAACATG
CTGGGAGCAAATGTACACCCCAGGAGGAGAAGTTAGAAACGATGATATTGATCA
AAGTTTAATTATTGCAGCCCGGAACATAGTGAGAAGAGCAACAGTATCAGCAGA
TCCACTAGCATCCCTACTGGAAATGTGCCACAGTACACAGATTGGTGGAACAAG
GATGGTAGACATCCTTAAGCAGAACCCAACAGAGGAACAAGCTGTGGATATATG
CAAAGCAGCAATGGGATTGAGAATTAGCTCATTCATTGCTTTGGTGGATTCACC
TTCAAAAGGACAAGTGGATCATCAGTCAAGAGAGAAGAAGAAATGCTTACGGGC
AACCTTCAAACATTGAAAATAAGAGTGCATGAGGGGCTATGAAGAATTCACAATG
GTCGGAAGAAGAGCAACAGCCATTATCAGAAAGGCAACCAGAAGATTGATTCAA
TTGATAGTAAGTGGGAGAGATGAACAATCAATTGCTGAAGCAATAATTGTAGCC
ATGGTGTTCGCAAGAAGATTGCATGATAAAAGCAGTTCGAGGCGATTTGAACT
TTGTTAATAGAGCAAATCAGCGTTTGAACCCCATGCATCAACTCTTGAGGCATTT
CCAAAAAGATGCAAAAGTGCTTTTCCAAAATTGGGGAATTGAACCCATCGACAA
TGTAATGGGGATGATTGGAATATTGCCTGACATGACCCCAAGCACCGAGATGTC
ATTGAGAGGAGTGAGAGTCAGCAAAATGGGAGTGGATGAGTACTCCAGCACTGA
GAGAGTGGTGGTGAGCATTGACCGTTTTTTAAGAGTTCGGGATCAAAGGGGAAA
CATACTACTGTCCCCTGAAGAAGTCAGTGAAACACAAGGAACGGAAAAAGCTGAC
AATAATTTATTCGTCATCAATGATGTGGGAGATTAATGGTCCCGAATCAGTGTTG
GTCAATACTTATCAATGGATCATCAGAAACTGGGAAATTGTAAAAATTGAGTGGT
CACAGGACCCCACAATGTTATACAATAAGATAGAATTTGAACCATTCGAATCCCT
GGTCCCTAGGGCCACCAGAAGCCAATACAGCGGTTTCGTAAGAACCCTGTTTCAG
CAAATGCGAGATGTACTTGGAACATTTGATACTGCTCAAATAATAAACTCCTCC
CTTTTGCCGCTGCTCCTCCGGAACAGAGTAGGATGCAGTTCTCTTTGACTGTT
AATGTAAGAGGTTTCGGGAATGAGGATACTTGTAAGAGGCAATTCCCCGGTGTTT
AACTACAATAAAGTCACTAAAAGGCTCACAGTCCTCGGAAGGATGCAGGTGCG
CTTACTGAGGACCCAGATGAAGGTACGGCTGGAGTAGAATCTGCTGTTCTAAGA
GGGTTTCTCATTTTAGGTAAAGAAAACAAGAGATATGGCCCAGCACTAAGCATC
AATGAACTTAGCAAACCTTGCAAAAGGGGAGAAAGCCAATGTACTAATTGGGCAA
GGGGACGTAGTGTTGGTAATGAAACGGAAACGTGACTCTAGCATACTTACTGAC
AGCCAGACAGCGACCAAAAGGATTCGGATGGCCATCAATTAGTGTTGAATTGTTT
AAAAACGACCTTGTTTCTACTAATACGAGACCATAT (SEQ ID NO: 15)

FIG. 15

14/14PB2 - Amino

MERIKELRDLMLQSRTREILTKTTVDHMAIKKYTSGRQEKNPALRMKWMMAMKY
PITADKRIMEMIPERNEQGQTLWSKTNDAGSDRVMVSPLAVTWWNRNGPTTNTIHY
PKVYKTYFEKVERLKHGTFGPVHFRNQVKIRRRVDVNPBGHADLSAKEAQDVIMEVV
FPNEVGARILTSESQTLTITKEKKEELQDCKIAPLMVAYMLERELVRKTRFLPVVGGTS
SVYIEVLHLTQGTCWEQMYTPGGEVRNDDIDQSLIAARNIVRRATVSADPLASLLE
MCHSTQIGGTRMVDILKQNPTEEQAVDICKAAMGLRISSSFSGGFTFKRTSGSSVKR
EEEMLTGNLQTLKIRVHEGYEEFTMVGRRATAIRKATRRLIQLIVSGRDEQSIAEAI
VAMVFSQEDCMIKAVRGDLNFVNRRANQRLNPMHQLLRHFQKDAKVLFFQNWGIEPI
DNVMGMIGILPDMTPSTEMSLRGVRVSKMGVDEYSSTERVVVSIDRFLRVRDQRGNI
LLSPEEVSETQGTEKLTIIYSSSMWEINGPESVLVNTYQWIIRNWEIVKIQWSQDPT
MLYNKIEFEPFQSLVPRATRSQYSGFVRTLFQQMRDVLGTFDTAQIIKLLPFAAAPPE
QSRMQFSSLTVNVVRGSGMRILVRGNSPVFNYNKVTKRLTVLGKDAGALTEDPDEGT
AGVESAVLRGFLILGKENKRYGPALSINELSKLAKGEKANVLIGQGDVVLVMKRKR
DSSILTDSQTATKRIRMAIN (SEQ ID NO: 16)

FIG. 16