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

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(52) **U.S. Cl.**

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424/206.1; 424/210.1; 435/236; 435/320.1;  
536/23.1; 530/380; 530/396

(58) **Field of Classification Search**

None  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

3,991,179 A 11/1976 Beare et al.  
4,009,258 A 2/1977 Kilbourne  
4,029,763 A 6/1977 Kilbourne  
4,140,762 A 2/1979 Bachmayer et al.  
4,278,662 A 7/1981 Löbmann et al.  
4,318,903 A 3/1982 Löbmann et al.  
4,338,296 A 7/1982 Löbmann et al.  
4,693,893 A 9/1987 Campbell  
4,826,687 A 5/1989 Nerome et al.  
5,136,019 A 8/1992 Judd et al.  
5,162,112 A 11/1992 Oxford et al.  
5,616,327 A 4/1997 Judd et al.  
5,741,493 A 4/1998 Moste-Deshairs et al.  
5,762,939 A 6/1998 Smith et al.  
6,245,532 B1 6/2001 Smith et al.  
6,605,457 B1 8/2003 Fiers et al.  
6,740,325 B1 5/2004 Arnon et al.  
7,959,929 B2\* 6/2011 Crawford et al. .... 424/206.1

2003/0129197 A1 7/2003 Fiers et al.  
2003/0199074 A1 10/2003 Dowling et al.  
2005/0089533 A1\* 4/2005 Frantz et al. .... 424/234.1  
2007/0048819 A1\* 3/2007 Minke et al. .... 435/69.1  
2007/0082012 A1\* 4/2007 Shields et al. .... 424/209.1

**FOREIGN PATENT DOCUMENTS**

WO WO 00/09702 8/2000  
WO WO 01/60849 2/2001  
WO WO 2006/116082 11/2006

**OTHER PUBLICATIONS**

GenBank Accession # ABA39850, hemagglutinin, partial [Influenza A virus (A/canine/Texas/1/2004 (H3N8))], Sep. 28, 2005.\*

GenBank Accession # DQ124196, Influenza A virus (A/canine/Texas/1/2004 (H3N8)) hemagglutinin gene, partial cds., Sep. 28, 2005.\*

GenBank Accession # AAX23575, hemagglutinin precursor [Influenza A virus (A/equine/Kentucky/5/2002 (H3N8))], Mar. 12, 2005.\*

GenBank Accession # AY855341, Influenza A virus, (A/equine/Kentucky/5/02 (H3N8)) hemagglutinin precursor, gene, complete cds., Mar. 12, 2005.\*

Kay et al., Screening Phage-Displayed Combinatorial Peptide Libraries, 2001, Methods, vol. 24, pp. 240-246.\*

Weis et al., "Structure of the Influenza virus haemagglutinin complexed with its receptor, sialic acid," *Nature* 333(2): 426-431 (1998).

Anderson et al., "Canine Influenza Virus Agglutination of Avian and Mammalian Red Blood Cells," *Proceedings of the American Association of Veterinary Laboratory Diagnosticians 49<sup>th</sup> Annual Conference*, p. 44 (2006).

Anderson et al., "Development of a Hemagglutination Inhibition Assay for Diagnosis of Canine Influenza Virus Infection," *Proceedings of the American Association of Veterinary Laboratory Diagnosticians 49<sup>th</sup> Annual Conference*, p. 45 (2006).

Crawford et al.: "Influenza A virus (A/canine/Texas/1/2004 (H3N9))" Database accession No. DQ124159 (2005).

Crawford et al., "Transmission of Equine Influenza Virus to Dogs," *Science*, 310: pp. 482-485 (2005).

Daly, "Equine Influenza in dogs: Too late to bolt the stable door?," *The Veterinary Journal* 171 pp. 7-8 (2006).

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, p. 158 (2005).

Ito, T. et al.: "Evolutionary analysis of the influenza A virus M gene with comparison of the M1 and M2 proteins," *Journal of Virology*, vol. 65, No. 10, 1991, pp. 5491-5498, ISSN: 0022-538X, 06173, the whole document (1991).

(Continued)

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(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.

**15 Claims, 14 Drawing Sheets**

(56)

**References Cited**

## OTHER PUBLICATIONS

Joly, "Canine Influenza Virus" *The Veterinary Record*, p. 527 (2005).

Keawcharoen et al., "Avian Influenza H5N1 in Tigers and Leopards," *Emerg. Infect. Dis.*, 10: pp. 2189-2191 (2004).

Lindstrom et al.: "Phylogenetic analyses of the matrix and non-structural genes of equine influenza viruses," *Archives of Virology*, New York, vol. 143, No. 8, 1998, pp. 1585-1598, NY, US, ISSN: 0304-8608, the whole document (1998).

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, pp. 103-106 (2001).

Peek, Simon F. et al: "Acute respiratory distress syndrome and fatal interstitial pneumonia associated with equine influenza in a neonatal foal," *Journal of Veterinary Internal Medicine*, Lippincott, Philadelphia, U.S., vol. 18, No. 1, pp. 132-134 (2004).

Peek et al.: Database accession No. Q30BG0 (2005).

Peek et al.: Database accession No. Q30BG2 (2005).

Peek et al.: Database accession No. Q30BG4 (2005).

Peek et al.: Database accession No. Q30BG5 (2005).

Peek et al.: Database accession No. Q30BG6 (2005).

Peek et al.: Database accession No. Q30BF7 (2005).

Peek et al.: Database accession No. Q30BF8 (2005).

Peek et al.: Database accession No. Q30BF9 (2005).

Quinlivan et al., "Attenuation of equine influenza viruses through truncations of the N protein," Database accession No. Q5BUA9 (2005).

Quinlivan et al., "Attenuation of equine influenza viruses through truncations of the N protein," Database accession No. Q5BUA7 (2005).

Quinlivan et al.; "Attenuation of equine influenza viruses through truncations of the N protein," Database accession No. Q5BUB2 (2005).

Quinlivan et al.: "Attenuation of equine influenza viruses through truncations of the N protein," Database accession No. Q5BUB3 (2005).

Smith et al., "Canine Influenza Virus" *The Veterinary Record*, p. 599 (2005).

Yoon et al., "Influenza Virus Infection in Racing Greyhounds," *Emerg. Infect. Dis.*, 11(12): pp. 1974-1976 (2005).

Yoon et al.: "Influenza virus A (A/canine/Iowa/13628/2005 (H3N8))," Database accession No. Q2XXL0 (2005).

Enserink, "Epidemiology. Horse Flu Virus Jumps to Dogs," *Science*, 309: 2147 (2005).

Wood et al., "The standardization of inactivated equine influenza vaccines by single-radial immunodiffusion," *Jrnl. Biol. Standardization*, 11: 133-136 (1983).

International Search Report issued in PCT/IB2006/002741 (2007).

\* cited by examiner

NM

AGTTTAAAATGAATCCAAATCAAAGATAATAGCAATTGGATTTGCATCATTGGG  
GATATTAATCATTAAATGTCATTCTCCATGTAGTCAGCATTATAGTAACAGTACTG  
GTCCTCAATAACAATAGAACAGATCTGAACTGCAAAGGGACGATCATAAGAGAA  
TACAATGAAACAGTAAGAGTAGAAAACTTACTCAATGGTATAATACCAGTACA  
ATTAAGTACATAGAGAGACCTTCAAATGAATACTACATGAATAACACTGAACCA  
CTTTGTGAGGCCCAAGGCTTTGCACCATTTTCCAAAGATAATGGAATACGAATTG  
GGTCGAGAGGCCATGTTTTTGTGATAAGAGAACCTTTTGTATCATGTTCCGCCCTC  
AGAATGTAGAACCCTTTTCTCACACAGGGCTCATTACTCAATGACAAACATTCT  
AACGGCACAATAAAGGATCGAAGCCCGTATAGGACTTTGATGAGTGTCAAATA  
GGGCAATCACCCAATGTATATCAAGCTAGGTTTGAATCGGTGGCATGGTCAGCA  
ACAGCATGCCATGATGGAAAAAATGGATGACAGTTGGAGTCACAGGGCCCGAC  
AATCAAGCAATTGCAGTAGTGA ACTATGGAGGTGTTCCGGTTGATACTATTAATT  
CATGGGCAGGGGATATTTTAAGAACCCAAGAATCATCATGCACCTGCAITAAAG  
GAGACTGTTATTGGGTAATGACTGATGGACCGGCAAATAGGCAAGCTAAATATA  
GGATATTCAAAGCAAAGATGGAAGAGTAATTGGACAAACTGATATAAGTTTCA  
ATGGGGGACACATAGAGGAGTGTTCTTGTTACCCCAATGAAGGGAAGGTGGAAT  
GCATATGCAGGGACAATTGGACTGGAACA AATAGACCAATTCTGGTAATATCTTC  
TGATCTATCGTACACAGTTGGATATTTGTGTGCTGGCATTCCCAC TGACACTCCTA  
GGGGAGAGGATAGTCAATTCACAGGCTCATGTACAAAGTCCTTTGGGAAATAAAG  
GATACGGTGTAAAAGGCTTCGGGTTTCGACAAGGAACTGACGTATGGGCCGGAA  
GGACAATTAGTAGGACTTCAAGATCAGGATTCGAAATAATAAAAATCAGGAATG  
GTTGGACACAGAACAGTAAGGACCAAATCAGGAGGCAAGTGATTATCGATGACC  
CAAATTGGTCAGGATATAGCGGTTCTTTCACATTGCCGGTTGAACTGACAAAAA  
GGGATGTTTGGTCCCCTGTTTCTGGGTTGAAATGATTAGAGGTAAACCTGAAGAA  
ACAACAATATGGACCTCTAGCAGCTCCATTGTGATGTGTGGAGTAGATCATAAAA  
TTGCCAGTTGGTCATGGCACGATGGAGCTATTCTTCCCTTTGACATCGATAAGAT  
GTAATTTACGAAAAAACTCCTTGTCTTCTACTA (SEQ ID NO: 1)

FIG. 1

NM - Amino

MNPNQKIIAIGFASLGILIIINVILHVVSIIIVTVLVLNNRRTDLNCKGTIIREYNETVRVEK  
LTQWYNTSTIKYIERPSNEYMNNTEPLCEAOGFAPFSKDNIGIRIGSRGHV FVIREPFV  
SCSPSECR TFFLTQGSLNDKHSNGTIKDRSPYRTLMSVKIGQSPNVYQARFESVAWS  
ATACHDGKKWMTVGVTGPDNQAIAVVNYGGVPVDTINSWAGDILRTQESSCTCIKG  
DCYWVMTDGPANRQAKYRIFKAKDGRVIGQTDISFNGGHIEECSCYPNEGKVECICR  
DNWTGTNRPII.VISSDI.SYTVGYLCAGIPTDTPRGEDSQFTGSCTSPLGNKGYGVKGF  
GFRQGTDVWAGRTISRTSRSGFEIIRNGWTQNSKDQIRRQVIIDDPNWSGYSGSFTL  
PYELTKKGCLVPCFWVEMIRGKPEETTIWTSSSSIVMCGVDHKIASWSWIIDGAILPF  
DIDKM (SEQ ID NO: 2)

FIG. 2

HA:

AGCAAAAGCAGGGGATATTTCTGTCAATCATGAAGACAACCATTATTTTAATACT  
ACTGACCCATTGGGCCTACAGTCAAAACCCAATCAGTGGCAATAACACAGCCAC  
ACTGTGTCTGGGACACCATGCAGTAGCAAATGGAACATTGGTAAAAACAATGAG  
TGATGATCAAATTGAGGTGACAAATGCTACAGAATTAGTTCAGAGCATTTCATG  
GGGAAAATATGCAACAAATCATATAGAATTCTAGATGGAAGAAATTGCACATTA  
ATAGATGCAATGCTAGGAGACCCCCACTGTGACGCCCTTCAGTATGAGAGTTGG  
GACCTCTTTATAGAAAGAAGCAGCGCTTTCAGCAATTGCTACCCATATGACATCC  
CTGACTATGCATCGCTCCGATCCATTGTAGCATCCTCAGGAACAGTTGAATTCAC  
AGCAGAGGGATTACATGGACAGGTGTAACCTCAAAACGGAAGAAGTGGAGCCTG  
CaaAAGGGGATCAGCCGATAGTTTCTTTAGCCGACTGAATTGGCTAACAAAATCT  
GGAAGCTCTTACCCACATTGAATGTGACAATGCCTAACAAATAAAAATTTGACA  
AGCTATACATCTGGGGGATTCATCACCCGAGCTCAAATCAAGAGCAGACAAAAT  
TGTACATCCAAGAATCAGGACGAGTAACAGTCTCAACAAAAGAAGTCAACAAA  
CAATAATCCCTAACATCGAATCTAGACCGTTGGTCAGAGGTCAATCAGGCAGGA  
TAAGCATATACTGGACCATTGTAAAACCTGGAGATATCCTAATGATAAACAGTA  
ATGGCAACTTAGTTGCACCCGCGGGGATATTTTAAATTGAACACAGGGAAAAGCT  
CTGTAAATGAGATCCGATGTACCCATAGACATTTGTGTGTCTGAAATGTATTACACC  
AAATGGAAGCATCTCCAACGACAAGCCATTCAAAATGTGAACAAAAGTTACATA  
TGGAAAATGCCCAAGTATATCAGGCAAAACACTTTAAAGCTGGCCACTGGGAT  
GAGGAATGTACCAGAAAAGCAAACCAGAGGAATCTTTGGAGCAATAGCGGGATT  
CATCGAAAACGGCTGGGAAGGAATGGTTGATGGGTGGTATGGGTTCCGATATCA  
AAACTCTGAAGGAACAGGGCAAGCTGCAGATCTAAAGAGCACTCAAGCAGCCAT  
TGACCAGATTAATGGAAAGTTAAACAGAGTGATTGAAAGAACCAATGAGAAATT  
CCATCAAAATAGAGAAGGAATTCTCAGAAAGTAGAAGGAAGGAATTCAGGACTTGG  
GAAATATGTAGAAGACACCAAAATAGACCTATGGTCCTACAATGCAGAATTGCT  
GGTGGCTCTAGAAAATCAACATACAATTGACTTAACAGATGCAGAAATGAATAA  
ATTATTTGAGAAGACTAGACGCCAGTTAAGAGAAAACGCAGAAGACATGGGAGG  
TGGATGTTTCAAGATTTACCACAAATGTGATAATGCATGCATTGAATCAATAAGA  
ACTGGGACATATGACCATTACATATACAGAGATGAAGCATTAAACAACCGATTT  
CAGATCAAAGGTGTAGAGTTGAAATCAGGCTACAAAGATTGGATACTGTGGATT  
TCATTCGCCATATCATGCTTCTTAATTTGCGTTGTTCTATTGGGTTTCATTATGTGG  
GCTTGCCAAAAGGCAACATCAGATGCAACATTTGCATTTGAGTAAACTGATAGT  
TAAAAACACCCCTTGTTTCTACT (SEQ ID NO:3)

FIG. 3

HA - Amino

MKTTIILILLTHWAYSQNPISGNNTATLCLGHHAVANGTLVKTMSDDQIEVTNATEL  
VQSISMGKICNKSYRILDGRNCTLIDAMLGDPHCDALQYESWDLFIERSSAFNSCYPY  
DIPDYASLRSIVASSGIVEFTAEFTWTGVTQNGRSGACKRGSADSFRLNWLTKS  
GSSYPTLNVTMPNNKNFDKLYIWGIHHPSSNQEQTCLYIQESGRVTVSTKRSQQTIIP  
NIESRPLVRGQSGRISYWTIVKPGDILMINSNGNLVAPRGYFKLNTGKSSVMRSDVPI  
DICVSECITPNGSISNDKPFQNVNKVTYGKCPKYIRQNTLKLATGMRNVPEKQTRGIF  
GAIAGFIENGWEGMVDGWYGFYQNSEGTGQAADLKSTQAAIDQINGKLN RV IERT  
NEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDAEMN  
KLFKTRRQIRENAEDMGGGCFKIYHKCDNACIESIRTGTYDHYIYRDEALNNRFQI  
KGVELKSGYKDWILWISFAISCFLICVLLGFIMWACQKGNIRCNICI (SEQ ID NO: 4)

FIG. 4

NP

CAGGGAGCAAAGCAGGGTAGATAATCACTCACTGAGTGACATCAAAGTCATGG  
CGTCTCAAGGCACCAAACGATCCTATGAACAGATGGAAACTGATGGGGAAACGCC  
AGAATGCAACTGAAATCAGAGCATCTGTCCGAAGGATGGTGGGAGGAATCGGAC  
GGTTTTATGTCCAGATGTGTACTGAGCTTAAACTAAACGACCATGAAGGGCGGCT  
GATTCAGAACAGCATAACAATAGAAAGGATGGTACTTTCAGCATTTCGACGAAAG  
AAGAAACAAGTATCTCGAGGAGCATCCCAGTGCTGGGAAAGACCCTAAGAAAAC  
GGGAGGCCCGATATACAGAAGAAAAGATGGGAAATGGATGAGGGAACTCATCC  
TCCATGATAAAGAAGAAATCATGAGAATCTGGCGTCAGGCCAACAATGGTGAAG  
ACGCTACTGCTGGTCTTACTCATATGATGATCTGGCACTCCAATCTCAATGACAC  
CACATACCAAAGAACAAGGGCTCTTGTTCCGACTGGGATGGATCCCAGAATGTG  
CTCTCTGATGCAAGGCTCAACCCTCCCACGGAGATCTGGAGCCGCTGGTGTGCA  
GTAAAAGGTGTTGGAACAATGGTAATGGAACCTCATCAGGATGATCAAACGCCGA  
ATAAATGATCGGAATTTCTGGAGAGGTGAAAATGGTCGAAGAACCAGAATTGCT  
TATGAAAGAATGTGCAATATCCTCAAAGGGAAATTTTCAGACAGCAGCACAAACGG  
GCTATGATGGACCAGGTGAGGGAAAGGCCGCAATCCTGGAAACGCTGAGATTGAG  
GATCTCATTTCCTTGGCACGATCAGCACTTATTTTGAGAGGATCAGTAGCCATA  
AATCATGCCTACCTGCCTGTGTTTATGGCCTTGCAGTAACCAGTGGGTATGACTTT  
GAGAAGGAAGGATACTCTCTGGTTGGAATTGATCCTTTCAAACCTACTCCAGAACA  
GTCAAATTTTCAGTCTAATCAGACCAAAGAAAACCCAGCACACAAAAGCCAGT  
TGGTGTGGATGGCATGCCATTCTGCAGCATTGAGGATCTGAGAGTTTTAAATTT  
CATTAGAGGAACCAAAGTAATCCCAAGAGGACAGTTAACAACCAGAGGAGTTCA  
AATTGCTTCAAATGAAAACATGGAGACAATAAATTTCTAGCACACTTGAAGTGAAG  
AAGCAAATATTGGGCAATAAGGACCAGAAGCGGAGGAAACACCAGTCAACAGA  
GAGCATTTCAGGACAGATAAGTGTGCAACCTACTTTCTCAGTACAGAGAAATCT  
TCCCTTTGAGAGAGCAACCATTATGGCTGCATTCACTGGTAACACTGAAGGGAGG  
ACTTCCGACATGAGAACGGAAATCATAAGGATGATGGAAAATGCCAAATCAGAA  
GATGTGTCTTTCCAGGGGCGGGGAGTCTTCGAGCTCTCGGACGAAAAGGCAACG  
AACCCGATCGTGGCTTCCCTTTGACATGAGCAATGAAGGGTCTTATTTCCTTCGGAG  
ACAATGCTGAGGAGTTTGACAGTTAAAGAAAATACCCTTGTTTCTACTAATACG  
AGACGATAT (SEQ ID NO: 5)

FIG. 5

NP - Amino

MASQGTKRSYEQMETDGERQNATEIRASVGRMVGGIGRFYVQMCTELKLNDHEGR  
LIQNSITIERMVLSAFDERRNKYLEEHPSAGKDPKKTGGPIYRRKDGKWMRELILHD  
KEEIMRIWRQANNGEDATAGLTHMMIWHSNLNDTTYQRTRALVRTGMDPRMCSL  
MQGSTLPRRSGAAGA AVKGVGTMMELIRM I KRGINDRNFWRGENGRRTRIAYER  
MCNILKGKFQTA AQRAMMDQVREGRNPGNAEIEDLIFLARSALILRGSVAHKSC LPA  
CVYGLAVTSGYDFEKEGYSLVGIDPFKLLQNSQIFSLIRPKENPAHKSQLVWMACHS  
AAFEDLRVLNFIRGTKVIPRGQLTTRGVQIASNENMETINSSTLELRSKYWAIRTRSG  
GNTSQQRAFAGQISVQPTFSVQRNLPFERATIMAAFTGNTEGRTSDMRTEIIRMMEN  
AKSEDVSFQGRGVFELSDEKATNPVPSFDMSNEGSYFFGDNAEEFDS (SEQ ID NO:  
6)

FIG. 6



MI

TATTCGTCTCAGGGAGCAAAAGCAGGTAGATATTTAAAGATGAGTCTTCTAACCG  
AGGTTCGAAACGTACGTTCTCTATCGTACCATCAGGCCCCCTCAAAGCCGAGAT  
CGCGCAGAGACTTGAAGATGTCTTTGCGGGAAAGAACACCGATCTTGAGGCACT  
CATGGAATGGCTAAAGACAAGACCAATCCTGTCACCTCTGACTAAAGGGATTTTA  
GGATTTGTATTCACGCTCACCGTGCCAGTGAGCGAGGACTGCAGCGTAGACGCT  
TTGTCCAAAATGCCCTTAGTGGAACGGAGATCCAAACAAACATGGACAGAGCAG  
TAAACTGTACAGGAAGCTTAAAAGAGAAATAACATTCCATGAGGCAAAAGAGG  
TGGCACTCAGCTATTCCACTGGTGCCTAGCCAGCTGCATGGGACTCATATACAA  
CAGAATGGGAAGTGTACAAACCGAAGTGGCATTGGCCTGGTATGCGCCACATGT  
GAACAGATTGCTGATTCCCAGCATCGATCTCACAGGCAGATGGTGACAACAACC  
AACCCATTAATCAGACATGAAAACAGAATGGTATTAGCCAGTACCACGGCTAAA  
GCCATGGAAACAGATGGCAGGATCGAGTGAGCAGGCAGCAGAGGCCATGGAGGT  
TGCTAGTAGGGCTAGGCAGATGGTACAGGCAATGAGAACCATTGGGACCCACCC  
TAGCTCCAGTGCCGGTTTGAAAGATGATCTCCTTGAAAATTTACAGGCCTACCAG  
AAACGGATGGGAGTGCAAATGCAGCGATTCAAGTGATCCTCTCGTTATTGCAGC  
AAGTATCATTGGAATCTTGCACTTGATATTGTGGATTCTTGATCGTCTTTTCTTCA  
AATTCATTTAICGICGCCITAAATACGGGTTGAAAAGAGGGCCTTCTACGGAAGG  
AGTACCIGAGTCTATGAGGGAAGAATAICGGCAGGAACAGCAGAAATGCTGTGGA  
TGTTGACGATGGTCATTTTGTCAACATAGAGCTGGAGTAAAAAACTACCTTGTT  
CTACTAATACGAGACGATAT (SEQ ID NO: 7)

FIG. 7

MI - Amino

MSLLTEVETYVLSIVPSGPLKAEIAQRLEDVFAGKNTDLEALMEWLKTRPILSPLTKG  
ILGFVFTLTVPSERGLQRRRFVQNALSGNGDPNNMDRAVKLYRKLKREITFHEAKEV  
ALSYSTGALASCMGLIYNRMGTVTTEVAFGLVCATCEQIADSQHRSHRQMVTNTNP  
LIRHENRMVLASTITAKAMEQMAGSSEQAAEAMEVASRARQMVMQAMRTIGTHPSSS  
AGLKDDLLENLQAYQKRMGVQMQRFK (SEQ ID NO: 8)

FIG. 8

NSI

GGAGCAAAGCAGGGTGACAAAACATAATGGATTCCAACACTGTGTCAAGCTT  
TCAGGTAGACTGTTTTCTTTGGCATGTCCGCAAACGATTCGCAGACCAAGAAGCTG  
GGTGATGCCCATTCCTTGACCGGCTTCGCCGAGACCAGAAGTCCCTAAGGGGA  
AGAGGTAGCACTCTTGGTCTGGACATCGAAACAGCCACTCATGCAGGAAAGCAG  
ATAGTGGAGCAGATTCTGGAAAAGGAATCAGATGAGGCACTTAAAATGACCATT  
GCCTCTGTTCCCTGCTTCACGCTACTTAACTGACATGACTCTTGATGAGATGTCAAG  
AGACTGGTTCATGCTCATGCCCAAGCAAAAAGTAACAGGCTCCCTATGTATAAG  
AATGGACCAAGCAATCATGGATAAGAACATCATACTTAAAGCAAACCTTTAGTGT  
GATTTTCGAAAGGCTGGAAACACTAATACTACTTAGAGCCTTCACCGAAGAAGG  
AGCAGTCGTTGGCGAAATTTACCATTACCTTCTCTCCAGGACATACTAATGAG  
GATGTCAAAAATGCAATTGGGGTCCTCATCGGAGGACTTAAATGGAATGATAAT  
ACGGTTAGAACTCTGAAACTCTACAGAGATTCGCTTGGAGAAGCAGTCATGAA  
AATGGGAGACCTTCATTCCCTTCAAAGCAGAAACGAAAAATGGAGAGAACAATT  
AAGCCAGAAATTTGAAGAAATAAGATGGTTGATTGAAGAAGTGCACATAGATT  
GAAAAATACAGAAAATAGTTTTGAACAAATAACATTTATGCAAGCCTTACAAC  
ATTGCTTGAAGTAGAACAAGAGATAAGAACTTCTCGTTTCAGCTTATTTAATGA  
T (SEQ ID NO: 9)

FIG. 9

NSI - Amino

MDSNTVSSFQVDCFLWIIVRKRFAEQELGDAPFLDRLRRDQKSLRGRGSLGLDIET  
ATHAGKQIVEQILEKESDEALKMTIASVPASRYLTDMTLDEMSTRDWFMLMPKQKVI  
GSLCIRMDQAIMDKNIILKANFSVIFERLETLILLRAFTEEGAVVGEISPLPSLPGHTNE  
DVKNAIGVLIGGLKWNDNTVRISETLQRFAWRSSHENGRPSFSPKQKRKMERTIKPEI  
(SEQ ID NO: 10)

FIG. 10

PA

TAAATGGAAGACTTTGTGCGACAGTGCTTCAATCCAATGATCGTCGAGCTTGCGG  
AAAAGGCAATGAAAGAATATGGAGAGAACCCGAAAATCGAAACAAACAAATTT  
GCAGCAATATGCACTCACTTGGAAAGTCTGCTTCATGTACTCGGATTTCCACTTTAT  
AAATGAACTGGGTGAGTCAGTGGTCATAGAGTCTGGTGACCCAAATGCTCTTTTG  
AAACACAGATTTGAAATCATTGAGGGGAGAGATCGAACAATGGCATGGACAGTA  
GTAAACAGCATCTGCAACACCACAAGAGCTGAAAAACCTAAATTTCTTCCAGATT  
TATACGACTATAAGGAGAACAGATTTGTTGAAATTGGTGTGACAAGGAGAGAAG  
TTCACATATACTACCTGGAGAAAGCCAACAAAATAAAGTCTGAGAAAACACATA  
TCCACATTTTCTCATTTACAGGAGAAGAAATGGCTACAAAAGCGGACTATACTCT  
TGATGAAGAGAGTAGAGCCAGGATCAAGACCAGACTATTCCTATAAGACAAGA  
AATGGCCAGTAGAGGCCTCTGGGATTCCTTTTCGTCAGTCCGAGAGAGGCGAAGA  
GACAATTGAAGAAAGATTTGAAATCACAGGAACGATGCGCAAGCTTGCCAATTA  
CAGTCTCCACCGAACTTCTCCAGCCTTGAAAATTTTAGAGTCTATATAGATGGA  
TTCGAACCGAACGGCTGCATTGAGAGTAAGCTTTCTCAAATGTCCAAGAAGTA  
AATGCCAAAATCGAACCATTTTCAAAGACAACACCCCGACCACTCAAATGCCA  
GGTGGTCCACCCTGCCATCAGCGATCCAAATTCTTGCATGATGGATGCTCTGAACT  
GAGCATTGAGGACCCAAGTCACGAGGGAGAGGGGATACCACTATATGATGCAAT  
CAAATGCATGAAAACCTTTCTTTGGATGGAAAGAGCCCAGTATTGTTAAACCACAT  
AAAAAGGGTATAAACCCGAACTATCTCCAAACTTGGAAGCAAGTATTAGAAGAA  
ATACAAGACCTTGAGAACGAAGAAAGGACCCCCAAGACCAAGAATATGAAAAA  
ACAAGCCAATTGAAATGGGCACTAGGTGAAAATATGGCACCAAGAGAAAGTGG  
ATTTTGAGGATTGTAAAGACATCAATGATTTAAACAATATGACAGTGATGAGCC  
AGAAGCAAGGTCTCTTGCAAGTTGGATTCAAAGTGAGTTCAACAAGGCTTGTGA  
GCTGACAGATTCAAGCTGGATAGAGCTCGATGAAATTGGGGAGGATGTGCGCCC  
AATAGAATACATTGCGAGCATGAGGAGAAATTATTTTACTGCTGAGATTTCCCAT  
TGTAGAGCAACAGAATATATAATGAAAGGAGTATACATCAACACTGCTCTACTC  
AATGCATCCTGTGCTGCGATGGATGAATTTCAATTAATTCCGATGATAAGTAAAT  
GCAGGACCAAGAAGGGAGAAGGAAAACAATTTATATGGATTCATAATAAAG  
GGAAGGTCCCATTTAAGAAATGATACTGACGTGGTGAACCTTTGTAAGTATGGAAT  
TTTCTCTCACTGATCCAAGATTTGAGCCACACAAATGGGAAAAATACTGCGTTCT  
AGAAATTGGAGACATGCTTCTAAGAAGTCTGTAGGTCAAGTGTCAAGACCCAT  
ATTTTGTATGTAAGGACAAATGGAACCTCTAAAATTAATAATGAAATGGGGAAAT  
GGAAATGAGACGCTGCCTCCTCAGTCTCTGCAACAGATTGAAAGCATGATCGA  
AGCTGAGTCCTCAGTCAAAGAAAAGGACATGACCAAAGAATTTTTTGAGAACAA  
ATCAGAGACATGGCCTATAGGAGAGTCCCCAAAGGAGTGGAAGAGGGCTCAAT  
CGGGAAGGTTTGCAGGACCTTATTAGCAAAAATCTGTGTTTAAACAGTTTATATGCA  
TCTCCACAACCTGGAAGGATTTTCAGCTGAATCTAGGAAATTACTTCTCATTGTTT  
AGGCTCTTAGAGATGACCTGGAACCTGGAACCTTTGATATTGGGGGGTTATATGA  
ATCAATTGAGGAGTGCCTGATTAATGATCCCTGGGTTTTGCTTAATGCATCTTGGT  
TCAACTCCTTCCTCACACATGCACTGAAGTAGTTCTGGCAATGCTACTATTTGTTA  
TCCATACTGTCCA (SEQ ID NO: 11)

FIG. 11

PA - Amino

MEDFVRQCFNPMIVELAEKAMKEYGENPKIETNKFAAICTHLEVCFMYSDFHFINEL  
GESVVIESGDPNALLKHRFEIIEGRDRTMAWTVVNSICNTTRA EKPKFLPDLYDYKEN  
RFVEIGVTRREVHIYYLEKANKIKSEKTHIHIFSFTGEEMATKADYTLDEESRARIKTR  
LFTIRQEMASRGLWDSFRQSERGEETIEERFEITGTMRKLANYSLPPNFSSLENFRVYI  
DGFEPNGCIESKLSQMSKEVNAKIEPFSKTTTPRPLKMPGGPPCHQRSKFLMDALKLS  
IEDPSHEGEGIPLYDAIKCMKTFFGWKEPSIVKPHKKGINPNYLQTWKQVLEEIQDLE  
NEERTPKTKNMKKTSQLKWALGENMAPEKVD FEDCKDINDLKQYDSDEPEARSLAS  
WIQSEFNKACELTDSSWIELDEIGEDVAPIEYIASMRRNYFTA EISHCRATEYIMKGVY  
INTALLNASCAAMDEFQLIPMISKCRTKEGRRKTNLYGFIKGRSILRNDTDV VNFVS  
MEFSLTDPRFEPHKWEKYCVLEIGDMLLRTAVGQVSRPIFLYVRTNGTSKIKMKWG  
MEMRRCLLQSLQQIESMIEAESSVKEKDMTKEFFENKSETWPIGESPKGVEEGSIGKV  
CRTLLAKSVFN SLYASPQLEGFSAESRKL LLLIVQALRDDLEPGTFDIGGLYESIEECLIN  
DPWVLLNASWFNSFLTHALK (SEQ ID NO: 12)

FIG. 12

PBI

GAAAGCAGGCAAACCATTTGAATGGATGTCAATCCGACTCTACTTTTCTTAAAGG  
TGCCAGCGCAAAATGCTATAAGCACAACATTCCCTTATACTGGAGATCCTCCCTA  
CAGTCATGGAACAGGGACAGGATACACCATGGATACTGTCAACAGAACACACCA  
ATATTCAGAAAAAGGGAAATGGACAACAAACACTGAGATTGGAGCACCACAACCT  
TAATCCAATCGATGGACCACCTTCTGAAGACAATGAACCAAGTGGGTACGCCA  
AACAGATTGTGTATTGGAAGCAATGGCTTTCCTTGAAGAATCCCATCCCGGAATC  
TTTGAAAATTCGTGTCTTGAAACGATGGAGGTGATTCAGCAGACAAGAGTGGAC  
AACTAACACAAGGCCGACAACTTATGATTGGACCTTGAATAGGAATCAACCT  
GCCGCAACAGCACTTGCTAATACGATTGAAGTATTCAGATCAAATGGTCTGACTT  
CCAATGAATCGGGGAGATTGATGGACTTCTCAAAGATGTCATGGAGTCCATGA  
ACAAGGAGGAAATGGAAATAACAACACACTTCCAACGGAAGAGAAGAGTAAGA  
GACAACATGACAAAGAGAATGATAACACAGAGAACCATAGGGAAGAAAAACA  
ACGATTAAGCAGAAAGAGCTATCTAATCAGAACATTAACCCTAACACAATGAC  
CAAGGACGCTGAAAGAGGGAAATGAAACGACGAGCAATCGCTACCCAGGGGA  
TGCAGATAAGAGGATTTGTATATTTTGTGAAACACTAGCTCGAAGAATATGTGA  
AAAGCTTGAACAATCAGGATTGCCAGTTGGCGGTAATGAGAAAAAGGCCAACT  
GGCTAATGTCGTCAGAAAAATGATGACTAATCCCAAGACACTGAACTCTCCTTC  
ACCATCACTGGGGACAATACCAAATGGAATGAAAATCAGAACCCACGCATATTC  
CTGGCAATGATCACATACTAGAAATCAGCCAGAATGGTTCAGAAATGTT  
CTAAGCATTGCACCGATTATGTTCTCAAATAAAATGGCAAGACTGGGGAAAGGA  
TATATGTTTGAAGCAAAAGTATGAAATTGAGAACTCAAATACCAGCAGAAATG  
CTAGCAAGCATTGACCTAAAATATTTCAATGATTCAACAAAAAAGAAAATTGAA  
AAGATACGACCCTCCTGGTTGACGGGACTGCTTCACTGAGTCTTGGCATGATGA  
TGGGAATGTTCAACATGTTGAGCACTGTGCTGGGTGTATCCATATTAACCTGGG  
CCAGAGGAAATATACAAAGACCACATACTGGTGGGATGGTCTGCAATCATCCGA  
TGACTTTGCTTTGATAGTGAATGCGCCTAATCATGAAGGAATACAAGCTGGAGTA  
GACAGATTCTATAGAACTTGCAAACCTGGTCGGGATCAACATGAGCAAAAAGAAG  
TCTTACATAAAATAGAACTGGAAACATTCGAATTCACAAGCTTTTCTTACCGGTATG  
GTTTTGTAGCCAATTTAGCATGGAACCTACCCAGTTTTGGGGTTTCCGGAATAAA  
TGAATCTGCAGACATGAGCATTGGAGTGACAGTCATCAAAAACAACATGATAAA  
TAATGATCTCGGTCCCTGCCACGGCACAATGGYACTCCAACCTTTCATTAAGGAT  
TATCGGTACACATACCGGTGCCATAGAGGTGATACCCAGATACAAACCAGAAGA  
TCTTTTIGAGTTGAAGAAACIGTGGGAACAGACTCGATCAAAGACTGGTCTACTGG  
TATCAGATGGGGGTCCAAACCTATATAACATCAGAAACCTACACATCCCGGAAG  
TCTGTTTAAAATGGGAGCTAATGGATGAAGATTATAAGGGGAGGCTATGCAATC  
CATTGAATCCTTTCGTAGTCACAAAGAAATTGAATCAGTCAACAGTGCAGTAGT  
AATGCCTGCGCATGGCCCTGCCAAAAGCATGGAGTATGATGCTGTGCAACAACA  
CATTCTTGGATCCCAAGAGGAACCGGTCCATATTGAACACAAGCCAAAGGGGA  
ATACTAGAAGATGAGCAGATGTATCAGAAATGCTGCAACCTGTTTGAAAAATTCT  
TCCCCAGCAGCTCATAACAGAAGACCAGTCGGAATTTCTAGTATGGTTGAGGCCAT  
GGTATCCAGGGCCCGCATTGATGCACGAATTGACTTCGAATCTGGACGGATAAA  
GAAGGATGAGTTCGCTGAGATCATGAAGATCTGTTCCACCATTGAAGAGCTCAG  
ACGGCAAAAATAGTGAA (SEQ ID NO: 13)

FIG. 13

PB1 - Amino

MDVNPTLLFLKVPAQNAISTTFPYTGDPYSHGTGTGYTMDTVNRTHQYSEK GKWT  
TNTEIGAPQLNPIDGPLPEDNEPSGYAQTDCVLEAMAFLEESHGIFENSCLETMEVIQ  
QTRVDKLTQGRQTYDWTLNRNQPAATALANTIEVFRSNGLTSNESGRLMDFLKDV  
MESMNKEEMEITTHFQRKRRVRDNMTKRMITQRTIGKKKQRLSRKSYLIRTLTLNT  
MTKDAERGKLRRAIATPGMQIRGFVYFVETLARRICEKLEQSGLPVGGNEKKAKL  
ANVVRKMMTNSQDTELSFTITGDNTKWNENQNPRIFLAMITYITRNQPEWFRNVLSI  
APIMFSNKMARLGKGYMFESKSMKLRTQIPAEMLASIDLKYFNDSTKKKIEKIRPLL  
DGTASLSPGMMMGMFNMLSTVLGVSILNLGQRKYTKTTYWWDGLQSSDDFALIVN  
APNHEGIQAGVDRFYRTCKLVGINMSKKKSYINRTGTFFETSFFYRYGFVANFSMELP  
SFGVSGINESADMSIGVTVIKNNMINNDLGPATAQMXLQLFIKDYRYTYRCHRGTQ  
IQTRRSFELKKLWEQTRSKTGLLVSDGGPNLYNIRNLHIPEVCLKWELMDEDYKGR  
CNPLNPFVSHKEIESVNSAVVMPAHGPAKSMEYDAVATTHSWIPKRNR SILNTSQRGI  
LEDEQMYQKCCNLFKFFPSSSYRRPVGISSMVEAMVSRARIDARIDFESGRIKKDEF  
AEIMKICSTIEELRRQK (SEQ ID NO: 14)

FIG. 14

PB2

TATTGGICTCAGGGAGCGAAAGCAGGTC AAAATATATTCAATATGGAGAGAATAA  
AAGAACTGAGAGATCTGATGTTACAATCCCGCACCCGCGAGATACTAACAAAA  
CTACTGTGGACCACATGGCCATAATCAAGAAATACACATCAGGAAGACAAGAGA  
AGAACCCTGCACTTAGGATGAAATGGATGATGGCAATGAAATACCCAATTACAG  
CAGATAAGAGGATAATGGAGATGATTCTTGAGAGAAATGAACAGGGACAAAACC  
CTTTGGAGCAAAACGAACGATGCTGGCTCAGACCGCGTAATGGTATCACCTCTGG  
CAGTGACATGGTGGAAATAGGAATGGACCAACAACGAACACAATTCAATTATCCGA  
AAGTCTACAAAACCTATTTTAAAAAGGTTGAAAGATTGAAACACGGAACCTTTG  
GCCCCGTTCATTTTAGGAATCAAGTCAAGATAAGACGAAGAGTTGATGTAAACC  
CTGGTCACGCGGACCTCAGTGCTAAAGAAGCACAAGATGTGATCATGGAAGTTG  
TTTTCCCAAATGAAGTGGGAGCCAGAATTCTAACATCAGAATCACAACATAAAT  
AACCAAAGAGAAAAAGGAAGAATTCAGGACTGCAAAAATTCCTCCCCTTIGATGGT  
AGCATAACATGCTAGAAAGAGAGTTGGTCCGAAAAACAAGGTTCCCTCCAGTAGT  
AGGCGGAACAAGCAGTGTATACATTGAAGTGTTCATCTGACTCAGGGAACATG  
CTGGGAGCAAATGTACACCCAGGAGGAGAAGTTAGAAACGATGATATTGATCA  
AAGTTTAATTATTGCAGCCCGAACATAGTGAGAAGAGCAACAGTATCAGCAGA  
TCCACTAGCATCCCTACTGGAAATGTGCCACAGTACACAGATTTGGTGGAAACAAG  
GATGGTAGACATCCTTAAGCAGAACCCAACAGAGGAACAAGCTGTGGATATATG  
CAAAGCAGCAATGGGATTGAGAATTAGCTCATCATTAGCTTTGGTGGATTACCC  
TTCAAAGGACAAGTGGATCATCAGTCAAGAGAGAAGAAGAAATGCTTACGGGC  
AACCTTCAAACATTGAAAATAAGAGTGCATGAGGGCTATGAAGAATTCACAATG  
GTCGGAAGAAGAGCAACAGCCATTATCAGAAAGGCAACCAGAAGATTGATTCAA  
TTGATAGTAAGTGGGAGAGATGAACAATCAATTGCTGAAGCAATAATTGTAGCC  
ATGGTGTTCGCAAGAAGATTGCATGATAAAAGCAGTTCGAGGCGATTTGAACT  
TTGTTAATAGAGCAAATCAGCGTTTGAACCCCATGCATCAACTCTTGAGGCATTT  
CCAAAAAGATGCAAAAGTGCCTTTCCAAAAATGGGGAAATGAACCCATCGACAA  
TGTAATGGGGATGATTGGAATATTGCCTGACATGACCCCAAGCACCGAGATGTC  
ATTGAGAGGAGTGAGAGTCAGCAAAATGGGAGTGGATGAGTACTCCAGCACTGA  
GAGAGTGGTGGTGGCATTGACCGTTTTTTAAGAGTTCGGGATCAAAGGGGAAA  
CATACTACTGTCCCCTGAAGAAGTCAGTGAACACAAGGAACGGAAAAGCTGAC  
AATAATTTATTCGTCATCAATGATGTGGGAGATTAATGGTCCCGAATCAGTGTG  
GTC AATACTTATCAATGGATCATCAGAAACTGGGAAATTGTAAAAATTCAGTGGT  
CACAGGACCCCACAATGTTATACAATAAGATAGAATTTGAACCATTCCAATCCCT  
GGTCCCTAGGGCCACCAGAAGCCAATACAGCGGTTTCGTAAGAACCCTGTTTCAG  
CAAATGCGAGATGTACTTGGAAACATTTGATACTGCTCAAATAAATAAACTCCTCC  
CTTTTGCCGCTGCTCCTCCGGAACAGAGTAGGATGCAGTTCTCTTCTTTGACTGTT  
AATGTAAGAGGTTTCGGGAATGAGGATACTTGTAAGAGGCAATTCGCCGGTGTTC  
AACTACAATAAAGTCACTAAAAGGCTCACAGTCCCTCGGAAAGGATGCAGGTGCG  
CTTACTGAGGACCCAGATGAAGGTACGGCTGGAGTAGAATCTGCTGTTCTAAGA  
GGGTTTCTCATTTTAGGTAAAGAAAACAAGAGATATGGCCCAGCACTAAGCATC  
AATGAACTTAGCAAACCTTGCAAAAGGGGAGAAAGCCAATGTACTAATTGGGCAA  
GGGGACGTAGTGTGGTAATGAAACGGAAACGTGACTCTAGCATACTTACTGAC  
AGCCAGACAGCGACCAAAAGGATTCCGGATGGCCATCAATTAGTGTGAAATTGTTT  
AAAAACGACCTTGTCTACTAATACGAGACCATAT (SEQ ID NO: 15)

FIG. 15

PB2 - Amino

MERIKELRDLMLQSRTREILTKTTVDHMAIHKKYTSGRQEKNPALRMKWMMAMKY  
PITADKRIMEMIPERNEQGQTLWSKTNDAGSDRVMVSPLAVTWWNRNGPTTNTIHY  
PKVYKTYFEKVERLKHGTFGPVHFRNQVKIRRRVDVNPBGHADLSAKEAQDVIMEVV  
FPNEVGARILTSESQLTITKEKKEELQDCKIAPLMVAYMLERELVRKTRFLPVVGGTS  
SVYIEVLHLTQGTCWEQMYTPGGEVRNDDIDQSLIAARNIVRRATVSADPLASLLE  
MCHSTQIGGTRMVDILKQNPTEEQAVDICKAAMGLRISSSFSGGFTFKRTSGSSVVR  
EEEMLTGNLQTLKIRVHEGYEFTMVGRRATAIRKATRRLIQLIVSGRDEQSI AEAI  
VAMVFSQEDCMIKAVRGDLNRFVNRANQRLNPMHQLLRHFQKDAKVLQFNWGIEPI  
DNVMGMIGILPDMTPSTEMSLRGVRYSKMGVDEYSSTERVVVSIDRFILRVRDQRGNI  
LLSPEEVSETQGTEKLTIIYSSSMWEINGPESVLVNTYQWIIRNWEIVKIQWSQDPT  
MLYNKIEFEPFQSLVPRATRSQYSGFVRTLFQQMRDVLGTFDTAQIIKLLPFAAAPPE  
QSRMQFSSLTVNVRGSGMRILVRGNSPVFNKVTKRLTVLGKDAGALTEDEPDEGT  
AGVESAVLRGFLILGKENKRYGPALSINELSKLAKGEKANVLIGQGDVVLMKRKR  
DSSILTDSQTATKRIRMAIN (SEQ ID NO: 16)

FIG. 16



## CANINE INFLUENZA VIRUS AND RELATED COMPOSITIONS AND METHODS OF USE

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.**

### CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application is a divisional of U.S. Non-Provisional patent application Ser. No. 11/539,123, filed Oct. 5, 2006, now issued as U.S. Pat. No. 7,468,187, which claims the benefit of U.S. Provisional Patent Application No. 60/727,808, filed Oct. 18, 2005, the contents of both the applications are incorporated herein by reference in their entirety.

### TECHNICAL FIELD OF THE INVENTION

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

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.

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).

Neuraminidase (NM), which splits the  $\alpha$ -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.

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)).

Other proteins include matrix (M or M1 and M2), non-structural (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.

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).

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 (Oct. 21, 2005; published online Sep. 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, N.C., Oct. 2005. p. 158; and Yoon et al., Emerg. Infect. Dis. 11(12): 1974-1976 (Dec. 2005)). Therefore, the host range of influenza virus is expanding.

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.

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

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 Jun. 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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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

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.

FIG. 6 is the deduced amino acid sequence (SEQ ID NO: 6) encoded by SEQ ID NO: 5.

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.

FIG. 8 is the deduced amino acid sequence (SEQ ID NO: 8) encoded by SEQ ID NO: 7.

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.

FIG. 10 is the deduced amino acid sequence (SEQ ID NO: 10) encoded by SEQ ID NO: 9.

## 5

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.

FIG. 12 is the deduced amino acid sequence (SEQ ID NO: 12) encoded by SEQ ID NO: 11.

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.

FIG. 14 is the deduced amino acid sequence (SEQ ID NO: 14) encoded by SEQ ID NO: 13.

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.

FIG. 16 is the deduced amino acid sequence (SEQ ID NO: 16) encoded by SEQ ID NO: 15.

## DETAILED DESCRIPTION OF THE INVENTION

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 Jun. 29, 2006, as Patent Deposit No. PTA-7694.

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 non-charged 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

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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.

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.

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 Layer 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.

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.

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,  $\beta$ -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,  $\gamma$ -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.

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 Marcol and/or Arlacel.

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.

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.

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.

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.

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.

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.

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

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.

An isolated or purified PB 1 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.

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.

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.

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, 11. 10 et seq).

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.

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.

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.

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.

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.

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.

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.

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.

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 polynucleotide 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.

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.

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.

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.

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.

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.

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.

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.

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  $\mu$  in diameter has been shown to have a remarkable adjuvant effect when administered orally.

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.

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.

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.

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).

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.

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.

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.

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  $10^7$  EID<sub>50</sub> (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.

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, LD<sub>50</sub>, 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  $\mu$ g. 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  $10^3$  TCID<sub>50</sub>.

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 Aug. 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.

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.

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, N.Y. (1988); Harlow and Lane, *Using Antibodies: A Laboratory Manual* (1998), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (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, Fla. (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.

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.

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.

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 idiotype antibodies raised against the polypeptide and screened for reactivity with the polypeptide and screening for antisera, which react with idiotype 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 idiotype 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.

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.

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.

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)), radioimmunoas-

says (RIA), enzyme-linked immunosorbent assays (ELISA), and enzyme-multiplied immunoassay technique (EMIT; see *Enzyme Immunoassay*, Maggio, ed., CRC Press, Inc., Boca Raton, Fla., 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.

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

#### EXAMPLE

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.

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 Apr. 2005. While a large percentage of affected dogs recovered, many succumbed to hemorrhagic pneumonia.

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.

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, Calif. Oct. 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 (Directgen™ 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.

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, N.C. Oct. 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 H3 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).

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, N.Y. 1981. pp. 164-180)), probably contributed to the severity of the disease.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference

to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

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.

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.

## SEQUENCE LISTING

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<213> ORGANISM: Influenza A virus

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          1              5              10

ttg ggg ata tta atc att aat gtc att ctc cat gta gtc agc att ata      98
Leu Gly Ile Leu Ile Ile Asn Val Ile Leu His Val Val Ser Ile Ile
15              20              25              30

gta aca gta ctg gtc ctc aat aac aat aga aca gat ctg aac tgc aaa      146
Val Thr Val Leu Val Leu Asn Asn Asn Arg Thr Asp Leu Asn Cys Lys
          35              40              45

ggg acg atc ata aga gaa tac aat gaa aca gta aga gta gaa aaa ctt      194
Gly Thr Ile Ile Arg Glu Tyr Asn Glu Thr Val Arg Val Glu Lys Leu
          50              55              60

act caa tgg tat aat acc agt aca att aag tac ata gag aga cct tca      242
Thr Gln Trp Tyr Asn Thr Ser Thr Ile Lys Tyr Ile Glu Arg Pro Ser
          65              70              75

aat gaa tac tac atg aat aac act gaa cca ctt tgt gag gcc caa ggc      290
Asn Glu Tyr Tyr Met Asn Asn Thr Glu Pro Leu Cys Glu Ala Gln Gly
          80              85              90

ttt gca cca ttt tcc aaa gat aat gga ata cga att ggg tcg aga ggc      338
Phe Ala Pro Phe Ser Lys Asp Asn Gly Ile Arg Ile Gly Ser Arg Gly
95              100              105              110

cat gtt ttt gtg ata aga gaa cct ttt gta tca tgt tcg ccc tca gaa      386
His Val Phe Val Ile Arg Glu Pro Phe Val Ser Cys Ser Pro Ser Glu

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-continued

	115	120	125	
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Ser Asn Gly Thr Ile Lys Asp Arg Ser Pro Tyr Arg Thr Leu Met Ser	145	150	155	
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Val Lys Ile Gly Gln Ser Pro Asn Val Tyr Gln Ala Arg Phe Glu Ser	160	165	170	
gtg gca tgg tca gca aca gca tgc cat gat gga aaa aaa tgg atg aca				578
Val Ala Trp Ser Ala Thr Ala Cys His Asp Gly Lys Lys Trp Met Thr	175	180	185	190
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Val Gly Val Thr Gly Pro Asp Asn Gln Ala Ile Ala Val Val Asn Tyr	195	200	205	
gga ggt gtt ccg gtt gat act att aat tca tgg gca ggg gat att tta				674
Gly Gly Val Pro Val Asp Thr Ile Asn Ser Trp Ala Gly Asp Ile Leu	210	215	220	
aga acc caa gaa tca tca tgc acc tgc att aaa gga gac tgt tat tgg				722
Arg Thr Gln Glu Ser Ser Cys Thr Cys Ile Lys Gly Asp Cys Tyr Trp	225	230	235	
gta atg act gat gga ccg gca aat agg caa gct aaa tat agg ata ttc				770
Val Met Thr Asp Gly Pro Ala Asn Arg Gln Ala Lys Tyr Arg Ile Phe	240	245	250	
aaa gca aaa gat gga aga gta att gga caa act gat ata agt ttc aat				818
Lys Ala Lys Asp Gly Arg Val Ile Gly Gln Thr Asp Ile Ser Phe Asn	255	260	265	270
ggg gga cac ata gag gag tgt tct tgt tac ccc aat gaa ggg aag gtg				866
Gly Gly His Ile Glu Glu Cys Ser Cys Tyr Pro Asn Glu Gly Lys Val	275	280	285	
gaa tgc ata tgc agg gac aat tgg act gga aca aat aga cca att ctg				914
Glu Cys Ile Cys Arg Asp Asn Trp Thr Gly Thr Asn Arg Pro Ile Leu	290	295	300	
gta ata tct tct gat cta tcg tac aca gtt gga tat ttg tgt gct ggc				962
Val Ile Ser Ser Asp Leu Ser Tyr Thr Val Gly Tyr Leu Cys Ala Gly	305	310	315	
att ccc act gac act cct agg gga gag gat agt caa ttc aca ggc tca				1010
Ile Pro Thr Asp Thr Pro Arg Gly Glu Asp Ser Gln Phe Thr Gly Ser	320	325	330	
tgt aca agt cct ttg gga aat aaa gga tac ggt gta aaa ggc ttc ggg				1058
Cys Thr Ser Pro Leu Gly Asn Lys Gly Tyr Gly Val Lys Gly Phe Gly	335	340	345	350
ttt cga caa gga act gac gta tgg gcc gga agg aca att agt agg act				1106
Phe Arg Gln Gly Thr Asp Val Trp Ala Gly Arg Thr Ile Ser Arg Thr	355	360	365	
tca aga tca gga ttc gaa ata ata aaa atc agg aat ggt tgg aca cag				1154
Ser Arg Ser Gly Phe Glu Ile Ile Lys Ile Arg Asn Gly Trp Thr Gln	370	375	380	
aac agt aag gac caa atc agg agg caa gtg att atc gat gac cca aat				1202
Asn Ser Lys Asp Gln Ile Arg Arg Gln Val Ile Ile Asp Asp Pro Asn	385	390	395	
tgg tca gga tat agc ggt tct ttc aca ttg ccg gtt gaa ctg aca aaa				1250
Trp Ser Gly Tyr Ser Gly Ser Phe Thr Leu Pro Val Glu Leu Thr Lys	400	405	410	
aag gga tgt ttg gtc ccc tgt ttc tgg gtt gaa atg att aga ggt aaa				1298
Lys Gly Cys Leu Val Pro Cys Phe Trp Val Glu Met Ile Arg Gly Lys	415	420	425	430
cct gaa gaa aca aca ata tgg acc tct agc agc tcc att gtg atg tgt				1346
Pro Glu Glu Thr Thr Ile Trp Thr Ser Ser Ser Ser Ile Val Met Cys				

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gga gta gat cat aaa att gcc agt tgg tca tgg cac gat gga gct att			1394
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450	455	460	
ctt ccc ttt gac atc gat aag atg taatttacga aaaaaactcc ttgtttctac			1448
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ta			1450
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	20	25	30
Val Leu Val Leu Asn Asn Asn Arg Thr Asp Leu Asn Cys Lys Gly Thr			
	35	40	45
Ile Ile Arg Glu Tyr Asn Glu Thr Val Arg Val Glu Lys Leu Thr Gln			
	50	55	60
Trp Tyr Asn Thr Ser Thr Ile Lys Tyr Ile Glu Arg Pro Ser Asn Glu			
65	70	75	80
Tyr Tyr Met Asn Asn Thr Glu Pro Leu Cys Glu Ala Gln Gly Phe Ala			
	85	90	95
Pro Phe Ser Lys Asp Asn Gly Ile Arg Ile Gly Ser Arg Gly His Val			
	100	105	110
Phe Val Ile Arg Glu Pro Phe Val Ser Cys Ser Pro Ser Glu Cys Arg			
	115	120	125
Thr Phe Phe Leu Thr Gln Gly Ser Leu Leu Asn Asp Lys His Ser Asn			
	130	135	140
Gly Thr Ile Lys Asp Arg Ser Pro Tyr Arg Thr Leu Met Ser Val Lys			
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Ile Gly Gln Ser Pro Asn Val Tyr Gln Ala Arg Phe Glu Ser Val Ala			
	165	170	175
Trp Ser Ala Thr Ala Cys His Asp Gly Lys Lys Trp Met Thr Val Gly			
	180	185	190
Val Thr Gly Pro Asp Asn Gln Ala Ile Ala Val Val Asn Tyr Gly Gly			
	195	200	205
Val Pro Val Asp Thr Ile Asn Ser Trp Ala Gly Asp Ile Leu Arg Thr			
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Gln Glu Ser Ser Cys Thr Cys Ile Lys Gly Asp Cys Tyr Trp Val Met			
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Thr Asp Gly Pro Ala Asn Arg Gln Ala Lys Tyr Arg Ile Phe Lys Ala			
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Lys Asp Gly Arg Val Ile Gly Gln Thr Asp Ile Ser Phe Asn Gly Gly			
	260	265	270
His Ile Glu Glu Cys Ser Cys Tyr Pro Asn Glu Gly Lys Val Glu Cys			
	275	280	285
Ile Cys Arg Asp Asn Trp Thr Gly Thr Asn Arg Pro Ile Leu Val Ile			
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Ser Ser Asp Leu Ser Tyr Thr Val Gly Tyr Leu Cys Ala Gly Ile Pro			
305	310	315	320

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 340 345 350

Gln Gly Thr Asp Val Trp Ala Gly Arg Thr Ile Ser Arg Thr Ser Arg  
 355 360 365

Ser Gly Phe Glu Ile Ile Lys Ile Arg Asn Gly Trp Thr Gln Asn Ser  
 370 375 380

Lys Asp Gln Ile Arg Arg Gln Val Ile Ile Asp Asp Pro Asn Trp Ser  
 385 390 395 400

Gly Tyr Ser Gly Ser Phe Thr Leu Pro Val Glu Leu Thr Lys Lys Gly  
 405 410 415

Cys Leu Val Pro Cys Phe Trp Val Glu Met Ile Arg Gly Lys Pro Glu  
 420 425 430

Glu Thr Thr Ile Trp Thr Ser Ser Ser Ser Ile Val Met Cys Gly Val  
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aca gcc aca ctg tgt ctg gga cac cat gca gta gca aat gga aca ttg 149  
 Thr Ala Thr Leu Cys Leu Gly His His Ala Val Ala Asn Gly Thr Leu  
 25 30 35 40

gta aaa aca atg agt gat gat caa att gag gtg aca aat gct aca gaa 197  
 Val Lys Thr Met Ser Asp Asp Gln Ile Glu Val Thr Asn Ala Thr Glu  
 45 50 55

tta gtt cag agc att tca atg ggg aaa ata tgc aac aaa tca tat aga 245  
 Leu Val Gln Ser Ile Ser Met Gly Lys Ile Cys Asn Lys Ser Tyr Arg  
 60 65 70

att cta gat gga aga aat tgc aca tta ata gat gca atg cta gga gac 293  
 Ile Leu Asp Gly Arg Asn Cys Thr Leu Ile Asp Ala Met Leu Gly Asp  
 75 80 85

ccc cac tgt gac gcc ctt cag tat gag agt tgg gac ctc ttt ata gaa 341  
 Pro His Cys Asp Ala Leu Gln Tyr Glu Ser Trp Asp Leu Phe Ile Glu  
 90 95 100

aga agc agc gct ttc agc aat tgc tac cca tat gac atc cct gac tat 389  
 Arg Ser Ser Ala Phe Ser Asn Cys Tyr Pro Tyr Asp Ile Pro Asp Tyr  
 105 110 115 120

gca tcg ctc cga tcc att gta gca tcc tca gga aca gtt gaa ttc aca 437  
 Ala Ser Leu Arg Ser Ile Val Ala Ser Ser Gly Thr Val Glu Phe Thr  
 125 130 135

gca gag gga ttc aca tgg aca ggt gta act caa aac gga aga agt gga 485  
 Ala Glu Gly Phe Thr Trp Thr Gly Val Thr Gln Asn Gly Arg Ser Gly  
 140 145 150

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cta aca aaa tct gga agc tct tac ccc aca ttg aat gtg aca atg cct	581
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170 175 180	
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Asn Asn Lys Asn Phe Asp Lys Leu Tyr Ile Trp Gly Ile His His Pro	
185 190 195 200	
agc tca aat caa gag cag aca aaa ttg tac atc caa gaa tca gga cga	677
Ser Ser Asn Gln Glu Gln Thr Lys Leu Tyr Ile Gln Glu Ser Gly Arg	
205 210 215	
gta aca gtc tca aca aaa aga agt caa caa aca ata atc cct aac atc	725
Val Thr Val Ser Thr Lys Arg Ser Gln Gln Thr Ile Ile Pro Asn Ile	
220 225 230	
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Glu Ser Arg Pro Leu Val Arg Gly Gln Ser Gly Arg Ile Ser Ile Tyr	
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Trp Thr Ile Val Lys Pro Gly Asp Ile Leu Met Ile Asn Ser Asn Gly	
250 255 260	
aac tta gtt gca ccg cgg gga tat ttt aaa ttg aac aca ggg aaa agc	869
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Ser Val Met Arg Ser Asp Val Pro Ile Asp Ile Cys Val Ser Glu Cys	
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Met Val Asp Gly Trp Tyr Gly Phe Arg Tyr Gln Asn Ser Glu Gly Thr	
365 370 375	
ggg caa gct gca gat cta aag agc act caa gca gcc att gac cag att	1205
Gly Gln Ala Ala Asp Leu Lys Ser Thr Gln Ala Ala Ile Asp Gln Ile	
380 385 390	
aat gga aag tta aac aga gtg att gaa aga acc aat gag aaa ttc cat	1253
Asn Gly Lys Leu Asn Arg Val Ile Glu Arg Thr Asn Glu Lys Phe His	
395 400 405	
caa ata gag aag gaa ttc tca gaa gta gaa gga aga att cag gac ttg	1301
Gln Ile Glu Lys Glu Phe Ser Glu Val Glu Gly Arg Ile Gln Asp Leu	
410 415 420	
gag aaa tat gta gaa gac acc aaa ata gac cta tgg tcc tac aat gca	1349
Glu Lys Tyr Val Glu Asp Thr Lys Ile Asp Leu Trp Ser Tyr Asn Ala	
425 430 435 440	
gaa ttg ctg gtg gct cta gaa aat caa cat aca att gac tta aca gat	1397
Glu Leu Leu Val Ala Leu Glu Asn Gln His Thr Ile Asp Leu Thr Asp	
445 450 455	
gca gaa atg aat aaa tta ttt gag aag act aga cgc cag tta aga gaa	1445
Ala Glu Met Asn Lys Leu Phe Glu Lys Thr Arg Arg Gln Leu Arg Glu	
460 465 470	

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aac gca gaa gac atg gga ggt gga tgt ttc aag att tac cac aaa tgt 1493
Asn Ala Glu Asp Met Gly Gly Gly Cys Phe Lys Ile Tyr His Lys Cys
      475                      480                      485

gat aat gca tgc att gaa tca ata aga act ggg aca tat gac cat tac 1541
Asp Asn Ala Cys Ile Glu Ser Ile Arg Thr Gly Thr Tyr Asp His Tyr
      490                      495                      500

ata tac aga gat gaa gca tta aac aac cga ttt cag atc aaa ggt gta 1589
Ile Tyr Arg Asp Glu Ala Leu Asn Asn Arg Phe Gln Ile Lys Gly Val
505                      510                      515                      520

gag ttg aaa tca ggc tac aaa gat tgg ata ctg tgg att tca ttc gcc 1637
Glu Leu Lys Ser Gly Tyr Lys Asp Trp Ile Leu Trp Ile Ser Phe Ala
      525                      530                      535

ata tca tgc ttc tta att tgc gtt gtt cta ttg ggt ttc att atg tgg 1685
Ile Ser Cys Phe Leu Ile Cys Val Val Leu Leu Gly Phe Ile Met Trp
      540                      545                      550

gct tgc caa aaa ggc aac atc aga tgc aac att tgc att tgagtaaact 1734
Ala Cys Gln Lys Gly Asn Ile Arg Cys Asn Ile Cys Ile
      555                      560                      565

gatagttaaa aacacccttg tttctact 1762

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<210> SEQ ID NO 4
<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Influenza A Virus

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<400> SEQUENCE: 4

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Met Lys Thr Thr Ile Ile Leu Ile Leu Leu Thr His Trp Ala Tyr Ser
1                      5                      10                      15

Gln Asn Pro Ile Ser Gly Asn Asn Thr Ala Thr Leu Cys Leu Gly His
20                      25                      30

His Ala Val Ala Asn Gly Thr Leu Val Lys Thr Met Ser Asp Asp Gln
35                      40                      45

Ile Glu Val Thr Asn Ala Thr Glu Leu Val Gln Ser Ile Ser Met Gly
50                      55                      60

Lys Ile Cys Asn Lys Ser Tyr Arg Ile Leu Asp Gly Arg Asn Cys Thr
65                      70                      75                      80

Leu Ile Asp Ala Met Leu Gly Asp Pro His Cys Asp Ala Leu Gln Tyr
85                      90                      95

Glu Ser Trp Asp Leu Phe Ile Glu Arg Ser Ser Ala Phe Ser Asn Cys
100                      105                      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                      160

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                      240

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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					320
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		
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> SEQ ID NO 5  
 <211> LENGTH: 1585  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A Virus  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (51)..(1544)

<400> SEQUENCE: 5

cagggagcaa aagcagggta gataatcact cactgagtga catcaaagtc atg gcg 56  
 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

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5	10	15	
cgc cag aat gca act gaa atc aga gca tct gtc gga agg atg gtg gga Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Arg Met Val Gly 20 25 30			152
gga atc gga cgg ttt tat gtc cag atg tgt act gag ctt aaa cta aac Gly Ile Gly Arg Phe Tyr Val Gln Met Cys Thr Glu Leu Lys Leu Asn 35 40 45 50			200
gac cat gaa ggg cgg ctg att cag aac agc ata aca ata gaa agg atg Asp His Glu Gly Arg Leu Ile Gln Asn Ser Ile Thr Ile Glu Arg Met 55 60 65			248
gta ctt tca gca ttc gac gaa aga aga aac aag tat ctc gag gag cat Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu Glu His 70 75 80			296
ccc agt gct ggg aaa gac cct aag aaa acg gga ggc ccg ata tac aga Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile Tyr Arg 85 90 95			344
aga aaa gat ggg aaa tgg atg agg gaa ctc atc ctc cat gat aaa gaa Arg Lys Asp Gly Lys Trp Met Arg Glu Leu Ile Leu His Asp Lys Glu 100 105 110			392
gaa atc atg aga atc tgg cgt cag gcc aac aat ggt gaa gac gct act Glu Ile Met Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp Ala Thr 115 120 125 130			440
gct ggt ctt act cat atg atg atc tgg cac tcc aat ctc aat gac acc Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn Asp Thr 135 140 145			488
aca tac caa aga aca agg gct ctt gtt cgg act ggg atg gat ccc aga Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp Pro Arg 150 155 160			536
atg tgc tct ctg atg caa ggc tca acc ctc cca cgg aga tct gga gcc Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser Gly Ala 165 170 175			584
gct ggt gct gca gta aaa ggt gtt gga aca atg gta atg gaa ctc atc Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu Leu Ile 180 185 190			632
agg atg atc aaa cgc gga ata aat gat cgg aat ttc tgg aga ggt gaa Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg Gly Glu 195 200 205 210			680
aat ggt cga aga acc aga att gct tat gaa aga atg tgc aat atc ctc Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn Ile Leu 215 220 225			728
aaa ggg aaa ttt cag aca gca gca caa cgg gct atg atg gac cag gtg Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp Gln Val 230 235 240			776
agg gaa ggc cgc aat cct gga aac gct gag att gag gat ctc att ttc Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu Ile Phe 245 250 255			824
ttg gca cga tca gca ctt att ttg aga gga tca gta gcc cat aaa tca Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His Lys Ser 260 265 270			872
tgc cta cct gcc tgt gtt tat ggc ctt gca gta acc agt ggg tat gac Cys Leu Pro Ala Cys Val Tyr Gly Leu Ala Val Thr Ser Gly Tyr Asp 275 280 285 290			920
ttt gag aag gaa gga tac tct ctg gtt gga att gat cct ttc aaa cta Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe Lys Leu 295 300 305			968
ctc cag aac agt caa att ttc agt cta atc aga cca aaa gaa aac cca Leu Gln Asn Ser Gln Ile Phe Ser Leu Ile Arg Pro Lys Glu Asn Pro 310 315 320			1016
gca cac aaa agc cag ttg gtg tgg atg gca tgc cat tct gca gca ttt Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala Ala Phe			1064



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325	330	335	
gag gat ctg aga gtt tta aat ttc att aga gga acc aaa gta atc cca Glu Asp Leu Arg Val Leu Asn Phe Ile Arg Gly Thr Lys Val Ile Pro 340	345	350	1112
aga gga cag tta aca acc aga gga gtt caa att gct tca aat gaa aac Arg Gly Gln Leu Thr Thr Arg Gly Val Gln Ile Ala Ser Asn Glu Asn 355	360	365 370	1160
atg gag aca ata aat tct agc aca ctt gaa ctg aga agc aaa tat tgg Met Glu Thr Ile Asn Ser Ser Thr Leu Glu Leu Arg Ser Lys Tyr Trp 375	380	385	1208
gca ata agg acc aga agc gga gga aac acc agt caa cag aga gca ttt Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Ser Gln Gln Arg Ala Phe 390	395	400	1256
gca gga cag ata agt gtg caa cct act ttc tca gta cag aga aat ctt Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg Asn Leu 405	410	415	1304
ccc ttt gag aga gca acc att atg gct gca ttc act ggt aac act gaa Pro Phe Glu Arg Ala Thr Ile Met Ala Ala Phe Thr Gly Asn Thr Glu 420	425	430	1352
ggg agg act tcc gac atg aga acg gaa atc ata agg atg atg gaa aat Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met Glu Asn 435	440	445 450	1400
gcc aaa tca gaa gat gtg tct ttc cag ggg cgg gga gtc ttc gag ctc Ala Lys Ser Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe Glu Leu 455	460	465	1448
tcg gac gaa aag gca acg aac ccg atc gtg cct tcc ttt gac atg agc Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp Met Ser 470	475	480	1496
aat gaa ggg tct tat ttc ttc gga gac aat gct gag gag ttt gac agt Asn Glu Gly Ser Tyr Phe Phe Gly Asp Asn Ala Glu Glu Phe Asp Ser 485	490	495	1544
taaagaaaa tacccttggt tctactaata cgagacgata t			1585

<210> SEQ ID NO 6  
 <211> LENGTH: 498  
 <212> TYPE: PRT  
 <213> ORGANISM: Influenza A Virus

<400> SEQUENCE: 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			

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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
		230		235		240
Gln Val Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu		245		250		255
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
		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
		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
		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> SEQ ID NO 7  
 <211> LENGTH: 1056  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A virus  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (40)..(795)

&lt;400&gt; SEQUENCE: 7

tattcgtctc agggagcaaa agcaggtaga tatttaaag atg agt ctt cta acc  
 Met Ser Leu Leu Thr

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															1	5	
gag gtc gaa acg tac gtt ctc tct atc gta cca tca ggc ccc ctc aaa	Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro Ser Gly Pro Leu Lys		10					15					20		102		
gcc gag atc gcg cag aga ctt gaa gat gtc ttt gcg gga aag aac acc	Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe Ala Gly Lys Asn Thr		25				30						35		150		
gat ctt gag gca ctc atg gaa tgg cta aag aca aga cca atc ctg tca	Asp Leu Glu Ala Leu Met Glu Trp Leu Lys Thr Arg Pro Ile Leu Ser		40			45						50		198			
cct ctg act aaa ggg att tta gga ttt gta ttc acg ctc acc gtg ccc	Pro Leu Thr Lys Gly Ile Leu Gly Phe Val Phe Thr Leu Thr Val Pro		55			60					65			246			
agt gag cga gga ctg cag cgt aga cgc ttt gtc caa aat gcc ctt agt	Ser Glu Arg Gly Leu Gln Arg Arg Arg Phe Val Gln Asn Ala Leu Ser		70			75			80				85	294			
gga aac gga gat cca aac aac atg gac aga gca gta aaa ctg tac agg	Gly Asn Gly Asp Pro Asn Asn Met Asp Arg Ala Val Lys Leu Tyr Arg		90					95					100	342			
aag ctt aaa aga gaa ata aca ttc cat gag gca aaa gag gtg gca ctc	Lys Leu Lys Arg Glu Ile Thr Phe His Glu Ala Lys Glu Val Ala Leu		105					110					115	390			
agc tat tcc act ggt gca cta gcc agc tgc atg gga ctc ata tac aac	Ser Tyr Ser Thr Gly Ala Leu Ala Ser Cys Met Gly Leu Ile Tyr Asn		120					125					130	438			
aga atg gga act gtt aca acc gaa gtg gca ttt ggc ctg gta tgc gcc	Arg Met Gly Thr Val Thr Thr Glu Val Ala Phe Gly Leu Val Cys Ala		135			140							145	486			
aca tgt gaa cag att gct gat tcc cag cat cga tct cac agg cag atg	Thr Cys Glu Gln Ile Ala Asp Ser Gln His Arg Ser His Arg Gln Met		150			155			160				165	534			
gtg aca aca acc aac cca tta atc aga cat gaa aac aga atg gta tta	Val Thr Thr Thr Asn Pro Leu Ile Arg His Glu Asn Arg Met Val Leu		170					175					180	582			
gcc agt acc acg gct aaa gcc atg gaa cag atg gca gga tcg agt gag	Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met Ala Gly Ser Ser Glu		185					190					195	630			
cag gca gca gag gcc atg gag gtt gct agt agg gct agg cag atg gta	Gln Ala Ala Glu Ala Met Glu Val Ala Ser Arg Ala Arg Gln Met Val		200			205							210	678			
cag gca atg aga acc att ggg acc cac cct agc tcc agt gcc ggt ttg	Gln Ala Met Arg Thr Ile Gly Thr His Pro Ser Ser Ser Ala Gly Leu		215			220						225		726			
aaa gat gat ctc ctt gaa aat tta cag gcc tac cag aaa cgg atg gga	Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr Gln Lys Arg Met Gly		230			235			240				245	774			
gtg caa atg cag cga ttc aag tgatcctctc gttattgcag caagtatcat	Val Gln Met Gln Arg Phe Lys		250											825			
tggaatcttg cacttgatat tgtggattct tgatcgtctt ttcttcaaat tcatttatcg														885			
tcgccttaaa tacgggttga aaagagggcc ttctacggaa ggagtacctg agtctatgag														945			
ggaagaatat cggcaggaac agcagaatgc tgtggatggt gacgatggtc atttgtcaa														1005			
catagagctg gagtaaaaaa ctaccttggt tctactaata cgagacgata t														1056			

&lt;210&gt; SEQ ID NO 8

&lt;211&gt; LENGTH: 252

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza A virus

-continued

&lt;400&gt; SEQUENCE: 8

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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
          20           25           30

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
          165          170          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

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&lt;210&gt; SEQ ID NO 9

&lt;211&gt; LENGTH: 870

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A virus

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: CDS

&lt;222&gt; LOCATION: (29)..(718)

&lt;400&gt; SEQUENCE: 9

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ggagcaaaag cagggtgaca aaaacata atg gat tcc aac act gtg tca agc      52
          Met Asp Ser Asn Thr Val Ser Ser
          1           5

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

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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
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 agatggttga ttgaagaagt gcgacataga ttgaaaaata cagaaaatag	778
ttttgaacaa ataacattta tgcaagcctt acaactattg cttgaagtag aacaagagat	838
aagaactttc tcgtttcagc ttatttaatg at	870

&lt;210&gt; SEQ ID NO 10

&lt;211&gt; LENGTH: 230

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza A virus

&lt;400&gt; SEQUENCE: 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	
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	

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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> SEQ ID NO 11  
 <211> LENGTH: 2191  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A virus  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (4)..(2151)

<400> SEQUENCE: 11

taa atg gaa gac ttt gtg cga cag tgc ttc aat cca atg atc gtc gag	48
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	
80 85 90 95	
aac acc aca aga gct gaa aaa cct aaa ttt ctt cca gat tta tac gac	336
Asn Thr Thr Arg Ala Glu Lys Pro Lys Phe Leu Pro Asp Leu Tyr Asp	
100 105 110	
tat aag gag aac aga ttt gtt gaa att ggt gtg aca agg aga gaa gtt	384
Tyr Lys Glu Asn Arg Phe Val Glu Ile Gly Val Thr Arg Arg Glu Val	
115 120 125	
cac ata tac tac ctg gag aaa gcc aac aaa ata aag tct gag aaa aca	432
His Ile Tyr Tyr Leu Glu Lys Ala Asn Lys Ile Lys Ser Glu Lys Thr	
130 135 140	
cat atc cac att ttc tca ttt aca gga gaa gaa atg gct aca aaa gcg	480
His Ile His Ile Phe Ser Phe Thr Gly Glu Glu Met Ala Thr Lys Ala	
145 150 155	
gac tat act ctt gat gaa gag agt aga gcc agg atc aag acc aga cta	528
Asp Tyr Thr Leu Asp Glu Glu Ser Arg Ala Arg Ile Lys Thr Arg Leu	
160 165 170 175	
ttc act ata aga caa gaa atg gcc agt aga ggc ctc tgg gat tcc ttt	576
Phe Thr Ile Arg Gln Glu Met Ala Ser Arg Gly Leu Trp Asp Ser Phe	
180 185 190	
cgt cag tcc gag aga ggc gaa gag aca att gaa gaa aga ttt gaa atc	624

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Arg	Gln	Ser	Glu	Arg	Gly	Glu	Glu	Thr	Ile	Glu	Glu	Arg	Phe	Glu	Ile				
			195					200					205						
aca	gga	acg	atg	cgc	aag	ctt	gcc	aat	tac	agt	ctc	cca	ccg	aac	ttc				672
Thr	Gly	Thr	Met	Arg	Lys	Leu	Ala	Asn	Tyr	Ser	Leu	Pro	Pro	Asn	Phe				
		210					215					220							
tcc	agc	ctt	gaa	aat	ttt	aga	gtc	tat	ata	gat	gga	ttc	gaa	ccg	aac				720
Ser	Ser	Leu	Glu	Asn	Phe	Arg	Val	Tyr	Ile	Asp	Gly	Phe	Glu	Pro	Asn				
		225				230					235								
ggc	tgc	att	gag	agt	aag	ctt	tct	caa	atg	tcc	aaa	gaa	gta	aat	gcc				768
Gly	Cys	Ile	Glu	Ser	Lys	Leu	Ser	Gln	Met	Ser	Lys	Glu	Val	Asn	Ala				
240					245					250					255				
aaa	atc	gaa	cca	ttt	tca	aag	aca	aca	ccc	cga	cca	ctc	aaa	atg	cca				816
Lys	Ile	Glu	Pro	Phe	Ser	Lys	Thr	Thr	Pro	Arg	Pro	Leu	Lys	Met	Pro				
				260						265					270				
ggt	ggt	cca	ccc	tgc	cat	cag	cga	tcc	aaa	ttc	ttg	cta	atg	gat	gct				864
Gly	Gly	Pro	Pro	Cys	His	Gln	Arg	Ser	Lys	Phe	Leu	Leu	Met	Asp	Ala				
				275				280							285				
ctg	aaa	ctg	agc	att	gag	gac	cca	agt	cac	gag	gga	gag	ggg	ata	cca				912
Leu	Lys	Leu	Ser	Ile	Glu	Asp	Pro	Ser	His	Glu	Gly	Glu	Gly	Ile	Pro				
				290				295						300					
cta	tat	gat	gca	atc	aaa	tgc	atg	aaa	act	ttc	ttt	gga	tgg	aaa	gag				960
Leu	Tyr	Asp	Ala	Ile	Lys	Cys	Met	Lys	Thr	Phe	Phe	Gly	Trp	Lys	Glu				
		305				310						315							
ccc	agt	att	gtt	aaa	cca	cat	aaa	aag	ggt	ata	aac	ccg	aac	tat	ctc				1008
Pro	Ser	Ile	Val	Lys	Pro	His	Lys	Lys	Gly	Ile	Asn	Pro	Asn	Tyr	Leu				
320						325						330			335				
caa	act	tgg	aag	caa	gta	tta	gaa	gaa	ata	caa	gac	ctt	gag	aac	gaa				1056
Gln	Thr	Trp	Lys	Gln	Val	Leu	Glu	Glu	Ile	Gln	Asp	Leu	Glu	Asn	Glu				
				340						345					350				
gaa	agg	acc	ccc	aag	acc	aag	aat	atg	aaa	aaa	aca	agc	caa	ttg	aaa				1104
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									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									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									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				
															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									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									510				
aga	aat	gat	act	gac	gtg	gtg	aac	ttt	gta	agt	atg	gaa	ttt	tct	ctc				1584





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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
	130					135					140				
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
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			

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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 Ile Val Gln Ala Leu  
 660 665 670  
 Arg Asp Asp Leu Glu Pro Gly Thr Phe Asp Ile Gly Gly Leu Tyr Glu  
 675 680 685  
 Ser Ile Glu Glu Cys Leu Ile Asn Asp Pro Trp Val Leu Leu Asn Ala  
 690 695 700  
 Ser Trp Phe Asn Ser Phe Leu Thr His Ala Leu Lys  
 705 710 715

<210> SEQ ID NO 13  
 <211> LENGTH: 2299  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A virus  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (22)..(2292)  
 <220> FEATURE:  
 <221> NAME/KEY: misc\_feature  
 <222> LOCATION: (547)..(547)  
 <223> OTHER INFORMATION: Xaa stands for Ala or Val

<400> SEQUENCE: 13

gaaagcaggc aaaccatttg a atg gat gtc aat ccg act cta ctt ttc tta 51  
 Met Asp Val Asn Pro Thr Leu Leu Phe Leu  
 1 5 10  
 aag gtg cca gcg caa aat gct ata agc aca aca ttc cct tat act gga 99  
 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

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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	ggc		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		
atg	gag	tcc	atg	aac	aag	gag	gaa	atg	gaa	ata	aca	aca	cac	ttc	caa		579
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		
		235				240					245				250		
ttt	gta	tat	ttt	ggt	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	ggt	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		
			270					275						280			
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		
			285					290					295				
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		
						320					325				330		
gaa	tgg	ttc	aga	aat	ggt	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		
					335					340					345		
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		
				350				355							360		
aaa	ttg	aga	act	caa	ata	cca	gca	gaa	atg	cta	gca	agc	att	gac	cta		1155
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	ggt	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		
					400					405					410		
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

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Gly	Gln	Arg	Lys	Tyr	Thr	Lys	Thr	Thr	Tyr	Trp	Trp	Asp	Gly	Leu	Gln	
			430					435					440			
tca	tcc	gat	gac	ttt	gct	ttg	ata	gtg	aat	gcg	cct	aat	cat	gaa	gga	1395
Ser	Ser	Asp	Asp	Phe	Ala	Leu	Ile	Val	Asn	Ala	Pro	Asn	His	Glu	Gly	
		445					450					455				
ata	caa	gct	gga	gta	gac	aga	ttc	tat	aga	act	tgc	aaa	ctg	gtc	ggg	1443
Ile	Gln	Ala	Gly	Val	Asp	Arg	Phe	Tyr	Arg	Thr	Cys	Lys	Leu	Val	Gly	
	460					465					470					
atc	aac	atg	agc	aaa	aag	aag	tcc	tac	ata	aat	aga	act	gga	aca	ttc	1491
Ile	Asn	Met	Ser	Lys	Lys	Lys	Ser	Tyr	Ile	Asn	Arg	Thr	Gly	Thr	Phe	
					480					485					490	
gaa	ttc	aca	agc	ttt	ttc	tac	cgg	tat	ggt	ttt	gta	gcc	aat	ttc	agc	1539
Glu	Phe	Thr	Ser	Phe	Phe	Tyr	Arg	Tyr	Gly	Phe	Val	Ala	Asn	Phe	Ser	
				495					500					505		
atg	gaa	cta	ccc	agt	ttt	ggg	ggt	tcc	gga	ata	aat	gaa	tct	gca	gac	1587
Met	Glu	Leu	Pro	Ser	Phe	Gly	Val	Ser	Gly	Ile	Asn	Glu	Ser	Ala	Asp	
			510					515					520			
atg	agc	att	gga	gtg	aca	gtc	atc	aaa	aac	aac	atg	ata	aat	aat	gat	1635
Met	Ser	Ile	Gly	Val	Thr	Val	Ile	Lys	Asn	Asn	Met	Ile	Asn	Asn	Asp	
			525				530						535			
ctc	ggt	cct	gcc	acg	gca	caa	atg	gya	ctc	caa	ctc	ttc	att	aag	gat	1683
Leu	Gly	Pro	Ala	Thr	Ala	Gln	Met	Xaa	Leu	Gln	Leu	Phe	Ile	Lys	Asp	
		540				545					550					
tat	cgg	tac	aca	tac	cgg	tgc	cat	aga	ggt	gat	acc	cag	ata	caa	acc	1731
Tyr	Arg	Tyr	Thr	Tyr	Arg	Cys	His	Arg	Gly	Asp	Thr	Gln	Ile	Gln	Thr	
					560					565					570	
aga	aga	tct	ttt	gag	ttg	aag	aaa	ctg	tgg	gaa	cag	act	cga	tca	aag	1779
Arg	Arg	Ser	Phe	Glu	Leu	Lys	Lys	Leu	Trp	Glu	Gln	Thr	Arg	Ser	Lys	
				575					580					585		
act	ggt	cta	ctg	gta	tca	gat	ggg	ggt	cca	aac	cta	tat	aac	atc	aga	1827
Thr	Gly	Leu	Leu	Val	Ser	Asp	Gly	Gly	Pro	Asn	Leu	Tyr	Asn	Ile	Arg	
			590					595					600			
aac	cta	cac	atc	ccg	gaa	gtc	tgt	tta	aaa	tgg	gag	cta	atg	gat	gaa	1875
Asn	Leu	His	Ile	Pro	Glu	Val	Cys	Leu	Lys	Trp	Glu	Leu	Met	Asp	Glu	
		605					610						615			
gat	tat	aag	ggg	agg	cta	tgc	aat	cca	ttg	aat	cct	ttc	ggt	agt	cac	1923
Asp	Tyr	Lys	Gly	Arg	Leu	Cys	Asn	Pro	Leu	Asn	Pro	Phe	Val	Ser	His	
		620				625					630					
aaa	gaa	att	gaa	tca	gtc	aac	agt	gca	gta	gta	atg	cct	gcg	cat	ggc	1971
Lys	Glu	Ile	Glu	Ser	Val	Asn	Ser	Ala	Val	Val	Met	Pro	Ala	His	Gly	
					640					645					650	
cct	gcc	aaa	agc	atg	gag	tat	gat	gct	ggt	gca	aca	aca	cat	tct	tgg	2019
Pro	Ala	Lys	Ser	Met	Glu	Tyr	Asp	Ala	Val	Ala	Thr	Thr	His	Ser	Trp	
				655					660					665		
atc	ccc	aag	agg	aac	cgg	tcc	ata	ttg	aac	aca	agc	caa	agg	gga	ata	2067
Ile	Pro	Lys	Arg	Asn	Arg	Ser	Ile	Leu	Asn	Thr	Ser	Gln	Arg	Gly	Ile	
				670					675					680		
cta	gaa	gat	gag	cag	atg	tat	cag	aaa	tgc	tgc	aac	ctg	ttt	gaa	aaa	2115
Leu	Glu	Asp	Glu	Gln	Met	Tyr	Gln	Lys	Cys	Cys	Asn	Leu	Phe	Glu	Lys	
		685					690					695				
ttc	ttc	ccc	agc	agc	tca	tac	aga	aga	cca	gtc	gga	att	tct	agt	atg	2163
Phe	Phe	Pro	Ser	Ser	Ser	Tyr	Arg	Arg	Pro	Val	Gly	Ile	Ser	Ser	Met	
		700					705				710					
ggt	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

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Cys Ser Thr Ile Glu Glu Leu Arg Arg Gln Lys  
750 755

<210> SEQ ID NO 14

<211> LENGTH: 757

<212> TYPE: PRT

<213> ORGANISM: Influenza A virus

<220> FEATURE:

<221> NAME/KEY: misc\_feature

<222> LOCATION: (547)..(547)

<223> OTHER INFORMATION: The 'Xaa' at location 547 stands for Ala, or Val.

<400> SEQUENCE: 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  
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





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



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Ser	Leu	Val	Pro	Arg	Ala	Thr	Arg	Ser	Gln	Tyr	Ser	Gly	Phe	Val	Arg					
			585					590					595							
acc	ctg	ttt	cag	caa	atg	cga	gat	gta	ctt	gga	aca	ttt	gat	act	gct	1880				
Thr	Leu	Phe	Gln	Gln	Met	Arg	Asp	Val	Leu	Gly	Thr	Phe	Asp	Thr	Ala					
		600					605					610								
caa	ata	ata	aaa	ctc	ctc	cct	ttt	gcc	gct	gct	cct	ccg	gaa	cag	agt	1928				
Gln	Ile	Ile	Lys	Leu	Leu	Pro	Phe	Ala	Ala	Ala	Pro	Pro	Glu	Gln	Ser					
		615				620					625									
agg	atg	cag	ttc	tct	tct	ttg	act	gtt	aat	gta	aga	ggt	tcg	gga	atg	1976				
Arg	Met	Gln	Phe	Ser	Ser	Leu	Thr	Val	Asn	Val	Arg	Gly	Ser	Gly	Met					
		630			635					640					645					
agg	ata	ctt	gta	aga	ggc	aat	tcc	ccg	gtg	ttc	aac	tac	aat	aaa	gtc	2024				
Arg	Ile	Leu	Val	Arg	Gly	Asn	Ser	Pro	Val	Phe	Asn	Tyr	Asn	Lys	Val					
				650					655					660						
act	aaa	agg	ctc	aca	gtc	ctc	gga	aag	gat	gca	ggt	gcg	ctt	act	gag	2072				
Thr	Lys	Arg	Leu	Thr	Val	Leu	Gly	Lys	Asp	Ala	Gly	Ala	Leu	Thr	Glu					
			665					670					675							
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	tagt	gttg	gaa	ttgt	ttta	aaaa	acg	ac	ctt	gt	ttct	act	aat	acg	agac	cat	at	2370	
Ile	Asn																			

&lt;210&gt; SEQ ID NO 16

&lt;211&gt; LENGTH: 759

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza A virus

&lt;400&gt; SEQUENCE: 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  
 405 410 415  
 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



15. A method of inducing an immune response to a canine influenza H3 virus in an animal, which method comprises administering to the animal the composition of claim 4 or claim 12, where upon an immune response to a canine influenza H3 virus is induced in the animal.

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