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

(71) Applicant: **Iowa State University Research Foundation, Inc.**, Ames, IA (US)

(72) Inventors: **Kyoung-Jin Yoon**, Ames, IA (US);
Vickie Cooper, Ames, IA (US)

(73) Assignee: **IOWA STATE UNIVERSITY RESEARCH FOUNDATION, INC.**, Ames, IA (US)

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See application file for complete search history.

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Primary Examiner — Benjamin P Blumel

(74) *Attorney, Agent, or Firm* — Barnes & Thornburg LLP

(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.

5 Claims, 14 Drawing Sheets

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NM

AGTTTAAAATGAATCCAAATCAAAGATAATAGCAATTGGATTTGCATCATTGGG
GATATTAATCATTAAATGTCATTCTCCATGTAGTCAGCATTATAGTAACAGTACTG
GTCCTCAATAACAATAGAACAGATCTGAACTGCAAAGGGACGATCATAAGAGAA
TACAATGAAACAGTAAGAGTAGAAAACTTACTCAATGGTATAATACCAGTACA
ATTAAGTACATAGAGAGACCTTCAAATGAATACTACATGAATAACACTGAACCA
CTTTGTGAGGCCCAAGGCTTTGCACCATTTTCCAAAGATAATGGAATACGAATTG
GGTCGAGAGGCCATGTTTTTGTGATAAGAGAACCTTTTTGTATCATGTTCCGCCCTC
AGAATGTAGAACCCTTTTTCCTCACACAGGGCTCATTACTCAATGACAAACATTCT
AACGGCACAATAAAGGATCGAAGCCCGTATAGGACTTTGATGAGTGTCAAATA
GGGCAATCACCCAATGTATATCAAGCTAGGTTTGAATCGGTGGCATGGTCAGCA
ACAGCATGCCATGATGGAAAAAATGGATGACAGTTGGAGTCACAGGGCCCGAC
AATCAAGCAATTGCAGTAGTGAACCTATGGAGGTGTTCCGGTTGATACTATTAATT
CATGGGCAGGGGATATTTTAAGAACCCAAGAATCATCATGCACCTGCATTAAG
GAGACTGTTATTGGGTAATGACTGATGGACCGGCAAATAGGCAAGCTAAATATA
GGATATTCAAAGCAAAGATGGAAGAGTAATTGGACAAACTGATATAAGTTTCA
ATGGGGGACACATAGAGGAGTGTCTTGTACCCCAATGAAGGGAAAGGTGGAAT
GCATATGCAGGGACAATTGGACTGGAACAAATAGACCAATTCTGGTAATATCTTIC
TGATCTATCGTACACAGTTGGATATTTGTGTGCTGGCATTCCCCTGACACTCCTA
GGGGAGAGGATAGTCAATTCACAGGCTCATGTACAAAGTCCTTTGGGAAATAAAG
GATACGGTGTAAAAGGCTTCGGGTTTCGACAAGGAACTGACGTATGGGCCGGAA
GGACAATTAGTAGGACTTCAAGATCAGGATTCGAAATAATAAAAATCAGGAATG
GTTGGACACAGAACAGTAAGGACCAATCAGGAGGCAAGTGATTATCGATGACC
CAAATTGGTCAGGATATAGCGGTTCTTTCACATTGCCGGTTGAACTGACAAAAAA
GGGATGTTTGGTCCCTGTTTTCTGGGTTGAAATGATTAGAGGTAAACCTGAAGAA
ACAACAATATGGACCTCTAGCAGCTCCATTGTGATGTGTGGAGTAGATCATAAAA
TTGCCAGTTGGTCATGGCACGATGGAGCTATTCTTCCCTTTGACATCGATAAGAT
GTAATTTACGAAAAAACTCCTTGTCTTCTACTA (SEQ ID NO: 1)

FIG. 1

NM - Amino

MNPNQKIIAIGFASLGILIIINVILIVVSIIVTVLVLNNRDTLNCCKGTIIREYNETVRVEK
LTQWYNTSTIKYIERPSNEYMNTEPLCEAQGFAPFSKDNIGIRIGSRGHVFEVIREPFV
SCSPSECRFFLTQGSLLNDKHSNGTIKDRSPYRTLMSVKIGQSPNVYQARFESVAWS
ATACHDGKKWMTVGVGTGPDNQAIAVVNYGGVPVDTINSWAGDILRTQESSCTCIKG
DCYWVMTDGPANRQAKYRIFKAKDGRVIGQTDISFNGGHIEECSCYPNEGKVECICR
DNWIGTNRPILVISSDLSYTVGYLCAGIPTDTPRGEDSQFTGSCTSPLGNKGYGVKGF
GFRQGTDVWAGRTISRTRSFGFEIKIRNGWTQNSKDQIRRQVIIDDPNWSGYSGSFTL
PVELTKKGCLVPCFWVEMIRGKPEETTIWTSSSSIVMCGVDHKIASWSWIIDGAILPF
DIDKM (SEQ ID NO: 2)

FIG. 2

HA:

AGCAAAAGCAGGGGATATTTCTGTCAATCATGAAGACAACCATTATTTTAATACT
ACTGACCCATTGGGCCTACAGTCAAAACCCAATCAGTGGCAATAACACAGCCAC
ACTGTGTCTGGGACACCATGCAGTAGCAAATGGAACATTGGTAAAAACAATGAG
TGATGATCAAATTGAGGTGACAAATGCTACAGAATTAGTTCAGAGCATTTC AATG
GGGAAAATATGCAACAAATCATATAGAATTCTAGATGGAAGAAATTGCACATTA
ATAGATGCAATGCTAGGAGACCCCCACTGTGACGCCCTTCAGTATGAGAGTTGG
GACCTCTTTATAGAAAGAAGCAGCGCTTTCAGCAATTGCTACCCATATGACATCC
CTGACTATGCATCGCTCCGATCCATTGTAGCATCCTCAGGAACAGTTGAATTCAC
AGCAGAGGGATTACATGGACAGGTGTA ACTCAAAACGGAAGAAGTGGAGCCTG
CaaAAGGGGATCAGCCGATAGTTTCTTTAGCCGACTGAATTGGCTAACAAAATCT
GGAAGCTCTTACCCACATTGAATGTGACAATGCCTAACATAAAAATTTTCGACA
AGCTATACATCTGGGGGATTCATCACCCGAGCTCAAATCAAGAGCAGACAAAAT
TGTACATCCAAGAATCAGGACGAGTAACAGTCTCAACAAAAAGAAGTCAACAAA
CAATAATCCCTAACATCGAATCTAGACCGTTGGTCAGAGGTCAATCAGGCAGGA
TAAGCATATACTGGACCATTGTAAAACCTGGAGATATCCTAATGATAAACAGTA
ATGGCAACTTAGTTGCACCGCGGGGATATTTTAAATTGAACACAGGGAAAAGCT
CTGTAATGAGATCCGATGTACCCATAGACATTTGTGTGTCTGAATGTATTACACC
AAATGGAAGCATCTCCAACGACAAGCCATTCCAAAATGTGAACAAAGTTACATA
TGGAAAATGCCCAAGTATATCAGGCAAAACACTTTAAAGCTGGCCACTGGGAT
GAGGAATGTACCAGAAAAGCAAACCAGAGGAATCTTTGGAGCAATAGCGGGATT
CATCGAAAACGGCTGGGAAGGAATGGTTGATGGGTGGTATGGGTTCCGATATCA
AAACTCTGAAGGAACAGGGCAAGCTGCAGATCTAAAGAGCACTCAAGCAGCCAT
TGACCAGATTAATGGAAAGTTAAACAGAGTGATTGAAAGAACCAATGAGAAATT
CCATCAAATAGAGAAGGAATTCTCAGAAGTAGAAGGAAGAATTCAGGACTTGGGA
GAAATATGTAGAAGACACCAAAATAGACCTATGGTCCTACAATGCAGAATTGCT
GGTGGCTCTAGAAAATCAACATACAATTGACTTAACAGATGCAGAAATGAATAA
ATTATTTGAGAAGACTAGACGCCAGTTAAGAGAAAACGCAGAAGACATGGGAGG
TGGATGTTTCAAGATTTACCACAAATGTGATAATGCATGCATTGAATCAATAAGA
ACTGGGACATATGACCATTACATATACAGAGATGAAGCATTAAACAACCGATTT
CAGATCAAAGGTGTAGAGTTGAAATCAGGCTACAAAGATTGGATACTGTGGATT
TCATTCGCCATATCATGCTTCTTAATTTGCGTTGTTCTATTGGGTTTCATTATGTGG
GCTTGCCAAAAGGCAACATCAGATGCAACATTTGCATTTGAGTAAACTGATAGT
TAAAACACCCTTGTTTCTACT (SEQ ID NO:3)

FIG. 3

HA - Amino

MKTTIILILLTHWAYSQNPISGNNTATLCLGHHAVANGTLVKTMSDDQIEVTNATEL
VQSISMGKICNKSYRILDGRNCTLIDAMLGDPHCDALQYESWDLFIERSSAFNCYPY
DIPDYASLRISIVASSGIVEFTAEGFTWTGVTQNGRSGACKRGSADSFRLNWLTKS
GSSYPTLNVTMPNNKNFDKLYIWGIHHPSSNQEQTCLYIQESGRVTVSTKRSQQTIIP
NIESRPLVRGQSGRISYWTIVKPGDILMINSNGNLVAPRGYFKLNTGKSSVMRSDVPI
DICVSECITPNGSISNDKPFQNVNKVTYGKCPKYIRQNTLKLATGMRNVPEKQTRGIF
GAIAGFIENGWEGMVDGWYGFYQNSEGTGQAADLKSTQAADQINGKLNRIERT
NEKFHQIEKEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDAEMN
KLFKTRRQIRENAEDMGGGCFKIYHKCDNACIESIRTGTYDHYIYRDEALNNRFQI
KGVELKSGYKDWILWISFAISCFLICVLLGFIMWACQKGNIRCNICI (SEQ ID NO: 4)

FIG. 4

NP

CAGGGAGCAAAAGCAGGGTAGATAATCACTCACTGAGTGACATCAAAGTCATGG
CGTCTCAAGGCACCAAACGATCCTATGAACAGATGGAAACTGATGGGGAACGCC
AGAATGCAACTGAAATCAGAGCATCTGTCCGGAAGGATGGTGGGAGGAATCGGAC
GGTTTTATGTCCAGATGTGTACTGAGCTTAAACTAAACGACCATGAAGGGCGGCT
GATTCAGAACAGCATAACAATAGAAAGGATGGTACTTTCAGCATTTCGACGAAAG
AAGAAACAAGTATCTCGAGGAGCATCCCAGTGCTGGGAAAGACCCTAAGAAAAC
GGGAGGCCCGATATACAGAAGAAAAGATGGGAAATGGATGAGGGAACTCATCC
TCCATGATAAAGAAGAATCATGAGAATCTGGCGTCAGGCCAACAAATGGTGAAG
ACGCTACTGCTGGTCTTACTCATATGATGATCTGGCACTCCAATCTCAATGACAC
CACATACCAAAGAACAAAGGGCTCTTGTTCCGACTGGGATGGATCCCAGAATGTG
CTCTCTGATGCAAGGCTCAACCCTCCCACGGAGATCTGGAGCCGCTGGTGCTGCA
GTAAAAGGTGTTGGAACAATGGTAATGGAACATCAGGATGATCAAACGCGGA
ATAAATGATCGGAATTTCTGGAGAGGTGAAAATGGTCGAAGAACCAGAATTGCT
TATGAAAGAATGTGCAATATCCTCAAAGGGAAATTTTCAGACAGCAGCACAAACGG
GCTATGATGGACCAGGTGAGGGAAAGGCCGCAATCCTGGAAACGCTGAGATTGAG
GATCTCATTTTCTTGGCACGATCAGCACTTATTTTGAGAGGATCAGTAGCCATA
AATCATGCCTACCTGCCTGTGTTTATGGCCTTGCAGTAACCAGTGGGTATGACTTT
GAGAAGGAAGGATACTCTCTGGTTGGAATTGATCCTTTCAAACACTCCAGAACA
GTCAAATTTTCAGTCTAATCAGACCAAAGAAAACCCAGCACACAAAAGCCAGT
TGGTGTGGATGGCATGCCATTCTGCAGCATTGAGGATCTGAGAGTTTTAAATTT
CATTAGAGGAACCAAAGTAATCCCAAGAGGACAGTTAACAACCAGAGGAGTTCA
AATTGCTTCAAATGAAAACATGGAGACAATAAATTTCTAGCACACTTGAACAGAG
AAGCAAATATTGGGCAATAAGGACCAGAAGCGGAGGAAACACCAGTCAACAGA
GAGCATTTCAGGACAGATAAGTGTGCAACCTACTTTCTCAGTACAGAGAAATCT
TCCCTTTGAGAGAGCAACCATTATGGCTGCATTCACTGGTAACACTGAAGGGAGG
ACTTCCGACATGAGAACGGAAATCATAAGGATGATGGAAAATGCCAAATCAGAA
GATGTGTCTTTCCAGGGGCGGGGAGTCTTCGAGCTCTCGGACGAAAAGGCAACG
AACCCGATCGTGCCTTCCTTTGACATGAGCAATGAAGGGTCTTATTTCTTCGGAG
ACAATGCTGAGGAGTTTGACAGTTAAAGAAAATACCCTTGTTTCTACTAATACG
AGACGATAT (SEQ ID NO: 5)

FIG. 5

NP - Amino

MASQGTKRSYEQMETDGERQNATEIRASVGRMVGGIGRFYVQMCTELKLNDHEGR
LIQNSITIERMVLSAFDERRNKYLEEHPSAGKDPKKTGGPIYRRKDGKWMRELILHD
KEEIMRIWRQANNGEDATAGLTHMMIWHSNLNDTTYQRTRALVRTGMDPRMCSL
MQGSTLPRRSGAAGA AVKGVGTMMELIRMIKRGINDRNFWRGENGRRTRIAYER
MCNILKGKFQTAAQRAMMDQVREGRNPGNAEIEDLIFLARSALILRGSVAHKSCLPA
CVYGLAVTSGYDFEKEGYSLVGIDPFKLLQNSQIFSLIRPKENPAHKSQLVWMACHS
AAFEDLRVLNFIRGTKVIPRGQLTTRGVQIASNENMETINSSTLELRSKYWAIRTRSG
GNTSQQRAAFAGQISVQPTFSVQRNLPFERATIMAAFTGNTEGRTSDMRTEIIRMMEN
AKSEDVSFQGRGVFELSDKATNPVPSFDMSNEGSYFFGDNAEFEDS (SEQ ID NO:
6)

FIG. 6

M1

TATTCGTCTCAGGGAGCAAAAGCAGGTAGATATTTAAAGATGAGTCTTCTAACCG
AGGTCGAAACGTACGTTCTCTCTATCGTACCATCAGGCCCCCTCAAAGCCGAGAT
CGCGCAGAGACTTGAAGATGTCTTTGCGGGAAAGAACACCGATCTTGAGGCACT
CATGGAATGGCTAAAGACAAGACCAATCCTGTACCTCTGACTAAAGGGATTTTA
GGATTTGTATTACGCTCACCGTGCCCAGTGAGCGAGGACTGCAGCGTAGACGCT
TTGTCCAAAATGCCCTTAGTGGAAACGGAGATCCAAACAACATGGACAGAGCAG
TAAACTGTACAGGAAGCTTAAAAGAGAAATAACATTCCATGAGGCCAAAAGAGG
TGGCACTCAGCTATTCCACTGGTGCACTAGCCAGCTGCATGGGACTCATATACAA
CAGAATGGGAACTGTTACAACCGAAGTGGCATTGGCCTGGTATGCGCCACATGT
GAACAGATTGCTGATTCCCAGCATCGATCTCACAGGCAGATGGTGACAACAACC
AACCCATTAATCAGACATGAAAACAGAATGGTATTAGCCAGTACCACGGCTAAA
GCCATGGAAACAGATGGCAGGATCGAGTGAGCAGGCAGCAGAGGCCATGGAGGT
TGCTAGTAGGGCTAGGCAGATGGTACAGGCAATGAGAACCATTGGGACCCACCC
TAGCTCCAGTGCCGGTTTGAAAGATGATCTCCTTGAAAATTTACAGGCCTACCAG
AAACGGATGGGAGTGCAAATGCAGCGATTCAAGTGATCCTCTCGTTATTGCAGC
AAGTATCATTGGAATCTTGCACCTTGATATTGTGGATTCTTGATCGTCTTTTCTTCA
AATTCATTTATCGTCGCCTTAAATACGGGTTGAAAAGAGGGCCTTCTACGGAAGG
AGTACCTGAGTCTATGAGGGAAGAATATCGGCAGGAACAGCAGAATGCTGTGGA
TGTTGACGATGGTCATTTTGTCAACATAGAGCTGGAGTAAAAAACTACCTTGTT
CTACTAATACGAGACGATAT (SEQ ID NO: 7)

FIG. 7

M1 - Amino

MSLLTEVETYVLSIVPSGPLKAEIAQRLEDVFAGKNTDLEALMEWLKTRPILSPLTKG
ILGFVFTLTVPSERGLQRRRFVQNALSGNGDPNNMDRAVKLYRKLKREITFHEAKEV
ALSYSTGALASCMGLIYNRMGTVTTEVAFGLVCATCEQIADSQHRSHRQMVTITNP
LIRHENRMVLASTIAKAMEQMAGSSEQAAEAMEVASRARQMVMQAMRTIGTHPSSS
AGLKDDLLENLQAYQKRMGVQMQRFK (SEQ ID NO: 8)

FIG. 8

NS1

GGAGCAAAAGCAGGGTGACAAAAACATAATGGATTCCAACACTGTGTCAAGCTT
TCAGGTAGACTGTTTTCTTTGGCATGTCCGCAAACGATTCGCAGACCAAGAAGCTG
GGTGATGCCCCATTCCTTGACCGGCTTCGCCGAGACCAGAAGTCCCTAAGGGGA
AGAGGTAGCACTCTTGGTCTGGACATCGAAACAGCCACTCATGCAGGAAAGCAG
ATAGTGGAGCAGATTCTGGAAAAGGAATCAGATGAGGCACTTAAAATGACCATT
GCCTCTGTTCCCTGCTTCACGCTACTTAACTGACATGACTCTTGATGAGATGTCAAG
AGACTGGTTCATGCTCATGCCCAAGCAAAAAGTAACAGGCTCCCTATGTATAAG
AATGGACCAAGCAATCATGGATAAGAACATCATACTTAAAGCAAACCTTTAGTGT
GATTTTCGAAAGGCTGGAAACACTAATACTACTTAGAGCCTTCACCGAAGAAGG
AGCAGTCGTTGGCGAAATTCACCATTACCTTCTCTCCAGGACATACTAATGAG
GATGTCAAAAATGCAATTGGGGTCTCATCGGAGGACTTAAATGGAATGATAAT
ACGGTTAGAACTCTGAAACTCTACAGAGATTTCGCTTGGAGAAGCAGTCATGAA
AATGGGAGACCTTCATTCCCTTCAAAGCAGAAACGAAAAATGGAGAGAACAATT
AAGCCAGAAATTTGAAGAAATAAGATGGTTGATTGAAGAAGTGCGACATAGATT
GAAAAATACAGAAAATAGTTTTGAACAAATAACATTTATGCAAGCCTTACAAC
ATTGCTTGAAGTAGAACAAGAGATAAGAACTTCTCGTTTCAGCTTATTTAATGA
T (SEQ ID NO: 9)

FIG. 9

NS1 - Amino

MDSNTVSSFQVDCFLWHVRKRFADQELGDAPFLDRLRRDQKSLRGRGSTLGLDIET
ATHAGKQIVEQILEKESDEALKMTIASVPASRYLTDMTLDEM SRDWFMLMPKQKVT
GSLCIRMDQAIMDKNIILKANFSVIFERLETLILLRAFTEEGAVVGEISPLPSLPGHTNE
DVKNAIGVLIGGLKWNDNTVRISETLQRFAWRSSHENGRPSFPSKQKRKMERTIKPEI
(SEQ ID NO: 10)

FIG. 10

PA

TAAATGGAAGACTTTGTGCGACAGTGCTTCAATCCAATGATCGTCGAGCTTGCGG
AAAAGGCAATGAAAGAATATGGAGAGAACCCGAAAATCGAAACAAACAAATTT
GCAGCAATATGCACTCACTTGGGAAGTCTGCTTCATGTACTCGGATTTCCACTTTAT
AAATGAACTGGGTGAGTCAGTGGTCATAGAGTCTGGTGACCCAAATGCTCTTTTG
AAACACAGATTTGAAATCATTGAGGGGAGAGATCGAACAATGGCATGGACAGTA
GTAAACAGCATCTGCAACACCACAAGAGCTGAAAAACCTAAATTTCTTCCAGATT
TATACGACTATAAGGAGAACAGATTTGTTGAAATTGGTGTGACAAGGAGAGAAG
TTCACATATACTACCTGGAGAAAGCCAACAAAATAAAGTCTGAGAAAACACATA
TCCACATTTTCTCATTACAGGAGAAGAAATGGCTACAAAAGCGGACTATACTCT
TGATGAAGAGAGTAGAGCCAGGATCAAGACCAGACTATTCACTATAAGACAAGA
AATGGCCAGTAGAGGCCTCTGGGATTCCTTTCGTCAGTCCGAGAGAGGGCGAAGA
GACAATTGAAGAAAGATTTGAAATCACAGGAACGATGCGCAAGCTTGCCAATTA
CAGTCTCCCACCGAACTTCTCCAGCCTTGAAAATTTTAGAGTCTATATAGATGGA
TTCGAACCGAACGGCTGCATTGAGAGTAAGCTTTCTCAAATGTCCAAAGAAGTA
AATGCCAAAATCGAACCATTTTCAAAGACAACACCCCGACCACTCAAATGCCA
GGTGGTCCACCCTGCCATCAGCGATCCAAATTCCTTGCAATGGATGCTCTGAAACT
GAGCATTGAGGACCCAAGTCACGAGGGAGAGGGGATACCACTATATGATGCAAT
CAAATGCATGAAAACCTTTCTTTGGATGGAAAGAGCCCAGTATTGTTAAACCACAT
AAAAAGGGTATAAACCCGAACCTATCTCCAAACTTGGGAAGCAAGTATTAGAAGAA
ATACAAGACCTTGAGAACGAAGAAAGGACCCCAAGACCAAGAATATGAAAAA
AACAAAGCCAATTGAAATGGGCACTAGGTGAAAATATGGCACCAGAGAAAGTGG
ATTTTGAGGATTGTAAGACATCAATGATTTAAAACAATATGACAGTGATGAGCC
AGAAGCAAGGTCTCTTGCAAGTTGGATTCAAAGTGAGTTCAACAAGGCTTGTGA
GCTGACAGATTCAAGCTGGATAGAGCTCGATGAAATTGGGGAGGATGTCGCCCC
AATAGAATACATTGCGAGCATGAGGAGAAATTATTTACTGCTGAGATTTCCCAT
TGTAGAGCAACAGAATATATAATGAAAGGACTATACATCAACACTGCTCTACTC
AATGCATCCTGTGCTGCGATGGATGAATTTCAATTAATTCCGATGATAAGTAAAT
GCAGGACCAAAGAAGGGAGAAGGAAAACAAATTTATATGGATTCATAATAAAG
GGAAGGTCCCATTAAAGAAATGATACTGACGTGGTGAACCTTTGTAAGTATGGAAT
TTTCTCTCACTGATCCAAGATTTGAGCCACACAAATGGGAAAAATACTGCGTTCT
AGAAATTGGAGACATGCTTCTAAGAACTGCTGTAGGTCAAGTGTCAAGACCCAT
ATTTTTGTATGTAAGGACAAATGGAACCTCTAAAATTTAAAATGAAATGGGGAAAT
GGAAATGAGACGCTGCCTCCTTCAGTCTCTGCAACAGATTGAAAGCATGATCGA
AGCTGAGTCCTCAGTCAAAGAAAAGGACATGACCAAAGAATTTTTTGAGAACAA
ATCAGAGACATGGCCTATAGGAGAGTCCCCCAAAGGAGTGGAAGAGGGCTCAAT
CGGGAAGGTTTGCAGGACCTTATTAGCAAAATCTGTGTTAACAGTTTATATGCA
TCTCCACAACCTGGAAGGATTTTCAGCTGAATCTAGGAAATTAATTCTCATTGTTT
AGGCTCTTAGAGATGACCTGGAACCTGGAACCTTTGATATTGGGGGGTTATATGA
ATCAATTGAGGAGTGCCTGATTAATGATCCCTGGGTTTTGCTTAATGCATCTTGGT
TCAACTCCTTCCTCACACATGCACTGAAGTAGTTGTGGCAATGCTACTATTTGTTA
TCCATACTGTCCA (SEQ ID NO: 11)

FIG. 11

PA - Amino

MEDFVRQCFNPMIVELAEKAMKEYGENPKIETNKFAAICTHLEVCFMYSDFHFINEL
GESVVIESGDPNALLKHRFEIIEGRDRTMAWTVVNSICNTTRA EKPKFLPDLYDYKEN
RFVEIGVTRREVHIYYLEKANKIKSEKTHIHIFSFTGEEMATKADYTLDEESRARIKTR
LFTIRQEMASRGLWDSFRQSERGEETIEERFEITGTMRKLANYSLPPNFSSLENFRVYI
DGFEPNGCIESKLSQMSKEVNAKIEPFSKTTTPRPLKMPGGPPCHQRSKFLMDALKLS
IEDPSHEGEGIPLYDAIKCMKTFFGWKEPSIVKPHKKGINPNYLQTWKQVLEEIQDLE
NEERTPKTKNMKKTSQLKWALGENMAPEKVDFEDCKDINDLKQYDSDEPEARSLAS
WIQSEFNKACELTDSSWIELDEIGEDVAPIEYIASMRRNYFTA EISHCRATEYIMKGVY
INTALLNASCAAMDEFQLIPMISKCRTKEGRRKTNLYGFIKGRSII LRNDTDVVNFVS
MEFSLTDPRFEPHKWEKYCVLEIGDMLLRTAVGQVSRPIFLYVRTNGTSKIKMKWG
MEMRRCLLQSLQQIESMIEAESSVKEKDMTKEFFENKSETWPIGESPKGVEEGSIGKV
CRTLLAKSVFNSLYASPQLEGFSAESRKL LLIVQALRDDLEPGTFDIGGLYESIEECLIN
DPWVLLNASWFNSFLTHALK (SEQ ID NO: 12)

FIG. 12

PB1

GAAAGCAGGCAAACCATTTGAATGGATGTCAATCCGACTCTACTTTTCTTAAAGG
TGCCAGCGCAAATGCTATAAGCACAAACATTCCCTTATACTGGAGATCCTCCCTA
CAGTCATGGAACAGGGACAGGATACACCATGGATACTGTCAACAGAACACACCA
ATATTCAGAAAAAGGGAAATGGACAACAAACACTGAGATTGGAGCACCACAACCT
TAATCCAATCGATGGACCACTTCCTGAAGACAATGAACCAAGTGGGTACGCCCA
AACAGATTGTGTATTGGAAAGCAATGGCTTTCCTTGAAGAATCCCATCCCCGGAATC
TTTGAAAATTCGTGTCTTGAAACGATGGAGGTGATTCAGCAGACAAGAGTGGAC
AACTAACACAAGGCCGACAAACTTATGATTGGACCTTGAATAGGAATCAACCT
GCCGCAACAGCACTTGCTAATACGATTGAAGTATTCAGATCAAATGGTCTGACTT
CCAATGAATCGGGGAGATTGATGGACTTCCTCAAAGATGTCATGGAGTCCATGA
ACAAGGAGGAAATGGAAATAACAACACACTTCCAACUGGAAGAGAAGAGTAAGA
GACAACATGACAAAGAGAATGATAACACAGAGAACCATAGGGGAAGAAAAACA
ACGATTAAGCAGAAAGAGCTATCTAATCAGAACATTAACCCTAAACACAAATGAC
CAAGGACGCTGAAAGAGGGAAATTGAAACGACGAGCAATCGCTACCCAGGGA
TGCAGATAAGAGGATTTGTATATTTTGTGAAACACTAGCTCGAAGAATATGTGA
AAAGCTTGAACAATCAGGATTGCCAGTTGGCGGTAATGAGAAAAGGCCAAACT
GGCTAATGTCGTCAGAAAAATGATGACTAATTCCTCAAGACACTGAACTCTCCTTC
ACCATCACTGGGGACAATAACCAATGGAATGAAAATCAGAACCCACGCATATTC
CTGGCAATGATCACATACATACTAGAAATCAGCCAGAATGGTTCAGAAATGTT
CTAAGCATTGCACCGATTATGTTCTCAAATAAAATGGCAAGACTGGGGAAAGGA
TATATGTTTGAAAGCAAAAGTATGAAATTGAGAACTCAAATACCAGCAGAAATG
CTAGCAAGCATTGACCTAAAATATTTCAATGATTCAACAAAAAAGAAAATTGAA
AAGATACGACCACTCCTGGTTGACGGGACTGCTTCACTGAGTCCTGGCATGATGA
TGGGAATGTTCAACATGTTGAGCACTGTGCTGGGTGTATCCATATTAACCTGGG
CCAGAGGAAATATACAAAGACCACATACTGGTGGGATGGTCTGCAATCATCCGA
TGACTTTGCTTTGATAGTGAATGCGCCTAATCATGAAGGAATACAAGCTGGAGTA
GACAGATTCTATAGA ACTTGCAA ACTGGTTCGGGATCAACATGAGCAAAAAGAAG
TCCTACATAAATAGA ACTTGGAACATTCGAATTCACAAGCTTTTTCTACCGGTATG
GTTTTGTAGCCAATTTCAAGCATGGA ACTACCCAGTTTTGGGGTTTTCCGGAATAAA
TGAATCTGCAGACATGAGCATTGGAGTGACAGTCATCAAAAACAACATGATAAA
TAATGATCTCGGTCTTGCCACGGCACAAATGGYACTCCA ACTCTTCATTAAGGAT
TATCGGTACACATAACCGGTGCCATAGAGGTGATACCCAGATACAAACCAGAAGA
TCTTTTGAGTTGAAGAAACTGTGGGAACAGACTCGATCAAAGACTGGTCTACTGG
TATCAGATGGGGGTCCAAACCTATATAACATCAGAAACCTACACATCCCCGGAAG
TCTGTTTAAAATGGGAGCTAATGGATGAAGATTATAAGGGGAGGCTATGCAATC
CATTGAATCCTTTTCGTTAGTCACAAAGAAATTGAATCAGTCAACAGTGCAGTAGT
AATGCCTGCGCATGGCCCTGCCAAAAGCATGGAGTATGATGCTGTGCAACAACA
CATTCTTGATCCCCAAGAGGAACCGGTCCATATTGAACACAAGCCAAAGGGGA
ATACTAGAAGATGAGCAGATGTATCAGAAATGCTGCAACCTGTTTGAAAAATTCT
TCCCAGCAGCTCATA CAGAAGACCAGTCGGAATTTCTAGTATGGTTGAGGCCAT
GGTATCCAGGGCCCCGATTGATGCACGAATTGACTTCGAATCTGGACGGATAAA
GAAGGATGAGTTCGCTGAGATCATGAAGATCTGTTCCACCATTGAAGAGCTCAG
ACGGCAAAAATAGTGAA (SEQ ID NO: 13)

FIG. 13

PB1 - Amino

MDVNPTLLFLKVPQAQNAISTTFPYTGDPPYSIHGTGTGYTMDTVNRTHIQYSEKGGKWT
TNTEIGAPQLNPIDGPLPEDNEPSGYAQTDCVLEAMAFLEESHHPGIFENSCLETMEVIQ
QTRVDKLTQGRQTYDWTLNRNQAATALANTIEVFRSNGLTSNESGRLMDFLKDV
MESMNKEEMEITTHFQRKRRVRDNMTKRMITQRTIGKKKQRLSRKSYLIRTLTLNT
MTKDAERGKLRRAIATPGMQIRGFVYFVETLARRICEKLEQSGLPVGGNEKKAKL
ANVVRKMMTNSQDTELSFTITGDNTKWNENQNPRIFLAMITYITRNQPEWFRNVLSI
APIMFSNKMARLGKGYMFESKSMKLRTQIPAEMLASIDLKYFNDSTKKKIEKIRPLL
DGTASLSPGMMMGMFNMLSTVLGVSILNLGQRKYTKTTYWWDGLQSSDDFALIVN
APNHEGIQAGVDRFYRTCKLVGINMSKKKSYINRTGTFFETSFFYRYGFVANFSMELP
SFGVSGINESADMSIGVTVIKNNMINNDLGPATAQMXLQLFIKDYRYTYRCHRGDGTQ
IQTRRSFELKKLWEQTRSKTGLLVSDGGPNLYNIRNLHIPEVCLKWELMDEYKGR
CNPLNPFVSHKEIESVNSAVVMPAHGPAKSMYDAVATTHSWIPKRNRNSILNTSQRGI
LEDEQMYQKCCNLFEKFFPSSSYRRPVGISSMVEAMVSRARIDARIDFESGRIKKDEF
AEIMKICSTIEELRRQK (SEQ ID NO: 14)

FIG. 14

PB2

TATTGGTCTCAGGGAGCGAAAGCAGGTCAAATATATTCAATATGGAGAGAATAA
AAGAACTGAGAGATCTGATGTTACAATCCCGCACCCGCGAGATACTAACAAAA
CTACTGTGGACCACATGGCCATAATCAAGAAATACACATCAGGAAGACAAGAGA
AGAACCCTGCACTTAGGATGAAATGGATGATGGCAATGAAATACCCAATTACAG
CAGATAAGAGGATAATGGAGATGATTCCTGAGAGAAATGAACAGGGACAAACC
CTTTGGAGCAAAACGAACGATGCTGGCTCAGACCGCGTAATGGTATCACCTCTGG
CAGTGACATGGTGGAAATAGGAATGGACCAACAACGAACACAATTCATTATCCGA
AAGTCTACAAAACCTATTTTGAAGAGGTTGAAAGATTGAAACACGGAACCTTTG
GCCCCGTTCAATTTAGGAATCAAGTCAAGATAAGACGAAGAGTTGATGTAAACC
CTGGTACACGGACCTCAGTGC'AAAGAAGCACAAGA'IGT'GAT'CA'IGGAAGT'IG
TTTTCCCAAATGAAGTGGGAGCCAGAATTCTAACATCAGAATCACAACATAACAAT
AACCAAAGAGAAAAAGGAAGAACTTCAGGACTGCAAAATTGCTCCCTTGATGGT
AGCATAACATGCTAGAAAGAGAGTTGGTCCGAAAAACAAGGTTCCCTCCAGTAGT
AGGCGGAACAAGCAGTGTATACATTGAAGTGTTCATCTGACTCAGGGAACATG
CTGGGAGCAAATGTACACCCCAAGGAGGAGAAAGTTAGAAAACGATGATATTGATCA
AAGTTTAATTATTGCAGCCCGGAACATAGTGAGAAGAGCAACAGTATCAGCAGA
TCCACTAGCA'CCCC'ACT'GGAAA'IG'IGCCACAGT'ACACAGA'ITGGTGGAAACAAG
GATGGTAGACATCCTTAAGCAGAACCCAACAGAGGAACAAGCTGTGGATATATG
CAAAGCAGCAATGGGATTGAGAATTAGCTCATCATTAGCTTTGGTGGATTCACC
TTCAAAGGACAAGTGGATCATCAGTCAAGAGAGAGAAGAAGAAATGCTTACGGGC
AACCTTCAAACATTGAAAATAAGAGTGCATGAGGGCTATGAAGAATTCACAATG
GTCGGAAGAAGAGCAACAGCCATTATCAGAAAGGCAACCAGAAGATTGATTCAA
TTGATAGTAAGTGGGAGAGATGAACAATCAATTGCTGAAGCAATAATTGTAGCC
ATGGTGTTTTCGCAAGAAGATTGCATGATAAAAGCAGTTCGAGGCGATTTGAACT
TTGTTAATAGAGCAAATCAGCGTTTGAACCCCATGCATCAACTCTTGAGGCATTT
CCAAAAGATGCAAAAGTGCTTTTCCAAAATTGGGGAATTGAACCCATCGACAA
TGTAATGGGGATGATTGGAATATTGCCTGACATGACCCCAAGCACCGAGATGTC
ATTGAGAGGAGTGAGAGTCAGCAAAATGGGAGTGGATGAGTACTCCAGCACTGA
GAGAGTGGTGGTGGAGCATTGACCGTTTTTTAAGAGTTCGGGATCAAAGGGGAAA
CATACTACTGTCCCCTGAAGAAGTCAGTGAAACACAAGGAACGGAAAAGCTGAC
AATAATTTATTCGTCATCAATGATGTGGGAGATTAATGGTCCCGAATCAGTGTTG
GTCAATACTTATCAATGGATCATCAGAAACTGGGAAATTGTAAAATTCAGTGGT
CACAGGACCCCAACAATGTTATAACAATAAGATAGAATTTGAACCATTCCAATCCCT
GGTCCCTAGGGCCACCAGAAGCCAATACAGCGGTTTCGTAAGAACCCTGTTTCAG
CAAATGCGAGATGTA'CTTGGAA'CAATTTGATACTGCTCAAATAATAAACTCCTCC
CTTTTGGCCGCTGCTCCTCCGGAACAGAGTAGGATGCAGTTCCTTCTTTGACTGTT
AATGTAAGAGGTTTCGGGAATGAGGATACTTGTAAGAGGCAATTC'CCCGGTGTT'
AACTACAATAAAGTCACTAAAAGGCTCACAGTCCCTCGGAAAGGATGCAGGTGCG
CTTACTGAGGACCCAGATGAAGGTACGGCTGGAGTAGAATCTGCTGTTCTAAGA
GGGTTTCTCATTTTAGGTAAAGAAAACAAGAGATATGGCCAGCACTAAGCATC
AATGAACTTAGCAAACTTGCAAAAGGGGAGAAAGCCAATGTA'CTAATTTGGGCAA
GGGGACGTAGTGTGGTAAATGAAAACGGAAACGTTGACTCTAGCATACTTACTGAC
AGCCAGACAGCGACCAAAAGGATTCGGATGGCCATCAATTAGTGTTGAATTGTTT
AAAACGACCTTGTTTCTACTAATACGAGACCATAT (SEQ ID NO: 15)

FIG. 15

PB2 - Amino

MERIKELRDLMLQSRTREILTKTTVDHMAIKKYTSGRQEKNPALRMKWMMAMKY
PITADKRIMEMIPERNEQGQTLWSKTNDAGSDRVMVSPLAVTWWNRRNGPTTNTIHY
PKVYKTYFEKVERLKHGTFGPVHFRNQVKIRRRVDVNPBGHADLSAKEAQDVIMEVV
FPNEVGARILTSESQLTITKEKKEELQDCKIAPLMVAYMLERELVRKTRFLPVVGGTS
SVYIEVLHLTQGTCWEQMYTPGGEVRNDDIDQSLIIAARNIVRRATVSADPLASLLE
MCHSTQIGGTRMVDILKQNPTEEQAVDICKAAMGLRISSSFSFGGFTFKRTSGSSVKR
EEEMLTGNLQTLKIRVHEGYEEFTMVGRRATAIIRKATRRLIQLIVSGRDEQSIAEAI
VAMVFSQEDCMIKAVRGDLNFVNRRANQRLNPMHQLLRHFQKDAKVLVFNWVIEPI
DNVMGMIGILPDMTPSTEMSLRGVRSKMGVDEYSSTERVVVSIDRFLRVRDQVRGNI
LLSPEEVSETQGTEKLTIIYSSSMMWEINGPESVLVNTYQWIIRNWEIVKIQWSQDPT
MLYNKIEFEPFQSLVPRA'RSQYSGFVR'ILFQQMRDVLGTFDTAQIKLLPFAAAPPE
QSRMQFSSLTVNVRGSGMRILVRGNPVPFNYNKVTKRLTVLGKDAGALTEDPDEGT
AGVESAVLRGFLILGKENKRYGPALSINELSKLAKGEKANVLIGQGDVVLVMMKRKR
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; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

Notice: More than one reissue application has been filed for the reissue of U.S. Pat. No. 7,842,295. The reissue applications are application Ser. Nos.: 13/688,990 and the present application, the present application being a divisional reissue of U.S. Pat. No. 7,842,295.

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application is a reissue divisional of application Ser. No. 13/688,990, filed Nov. 29, 2012 (now U.S. Pat. No. Re. 44,916), which is a reissue of U.S. patent application Ser. No. 12/210,837, filed Sep. 15, 2008 (now U.S. Pat. No. 7,842,295), which 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] which 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 α -keto bond that joins a terminal sialic acid and the next sugar residue, thereby allowing the release of viral progeny from infected cells, is encoded by the sixth segment. Nine subtypes (N1-N9) of this enzyme have been identified. All subtypes have two structural regions—a stalk and a head. All N8 proteins have 470 amino acids, the first eight of which are highly conserved. The following region is rich in hydrophobic amino acids and is considered to be the transmembrane domain. The next 51 amino acids make up the stalk region, and the head region begins at Cys91. The last region contains the catalytic site of

the enzyme. Cysteine residues in the head and stalk region tend to be highly conserved. There are 6-8 putative N-glycosylation sites.

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 GenBankAcc. 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 GenBankAcc. 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.

5

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.

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

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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 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, β -propiolacton or derivative thereof, ethyleneimine or derivative thereof, an organic solvent (e.g., halogenated hydrocarbon), and/or a detergent (e.g., Tween®, Triton X®, sodium desoxycholate, sulfobetain, or cetyltrimethylammonium salts). If necessary, chemically activated compositions can be neutralized. For example, if formaldehyde is used to deactivate the composition, the composition can be neutralized with thio-sulphate. If required, the pH subsequently can be returned to a value of about 7. Alternatively, the virus can be extracted with a mixture of ether and ethanol, the aqueous and organic phases can be separated, and residual ether can be removed from the viral suspension under reduced pressure (see, e.g.,

U.S. Pat. No. 4,431,633). Physical inactivation advantageously can be carried by subjecting the virus to energy-rich radiation, such as ultraviolet light, γ -radiation, or X-rays. Inactivated forms require a relatively high amount of inoculum and, therefore, a correspondingly large quantity of antigenic material, which has to be manufactured, tested, and distributed.

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 com-

prising 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 8N8O5, 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 μ 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, aluminium (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 EID₅₀ (50% egg-infective dose) of virus. In the latter situation, the freeze-dried vaccine is reconstituted by addition of water or another pharmaceutically acceptable diluent prior to administration, such as in the form of a nasal spray or nasal drops. If desired, the vaccine can be administered in two successive dosages at a one-week interval.

The composition can be administered to puppies as a single dose at the age of 12 weeks, or repeatedly starting from the age of 6 weeks (e.g., at 6, 9 and 12 weeks), or weekly from 4 weeks on. The effective dosage and route of administration are determined by the nature of the composition, the nature of the expression product, LD₅₀, and, if recombinant vector is used, the expression level of the vector, as well as the breed of dog and its age, sex, weight, and condition. Dosages of expressed product can range from a few to a few hundred micrograms, e.g., 5-500 μ 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 TCID₅₀.

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)), radioimmunoassays (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 H3N8 subtype. The virus isolate was subtyped as H3N8 using HA-inhibition and NM-inhibition assays. The virus isolate was recognized by antisera raised against various H3 equine influenza viruses, including Miami ((A/Eq/MI/1/63-H3N8) 640-1280), AK((A/Eq/AK/29759/91-H3N8) 320-640), and Kentucky ((A/Eq/Kentucky/81-H3N8) 160-320).

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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Val Thr Val Leu Val Leu Asn Asn Asn Arg Thr Asp Leu Asn Cys Lys
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ggg acg atc ata aga gaa tac aat gaa aca gta aga gta gaa aaa ctt      194
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aat gaa tac tac atg aat aac act gaa cca ctt tgt gag gcc caa ggc      290

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Cys	Arg	Thr	Phe	Phe	Leu	Thr	Gln	Gly	Ser	Leu	Leu	Asn	Asp	Lys	His	
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Val	Ala	Trp	Ser	Ala	Thr	Ala	Cys	His	Asp	Gly	Lys	Lys	Trp	Met	Thr	
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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	
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Arg	Thr	Gln	Glu	Ser	Ser	Cys	Thr	Cys	Ile	Lys	Gly	Asp	Cys	Tyr	Trp	
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Lys	Ala	Lys	Asp	Gly	Arg	Val	Ile	Gly	Gln	Thr	Asp	Ile	Ser	Phe	Asn	
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Lys Gly Cys Leu Val Pro Cys Phe Trp Val Glu Met Ile Arg Gly Lys	
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Leu Leu Thr His Trp Ala Tyr Ser Gln Asn Pro Ile Ser Gly Asn Asn	
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Thr Ala Thr Leu Cys Leu Gly His His Ala Val Ala Asn Gly Thr Leu	
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75 80 85	
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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	
gcc tgc aaa agg gga tca gcc gat agt ttc ttt agc cga ctg aat tgg	533
Ala Cys Lys Arg Gly Ser Ala Asp Ser Phe Phe Ser Arg Leu Asn Trp	
155 160 165	
cta aca aaa tct gga agc tct tac ccc aca ttg aat gtg aca atg cct	581
Leu Thr Lys Ser Gly Ser Ser Tyr Pro Thr Leu Asn Val Thr Met Pro	
170 175 180	
aac aat aaa aat ttc gac aag cta tac atc tgg ggg att cat cac ccg	629
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	
gaa tct aga ccg ttg gtc aga ggt caa tca ggc agg ata agc ata tac	773
Glu Ser Arg Pro Leu Val Arg Gly Gln Ser Gly Arg Ile Ser Ile Tyr	
235 240 245	
tgg acc att gta aaa cct gga gat atc cta atg ata aac agt aat ggc	821
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
Asn Leu Val Ala Pro Arg Gly Tyr Phe Lys Leu Asn Thr Gly Lys Ser	
265 270 275 280	
tct gta atg aga tcc gat gta ccc ata gac att tgt gtg tct gaa tgt	917
Ser Val Met Arg Ser Asp Val Pro Ile Asp Ile Cys Val Ser Glu Cys	
285 290 295	
att aca cca aat gga agc atc tcc aac gac aag cca ttc caa aat gtg	965
Ile Thr Pro Asn Gly Ser Ile Ser Asn Asp Lys Pro Phe Gln Asn Val	
300 305 310	
aac aaa gtt aca tat gga aaa tgc ccc aag tat atc agg caa aac act	1013
Asn Lys Val Thr Tyr Gly Lys Cys Pro Lys Tyr Ile Arg Gln Asn Thr	
315 320 325	
tta aag ctg gcc act ggg atg agg aat gta cca gaa aag caa acc aga	1061
Leu Lys Leu Ala Thr Gly Met Arg Asn Val Pro Glu Lys Gln Thr Arg	
330 335 340	
gga atc ttt gga gca ata gcg gga ttc atc gaa aac ggc tgg gaa gga	1109
Gly Ile Phe Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly	
345 350 355 360	
atg gtt gat ggg tgg tat ggg ttc cga tat caa aac tct gaa gga aca	1157
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	

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410	415	420	
gag aaa tat gta gaa gac acc aaa ata gac cta tgg tcc tac aat gca Glu Lys Tyr Val Glu Asp Thr Lys Ile Asp Leu Trp Ser Tyr Asn Ala 425 430 435 440			1349
gaa ttg ctg gtg gct cta gaa aat caa cat aca att gac tta aca gat Glu Leu Leu Val Ala Leu Glu Asn Gln His Thr Ile Asp Leu Thr Asp 445 450 455			1397
gca gaa atg aat aaa tta ttt gag aag act aga cgc cag tta aga gaa Ala Glu Met Asn Lys Leu Phe Glu Lys Thr Arg Arg Gln Leu Arg Glu 460 465 470			1445
aac gca gaa gac atg gga ggt gga tgt ttc aag att tac cac aaa tgt Asn Ala Glu Asp Met Gly Gly Gly Cys Phe Lys Ile Tyr His Lys Cys 475 480 485			1493
gat aat gca tgc att gaa tca ata aga act ggg aca tat gac cat tac Asp Asn Ala Cys Ile Glu Ser Ile Arg Thr Gly Thr Tyr Asp His Tyr 490 495 500			1541
ata tac aga gat gaa gca tta aac aac cga ttt cag atc aaa ggt gta Ile Tyr Arg Asp Glu Ala Leu Asn Asn Arg Phe Gln Ile Lys Gly Val 505 510 515 520			1589
gag ttg aaa tca ggc tac aaa gat tgg ata ctg tgg att tca ttc gcc Glu Leu Lys Ser Gly Tyr Lys Asp Trp Ile Leu Trp Ile Ser Phe Ala 525 530 535			1637
ata tca tgc ttc tta att tgc gtt gtt cta ttg ggt ttc att atg tgg Ile Ser Cys Phe Leu Ile Cys Val Val Leu Leu Gly Phe Ile Met Trp 540 545 550			1685
gct tgc caa aaa ggc aac atc aga tgc aac att tgc att tgagtaaact Ala Cys Gln Lys Gly Asn Ile Arg Cys Asn Ile Cys Ile 555 560 565			1734
gatagttaaa aacacccttg tttctact			1762

<210> SEQ ID NO 4

<211> LENGTH: 565

<212> TYPE: PRT

<213> ORGANISM: Influenza A Virus

<400> SEQUENCE: 4

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

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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
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												

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<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
      5                               10                               15

cgc cag aat gca act gaa atc aga gca tct gtc gga agg atg gtg gga      152
Arg Gln Asn Ala Thr Glu Ile Arg Ala Ser Val Gly Arg Met Val Gly
      20                               25                               30

gga atc gga cgg ttt tat gtc cag atg tgt act gag ctt aaa cta aac      200
Gly Ile Gly Arg Phe Tyr Val Gln Met Cys Thr Glu Leu Lys Leu Asn
      35                               40                               45                               50

gac cat gaa ggg cgg ctg att cag aac agc ata aca ata gaa agg atg      248
Asp His Glu Gly Arg Leu Ile Gln Asn Ser Ile Thr Ile Glu Arg Met
      55                               60                               65

gta ctt tca gca ttc gac gaa aga aga aac aag tat ctc gag gag cat      296
Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu Glu His
      70                               75                               80

ccc agt gct ggg aaa gac cct aag aaa acg gga ggc ccg ata tac aga      344
Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile Tyr Arg
      85                               90                               95

aga aaa gat ggg aaa tgg atg agg gaa ctc atc ctc cat gat aaa gaa      392
Arg Lys Asp Gly Lys Trp Met Arg Glu Leu Ile Leu His Asp Lys Glu
      100                              105                              110

gaa atc atg aga atc tgg cgt cag gcc aac aat ggt gaa gac gct act      440
Glu Ile Met Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp Ala Thr
      115                              120                              125                              130

gct ggt ctt act cat atg atg atc tgg cac tcc aat ctc aat gac acc      488
Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn Asp Thr
      135                              140                              145

aca tac caa aga aca agg gct ctt gtt cgg act ggg atg gat ccc aga      536
Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp Pro Arg
      150                              155                              160

atg tgc tct ctg atg caa ggc tca acc ctc cca cgg aga tct gga gcc      584
Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser Gly Ala
      165                              170                              175

gct ggt gct gca gta aaa ggt gtt gga aca atg gta atg gaa ctc atc      632
Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu Leu Ile
      180                              185                              190

agg atg atc aaa cgc gga ata aat gat cgg aat ttc tgg aga ggt gaa      680
Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg Gly Glu
      195                              200                              205                              210

aat ggt cga aga acc aga att gct tat gaa aga atg tgc aat atc ctc      728
Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn Ile Leu
      215                              220                              225

aaa ggg aaa ttt cag aca gca gca caa cgg gct atg atg gac cag gtg      776
Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp Gln Val
      230                              235                              240

agg gaa ggc cgc aat cct gga aac gct gag att gag gat ctc att ttc      824
Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu Ile Phe
      245                              250                              255

ttg gca cga tca gca ctt att ttg aga gga tca gta gcc cat aaa tca      872
Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His Lys Ser

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

<210> 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

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Arg Met Val Leu Ser Ala Phe Asp Glu Arg Arg Asn Lys Tyr Leu Glu
 65 70 75 80
 Glu His Pro Ser Ala Gly Lys Asp Pro Lys Lys Thr Gly Gly Pro Ile
 85 90 95
 Tyr Arg Arg Lys Asp Gly Lys Trp Met Arg Glu Leu Ile Leu His Asp
 100 105 110
 Lys Glu Glu Ile Met Arg Ile Trp Arg Gln Ala Asn Asn Gly Glu Asp
 115 120 125
 Ala Thr Ala Gly Leu Thr His Met Met Ile Trp His Ser Asn Leu Asn
 130 135 140
 Asp Thr Thr Tyr Gln Arg Thr Arg Ala Leu Val Arg Thr Gly Met Asp
 145 150 155 160
 Pro Arg Met Cys Ser Leu Met Gln Gly Ser Thr Leu Pro Arg Arg Ser
 165 170 175
 Gly Ala Ala Gly Ala Ala Val Lys Gly Val Gly Thr Met Val Met Glu
 180 185 190
 Leu Ile Arg Met Ile Lys Arg Gly Ile Asn Asp Arg Asn Phe Trp Arg
 195 200 205
 Gly Glu Asn Gly Arg Arg Thr Arg Ile Ala Tyr Glu Arg Met Cys Asn
 210 215 220
 Ile Leu Lys Gly Lys Phe Gln Thr Ala Ala Gln Arg Ala Met Met Asp
 225 230 235 240
 Gln Val Arg Glu Gly Arg Asn Pro Gly Asn Ala Glu Ile Glu Asp Leu
 245 250 255
 Ile Phe Leu Ala Arg Ser Ala Leu Ile Leu Arg Gly Ser Val Ala His
 260 265 270
 Lys Ser Cys Leu Pro Ala Cys Val Tyr Gly Leu Ala Val Thr Ser Gly
 275 280 285
 Tyr Asp Phe Glu Lys Glu Gly Tyr Ser Leu Val Gly Ile Asp Pro Phe
 290 295 300
 Lys Leu Leu Gln Asn Ser Gln Ile Phe Ser Leu Ile Arg Pro Lys Glu
 305 310 315 320
 Asn Pro Ala His Lys Ser Gln Leu Val Trp Met Ala Cys His Ser Ala
 325 330 335
 Ala Phe Glu Asp Leu Arg Val Leu Asn Phe Ile Arg Gly Thr Lys Val
 340 345 350
 Ile Pro Arg Gly Gln Leu Thr Thr Arg Gly Val Gln Ile Ala Ser Asn
 355 360 365
 Glu Asn Met Glu Thr Ile Asn Ser Ser Thr Leu Glu Leu Arg Ser Lys
 370 375 380
 Tyr Trp Ala Ile Arg Thr Arg Ser Gly Gly Asn Thr Ser Gln Gln Arg
 385 390 395 400
 Ala Phe Ala Gly Gln Ile Ser Val Gln Pro Thr Phe Ser Val Gln Arg
 405 410 415
 Asn Leu Pro Phe Glu Arg Ala Thr Ile Met Ala Ala Phe Thr Gly Asn
 420 425 430
 Thr Glu Gly Arg Thr Ser Asp Met Arg Thr Glu Ile Ile Arg Met Met
 435 440 445
 Glu Asn Ala Lys Ser Glu Asp Val Ser Phe Gln Gly Arg Gly Val Phe
 450 455 460
 Glu Leu Ser Asp Glu Lys Ala Thr Asn Pro Ile Val Pro Ser Phe Asp
 465 470 475 480

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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)

<400> SEQUENCE: 7

tattcgtctc agggagcaaa agcaggtaga tatttaaag atg agt ctt cta acc 54
 Met Ser Leu Leu Thr
 1 5

gag gtc gaa acg tac gtt ctc tct atc gta cca tca ggc ccc ctc aaa 102
 Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro Ser Gly Pro Leu Lys
 10 15 20

gcc gag atc gcg cag aga ctt gaa gat gtc ttt gcg gga aag aac acc 150
 Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe Ala Gly Lys Asn Thr
 25 30 35

gat ctt gag gca ctc atg gaa tgg cta aag aca aga cca atc ctg tca 198
 Asp Leu Glu Ala Leu Met Glu Trp Leu Lys Thr Arg Pro Ile Leu Ser
 40 45 50

cct ctg act aaa ggg att tta gga ttt gta ttc acg ctc acc gtg ccc 246
 Pro Leu Thr Lys Gly Ile Leu Gly Phe Val Phe Thr Leu Thr Val Pro
 55 60 65

agt gag cga gga ctg cag cgt aga cgc ttt gtc caa aat gcc ctt agt 294
 Ser Glu Arg Gly Leu Gln Arg Arg Arg Phe Val Gln Asn Ala Leu Ser
 70 75 80 85

gga aac gga gat cca aac aac atg gac aga gca gta aaa ctg tac agg 342
 Gly Asn Gly Asp Pro Asn Asn Met Asp Arg Ala Val Lys Leu Tyr Arg
 90 95 100

aag ctt aaa aga gaa ata aca ttc cat gag gca aaa gag gtg gca ctc 390
 Lys Leu Lys Arg Glu Ile Thr Phe His Glu Ala Lys Glu Val Ala Leu
 105 110 115

agc tat tcc act ggt gca cta gcc agc tgc atg gga ctc ata tac aac 438
 Ser Tyr Ser Thr Gly Ala Leu Ala Ser Cys Met Gly Leu Ile Tyr Asn
 120 125 130

aga atg gga act gtt aca acc gaa gtg gca ttt ggc ctg gta tgc gcc 486
 Arg Met Gly Thr Val Thr Thr Glu Val Ala Phe Gly Leu Val Cys Ala
 135 140 145

aca tgt gaa cag att gct gat tcc cag cat cga tct cac agg cag atg 534
 Thr Cys Glu Gln Ile Ala Asp Ser Gln His Arg Ser His Arg Gln Met
 150 155 160 165

gtg aca aca acc aac cca tta atc aga cat gaa aac aga atg gta tta 582
 Val Thr Thr Thr Asn Pro Leu Ile Arg His Glu Asn Arg Met Val Leu
 170 175 180

gcc agt acc acg gct aaa gcc atg gaa cag atg gca gga tcg agt gag 630
 Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met Ala Gly Ser Ser Glu
 185 190 195

cag gca gca gag gcc atg gag gtt gct agt agg gct agg cag atg gta 678
 Gln Ala Ala Glu Ala Met Glu Val Ala Ser Arg Ala Arg Gln Met Val
 200 205 210

cag gca atg aga acc att ggg acc cac cct agc tcc agt gcc ggt ttg 726
 Gln Ala Met Arg Thr Ile Gly Thr His Pro Ser Ser Ser Ala Gly Leu
 215 220 225

aaa gat gat ctc ctt gaa aat tta cag gcc tac cag aaa cgg atg gga 774
 Lys Asp Asp Leu Leu Glu Asn Leu Gln Ala Tyr Gln Lys Arg Met Gly
 230 235 240 245

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gtg caa atg cag cga ttc aag tgatcctctc gttattgcag caagtatcat 825
 Val Gln Met Gln Arg Phe Lys
 250

tggaatcttg cacttgatat tgtggattct tgatcgtctt ttcttcaaat tcatttatcg 885

tcgccttaaa tacgggttga aaagagggcc ttctacggaa ggagtacctg agtctatgag 945

ggaagaatat cggcaggaac agcagaatgc tgtggatggt gacgatggtc attttgtcaa 1005

catagagctg gagtaaaaaa ctaccttggt tctactaata cgagacgata t 1056

<210> SEQ ID NO 8
 <211> LENGTH: 252
 <212> TYPE: PRT
 <213> ORGANISM: Influenza A virus

<400> SEQUENCE: 8

Met Ser Leu Leu Thr Glu Val Glu Thr Tyr Val Leu Ser Ile Val Pro
 1 5 10 15

Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val Phe
 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

<210> SEQ ID NO 9
 <211> LENGTH: 870
 <212> TYPE: DNA
 <213> ORGANISM: Influenza A virus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (29)..(718)

<400> 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

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

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<210> SEQ ID NO 10

<211> LENGTH: 230

<212> TYPE: PRT

<213> ORGANISM: Influenza A virus

<400> SEQUENCE: 10

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

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

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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 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 Met Glu Asp Phe Val Arg Gln Cys Phe Asn Pro Met Ile Val Glu 1 5 10 15	48
ctt gcg gaa aag gca atg aaa gaa tat gga gag aac ccg aaa atc gaa Leu Ala Glu Lys Ala Met Lys Glu Tyr Gly Glu Asn Pro Lys Ile Glu 20 25 30	96
aca aac aaa ttt gca gca ata tgc act cac ttg gaa gtc tgc ttc atg Thr Asn Lys Phe Ala Ala Ile Cys Thr His Leu Glu Val Cys Phe Met 35 40 45	144
tac tcg gat ttc cac ttt ata aat gaa ctg ggt gag tca gtg gtc ata Tyr Ser Asp Phe His Phe Ile Asn Glu Leu Gly Glu Ser Val Val Ile 50 55 60	192
gag tct ggt gac cca aat gct ctt ttg aaa cac aga ttt gaa atc att Glu Ser Gly Asp Pro Asn Ala Leu Leu Lys His Arg Phe Glu Ile Ile 65 70 75	240
gag ggg aga gat cga aca atg gca tgg aca gta gta aac agc atc tgc Glu Gly Arg Asp Arg Thr Met Ala Trp Thr Val Val Asn Ser Ile Cys 80 85 90 95	288
aac acc aca aga gct gaa aaa cct aaa ttt ctt cca gat tta tac gac Asn Thr Thr Arg Ala Glu Lys Pro Lys Phe Leu Pro Asp Leu Tyr Asp 100 105 110	336

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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
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	
ggg 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	

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420	425	430	
gtc gcc cca ata gaa tac att gcg agc atg agg aga aat tat ttt act Val Ala Pro Ile Glu Tyr Ile Ala Ser Met Arg Arg Asn Tyr Phe Thr 435 440 445			1344
gct gag att tcc cat tgt aga gca aca gaa tat ata atg aaa gga gta Ala Glu Ile Ser His Cys Arg Ala Thr Glu Tyr Ile Met Lys Gly Val 450 455 460			1392
tac atc aac act gct cta ctc aat gca tcc tgt gct gcg atg gat gaa Tyr Ile Asn Thr Ala Leu Leu Asn Ala Ser Cys Ala Ala Met Asp Glu 465 470 475			1440
ttt caa tta att ccg atg ata agt aaa tgc agg acc aaa gaa ggg aga Phe Gln Leu Ile Pro Met Ile Ser Lys Cys Arg Thr Lys Glu Gly Arg 480 485 490 495			1488
agg aaa aca aat tta tat gga ttc ata ata aag gga agg tcc cat tta Arg Lys Thr Asn Leu Tyr Gly Phe Ile Ile Lys Gly Arg Ser His Leu 500 505 510			1536
aga aat gat act gac gtg gtg aac ttt gta agt atg gaa ttt tct ctc Arg Asn Asp Thr Asp Val Val Asn Phe Val Ser Met Glu Phe Ser Leu 515 520 525			1584
act gat cca aga ttt gag cca cac aaa tgg gaa aaa tac tgc gtt cta Thr Asp Pro Arg Phe Glu Pro His Lys Trp Glu Lys Tyr Cys Val Leu 530 535 540			1632
gaa att gga gac atg ctt cta aga act gct gta ggt caa gtg tca aga Glu Ile Gly Asp Met Leu Leu Arg Thr Ala Val Gly Gln Val Ser Arg 545 550 555			1680
ccc ata ttt ttg tat gta agg aca aat gga acc tct aaa att aaa atg Pro Ile Phe Leu Tyr Val Arg Thr Asn Gly Thr Ser Lys Ile Lys Met 560 565 570 575			1728
aaa tgg gga atg gaa atg aga cgc tgc ctc ctt cag tct ctg caa cag Lys Trp Gly Met Glu Met Arg Arg Cys Leu Leu Gln Ser Leu Gln Gln 580 585 590			1776
att gaa agc atg atc gaa gct gag tcc tca gtc aaa gaa aag gac atg Ile Glu Ser Met Ile Glu Ala Glu Ser Ser Val Lys Glu Lys Asp Met 595 600 605			1824
acc aaa gaa ttt ttt gag aac aaa tca gag aca tgg cct ata gga gag Thr Lys Glu Phe Phe Glu Asn Lys Ser Glu Thr Trp Pro Ile Gly Glu 610 615 620			1872
tcc ccc aaa gga gtg gaa gag ggc tca atc ggg aag gtt tgc agg acc Ser Pro Lys Gly Val Glu Glu Gly Ser Ile Gly Lys Val Cys Arg Thr 625 630 635			1920
tta tta gca aaa tct gtg ttt aac agt tta tat gca tct cca caa ctg Leu Leu Ala Lys Ser Val Phe Asn Ser Leu Tyr Ala Ser Pro Gln Leu 640 645 650 655			1968
gaa gga ttt tca gct gaa tct agg aaa tta ctt ctc att gtt cag gct Glu Gly Phe Ser Ala Glu Ser Arg Lys Leu Leu Leu Ile Val Gln Ala 660 665 670			2016
ctt aga gat gac ctg gaa cct gga acc ttt gat att ggg ggg tta tat Leu Arg Asp Asp Leu Glu Pro Gly Thr Phe Asp Ile Gly Gly Leu Tyr 675 680 685			2064
gaa tca att gag gag tgc ctg att aat gat ccc tgg gtt ttg ctt aat Glu Ser Ile Glu Glu Cys Leu Ile Asn Asp Pro Trp Val Leu Leu Asn 690 695 700			2112
gca tct tgg ttc aac tcc ttc ctc aca cat gca ctg aag tagttgtggc Ala Ser Trp Phe Asn Ser Phe Leu Thr His Ala Leu Lys 705 710 715			2161
aatgctacta tttggtatcc atactgtcca			2191

<210> SEQ ID NO 12

<211> LENGTH: 716

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<212> TYPE: PRT

<213> ORGANISM: Influenza A virus

<400> SEQUENCE: 12

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

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Arg Ser Leu Ala Ser Trp Ile Gln Ser Glu Phe Asn Lys Ala Cys Glu
 405 410 415

Leu Thr Asp Ser Ser Trp Ile Glu Leu Asp Glu Ile Gly Glu Asp Val
 420 425 430

Ala Pro Ile Glu Tyr Ile Ala Ser Met Arg Arg Asn Tyr Phe Thr Ala
 435 440 445

Glu Ile Ser His Cys Arg Ala Thr Glu Tyr Ile Met Lys Gly Val Tyr
 450 455 460

Ile Asn Thr Ala Leu Leu Asn Ala Ser Cys Ala Ala Met Asp Glu Phe
 465 470 475 480

Gln Leu Ile Pro Met Ile Ser Lys Cys Arg Thr Lys Glu Gly Arg Arg
 485 490 495

Lys Thr Asn Leu Tyr Gly Phe Ile Ile Lys Gly Arg Ser His Leu Arg
 500 505 510

Asn Asp Thr Asp Val Val Asn Phe Val Ser Met Glu Phe Ser Leu Thr
 515 520 525

Asp Pro Arg Phe Glu Pro His Lys Trp Glu Lys Tyr Cys Val Leu Glu
 530 535 540

Ile Gly Asp Met Leu Leu Arg Thr Ala Val Gly Gln Val Ser Arg Pro
 545 550 555 560

Ile Phe Leu Tyr Val Arg Thr Asn Gly Thr Ser Lys Ile Lys Met Lys
 565 570 575

Trp Gly Met Glu Met Arg Arg Cys Leu Leu Gln Ser Leu Gln Gln Ile
 580 585 590

Glu Ser Met Ile Glu Ala Glu Ser Ser Val Lys Glu Lys Asp Met Thr
 595 600 605

Lys Glu Phe Phe Glu Asn Lys Ser Glu Thr Trp Pro Ile Gly Glu Ser
 610 615 620

Pro Lys Gly Val Glu Glu Gly Ser Ile Gly Lys Val Cys Arg Thr Leu
 625 630 635 640

Leu Ala Lys Ser Val Phe Asn Ser Leu Tyr Ala Ser Pro Gln Leu Glu
 645 650 655

Gly Phe Ser Ala Glu Ser Arg Lys Leu Leu Leu Ile Val Gln Ala Leu
 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

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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
Cys Leu Glu Thr Met Glu Val Ile Gln Gln Thr Arg Val Asp Lys Leu	
110 115 120	
aca caa ggc cga caa act tat gat tgg acc ttg aat agg aat caa cct	435
Thr Gln Gly Arg Gln Thr Tyr Asp Trp Thr Leu Asn Arg Asn Gln Pro	
125 130 135	
gcc gca aca gca ctt gct aat acg att gaa gta ttc aga tca aat ggt	483
Ala Ala Thr Ala Leu Ala Asn Thr Ile Glu Val Phe Arg Ser Asn Gly	
140 145 150	
ctg act tcc aat gaa tcg ggg aga ttg atg gac ttc ctc aaa gat gtc	531
Leu Thr Ser Asn Glu Ser Gly Arg Leu Met Asp Phe Leu Lys Asp Val	
155 160 165 170	
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 gtt gaa aca cta gct cga aga ata tgt gaa aag ctt	819
Phe Val Tyr Phe Val Glu Thr Leu Ala Arg Arg Ile Cys Glu Lys Leu	
255 260 265	
gaa caa tca gga ttg cca gtt ggc ggt aat gag aaa aag gcc aaa ctg	867
Glu Gln Ser Gly Leu Pro Val Gly Gly Asn Glu Lys Lys Ala Lys Leu	
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	

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315	320	325	330	
gaa tgg ttc aga aat gtt cta agc att gca ccg att atg ttc tca aat				1059
Glu Trp Phe Arg Asn Val Leu Ser Ile Ala Pro Ile Met Phe Ser Asn				
	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 gtt gac ggg act gct tca ctg agt cct ggc atg atg atg gga				1251
Leu Leu Val Asp Gly Thr Ala Ser Leu Ser Pro Gly Met Met Met Gly				
	395	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
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				
	475	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 gtt 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				
	555	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 gtt 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

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Lys 635	Glu	Ile	Glu	Ser	Val 640	Asn	Ser	Ala	Val	Val 645	Met	Pro	Ala	His	Gly 650	
cct	gcc	aaa	agc	atg	gag	tat	gat	gct	gtt	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						
gtt	gag	gcc	atg	gta	tcc	agg	gcc	cgc	att	gat	gca	cga	att	gac	ttc	2211
Val	Glu	Ala	Met	Val	Ser	Arg	Ala	Arg	Ile	Asp	Ala	Arg	Ile	Asp	Phe	
715				720				725						730		
gaa	tct	gga	cgg	ata	aag	aag	gat	gag	ttc	gct	gag	atc	atg	aag	atc	2259
Glu	Ser	Gly	Arg	Ile	Lys	Lys	Asp	Glu	Phe	Ala	Glu	Ile	Met	Lys	Ile	
				735				740						745		
tgt	tcc	acc	att	gaa	gag	ctc	aga	cgg	caa	aaa	tagtgaa					2299
Cys	Ser	Thr	Ile	Glu	Glu	Leu	Arg	Arg	Gln	Lys						
			750					755								

<210> 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	

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Asp Asn Met Thr Lys Arg Met Ile Thr Gln Arg Thr Ile Gly Lys Lys
 195 200 205
 Lys Gln Arg Leu Ser Arg Lys Ser Tyr Leu Ile Arg Thr Leu Thr Leu
 210 215 220
 Asn Thr Met Thr Lys Asp Ala Glu Arg Gly Lys Leu Lys Arg Arg Ala
 225 230 235 240
 Ile Ala Thr Pro Gly Met Gln Ile Arg Gly Phe Val Tyr Phe Val Glu
 245 250 255
 Thr Leu Ala Arg Arg Ile Cys Glu Lys Leu Glu Gln Ser Gly Leu Pro
 260 265 270
 Val Gly Gly Asn Glu Lys Lys Ala Lys Leu Ala Asn Val Val Arg Lys
 275 280 285
 Met Met Thr Asn Ser Gln Asp Thr Glu Leu Ser Phe Thr Ile Thr Gly
 290 295 300
 Asp Asn Thr Lys Trp Asn Glu Asn Gln Asn Pro Arg Ile Phe Leu Ala
 305 310 315 320
 Met Ile Thr Tyr Ile Thr Arg Asn Gln Pro Glu Trp Phe Arg Asn Val
 325 330 335
 Leu Ser Ile Ala Pro Ile Met Phe Ser Asn Lys Met Ala Arg Leu Gly
 340 345 350
 Lys Gly Tyr Met Phe Glu Ser Lys Ser Met Lys Leu Arg Thr Gln Ile
 355 360 365
 Pro Ala Glu Met Leu Ala Ser Ile Asp Leu Lys Tyr Phe Asn Asp Ser
 370 375 380
 Thr Lys Lys Lys Ile Glu Lys Ile Arg Pro Leu Leu Val Asp Gly Thr
 385 390 395 400
 Ala Ser Leu Ser Pro Gly Met Met Met Gly Met Phe Asn Met Leu Ser
 405 410 415
 Thr Val Leu Gly Val Ser Ile Leu Asn Leu Gly Gln Arg Lys Tyr Thr
 420 425 430
 Lys Thr Thr Tyr Trp Trp Asp Gly Leu Gln Ser Ser Asp Asp Phe Ala
 435 440 445
 Leu Ile Val Asn Ala Pro Asn His Glu Gly Ile Gln Ala Gly Val Asp
 450 455 460
 Arg Phe Tyr Arg Thr Cys Lys Leu Val Gly Ile Asn Met Ser Lys Lys
 465 470 475 480
 Lys Ser Tyr Ile Asn Arg Thr Gly Thr Phe Glu Phe Thr Ser Phe Phe
 485 490 495
 Tyr Arg Tyr Gly Phe Val Ala Asn Phe Ser Met Glu Leu Pro Ser Phe
 500 505 510
 Gly Val Ser Gly Ile Asn Glu Ser Ala Asp Met Ser Ile Gly Val Thr
 515 520 525
 Val Ile Lys Asn Asn Met Ile Asn Asn Asp Leu Gly Pro Ala Thr Ala
 530 535 540
 Gln Met Xaa Leu Gln Leu Phe Ile Lys Asp Tyr Arg Tyr Thr Tyr Arg
 545 550 555 560
 Cys His Arg Gly Asp Thr Gln Ile Gln Thr Arg Arg Ser Phe Glu Leu
 565 570 575
 Lys Lys Leu Trp Glu Gln Thr Arg Ser Lys Thr Gly Leu Leu Val Ser
 580 585 590
 Asp Gly Gly Pro Asn Leu Tyr Asn Ile Arg Asn Leu His Ile Pro Glu
 595 600 605

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

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

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

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

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

Tyr Gln Lys Cys Cys Asn Leu Phe Glu Lys Phe Phe Pro Ser Ser Ser
 690 695 700

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

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

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

Leu Arg Arg Gln Lys
 755

<210> SEQ ID NO 15
 <211> LENGTH: 2370
 <212> TYPE: DNA
 <213> ORGANISM: Influenza A virus
 <220> FEATURE:
 <221> NAME/KEY: CDS
 <222> LOCATION: (42)..(2318)

<400> SEQUENCE: 15

tattggtctc agggagcgaa agcagggtcaa atatattcaa t atg gag aga ata aaa 56
 Met Glu Arg Ile Lys
 1 5

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

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

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

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

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

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

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

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

cat ttt agg aat caa gtc aag ata aga cga aga gtt gat gta aac cct 488
 His Phe Arg Asn Gln Val Lys Ile Arg Arg Arg Val Asp Val Asn Pro

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135	140	145	
ggt cac gcg gac ctc agt gct aaa gaa gca caa gat gtg atc atg gaa Gly His Ala Asp Leu Ser Ala Lys Glu Ala Gln Asp Val Ile Met Glu 150 155 160 165			536
ggt gtt ttc cca aat gaa gtg gga gcc aga att cta aca tca gaa tca Val Val Phe Pro Asn Glu Val Gly Ala Arg Ile Leu Thr Ser Glu Ser 170 175 180			584
caa cta aca ata acc aaa gag aaa aag gaa gaa ctt cag gac tgc aaa Gln Leu Thr Ile Thr Lys Glu Lys Lys Glu Glu Leu Gln Asp Cys Lys 185 190 195			632
att gct ccc ttg atg gta gca tac atg cta gaa aga gag ttg gtc cga Ile Ala Pro Leu Met Val Ala Tyr Met Leu Glu Arg Glu Leu Val Arg 200 205 210			680
aaa aca agg ttc ctc cca gta gta ggc gga aca agc agt gta tac att Lys Thr Arg Phe Leu Pro Val Val Gly Gly Thr Ser Ser Val Tyr Ile 215 220 225			728
gaa gtg ttg cat ctg act cag gga aca tgc tgg gag caa atg tac acc Glu Val Leu His Leu Thr Gln Gly Thr Cys Trp Glu Gln Met Tyr Thr 230 235 240 245			776
cca gga gga gaa gtt aga aac gat gat att gat caa agt tta att att Pro Gly Gly Glu Val Arg Asn Asp Asp Ile Asp Gln Ser Leu Ile Ile 250 255 260			824
gca gcc cgg aac ata gtg aga aga gca aca gta tca gca gat cca cta Ala Ala Arg Asn Ile Val Arg Arg Ala Thr Val Ser Ala Asp Pro Leu 265 270 275			872
gca tcc cta ctg gaa atg tgc cac agt aca cag att ggt gga aca agg Ala Ser Leu Leu Glu Met Cys His Ser Thr Gln Ile Gly Gly Thr Arg 280 285 290			920
atg gta gac atc ctt aag cag aac cca aca gag gaa caa gct gtg gat Met Val Asp Ile Leu Lys Gln Asn Pro Thr Glu Glu Gln Ala Val Asp 295 300 305			968
ata tgc aaa gca gca atg gga ttg aga att agc tca tca ttc agc ttt Ile Cys Lys Ala Ala Met Gly Leu Arg Ile Ser Ser Ser Phe Ser Phe 310 315 320 325			1016
ggt gga ttc acc ttc aaa agg aca agt gga tca tca gtc aag aga gaa Gly Gly Phe Thr Phe Lys Arg Thr Ser Gly Ser Ser Val Lys Arg Glu 330 335 340			1064
gaa gaa atg ctt acg ggc aac ctt caa aca ttg aaa ata aga gtg cat Glu Glu Met Leu Thr Gly Asn Leu Gln Thr Leu Lys Ile Arg Val His 345 350 355			1112
gag ggc tat gaa gaa ttc aca atg gtc gga aga aga gca aca gcc att Glu Gly Tyr Glu Glu Phe Thr Met Val Gly Arg Arg Ala Thr Ala Ile 360 365 370			1160
atc aga aag gca acc aga aga ttg att caa ttg ata gta agt ggg aga Ile Arg Lys Ala Thr Arg Arg Leu Ile Gln Leu Ile Val Ser Gly Arg 375 380 385			1208
gat gaa caa tca att gct gaa gca ata att gta gcc atg gtg ttt tcg Asp Glu Gln Ser Ile Ala Glu Ala Ile Ile Val Ala Met Val Phe Ser 390 395 400 405			1256
caa gaa gat tgc atg ata aaa gca gtt cga ggc gat ttg aac ttt gtt Gln Glu Asp Cys Met Ile Lys Ala Val Arg Gly Asp Leu Asn Phe Val 410 415 420			1304
aat aga gca aat cag cgt ttg aac ccc atg cat caa ctc ttg agg cat Asn Arg Ala Asn Gln Arg Leu Asn Pro Met His Gln Leu Leu Arg His 425 430 435			1352
ttc caa aaa gat gca aaa gtg ctt ttc caa aat tgg gga att gaa ccc Phe Gln Lys Asp Ala Lys Val Leu Phe Gln Asn Trp Gly Ile Glu Pro 440 445 450			1400
atc gac aat gta atg ggg atg att gga ata ttg cct gac atg acc cca 455 460 465			1448

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<210> SEQ ID NO 16
<211> LENGTH: 759
<212> TYPE: PRT
<213> ORGANISM: Influenza A virus

<400> 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

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

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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	565	570	575	
Phe	Glu	Pro	Phe	Gln	Ser	Leu	Val	Pro	Arg	Ala	Thr	Arg	Ser	Gln	Tyr	580	585	590	
Ser	Gly	Phe	Val	Arg	Thr	Leu	Phe	Gln	Gln	Met	Arg	Asp	Val	Leu	Gly	595	600	605	
Thr	Phe	Asp	Thr	Ala	Gln	Ile	Ile	Lys	Leu	Leu	Pro	Phe	Ala	Ala	Ala	610	615	620	
Pro	Pro	Glu	Gln	Ser	Arg	Met	Gln	Phe	Ser	Ser	Leu	Thr	Val	Asn	Val	625	630	635	640
Arg	Gly	Ser	Gly	Met	Arg	Ile	Leu	Val	Arg	Gly	Asn	Ser	Pro	Val	Phe	645	650	655	
Asn	Tyr	Asn	Lys	Val	Thr	Lys	Arg	Leu	Thr	Val	Leu	Gly	Lys	Asp	Ala	660	665	670	
Gly	Ala	Leu	Thr	Glu	Asp	Pro	Asp	Glu	Gly	Thr	Ala	Gly	Val	Glu	Ser	675	680	685	
Ala	Val	Leu	Arg	Gly	Phe	Leu	Ile	Leu	Gly	Lys	Glu	Asn	Lys	Arg	Tyr	690	695	700	
Gly	Pro	Ala	Leu	Ser	Ile	Asn	Glu	Leu	Ser	Lys	Leu	Ala	Lys	Gly	Glu	705	710	715	720
Lys	Ala	Asn	Val	Leu	Ile	Gly	Gln	Gly	Asp	Val	Val	Leu	Val	Met	Lys	725	730	735	
Arg	Lys	Arg	Asp	Ser	Ser	Ile	Leu	Thr	Asp	Ser	Gln	Thr	Ala	Thr	Lys	740	745	750	
Arg	Ile	Arg	Met	Ala	Ile	Asn	755												

What is claimed is:

[1. 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.]

[2. A composition comprising the isolated or purified HA of claim 1 in an amount sufficient to induce an immune response in an animal and a biologically acceptable carrier.]

[3. A method of inducing an immune response to canine influenza virus in an animal, which method comprises administering to the animal the composition of claim 2, whereupon an immune response to canine influenza virus is induced in the animal.]

[4. An isolated or purified nucleic acid encoding the HA of claim 1, optionally as part of a vector.]

[5. The isolated or purified nucleic acid of claim 4, wherein the nucleic acid encoding the HA comprises the nucleotide sequence of SEQ ID NO: 3.]

[6. A composition comprising the isolated or purified nucleic acid of claim 4, which expresses HA in an amount sufficient to induce an immune response in an animal, and a biologically acceptable carrier.]

[7. An isolated or purified HA peptide comprising a contiguous nine amino acid fragment of SEQ ID NO: 4, or a contiguous nine amino acid fragment of an amino acid sequence that is greater than 99% identical to SEQ ID NO: 4, that either includes the Leu at position 94 of SEQ ID NO: 4 or the Glu at position 233 of SEQ ID NO: 4.]

[8. A composition comprising the isolated or purified HA peptide of claim 7 in an amount sufficient to induce an immune response in an animal and a biologically acceptable carrier.]

[9. A method of inducing an immune response to canine influenza virus in an animal, which method comprises administering to the animal the composition of claim 8, whereupon an immune response to canine influenza virus is induced in the animal.]

[10. An isolated or purified nucleic acid encoding the HA peptide of claim 7, optionally as part of a vector.]

[11. A composition comprising the isolated or purified nucleic acid of claim 10, which expresses the HA peptide in an amount sufficient to induce an immune response in an animal, and a biologically acceptable carrier.]

12. A method of inducing an immune response to canine influenza virus in a canid animal suffering from infection by canine influenza virus, said method comprising administering to said canid animal a composition comprising an isolated canine influenza virus of subtype H3N8 and a biologically acceptable carrier, wherein the isolated H3N8 canine influenza virus is deposited with the American Type Culture Collection as Patent Deposit No. PTA-7694.

13. The method of claim 12, wherein the canid animal is a dog.

14. The method of claim 12, wherein the isolated H3N8 canine influenza virus is inactivated.

15. The method of claim 12, wherein the isolated H3N8 canine influenza virus is administered in an amount of 10^3 to 10^6 pfu per dose.

16. The method of claim 12, wherein the composition is formulated as a controlled-release composition.

* * * * *