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Ciaramella et al.

(54) BETACORONAVIRUS MRNA VACCINE

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(57) ABSTRACT

The disclosure relates to respiratory virus ribonucleic acid (RNA) vaccines and combination vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.

26 Claims, 24 Drawing Sheets

Specification includes a Sequence Listing.

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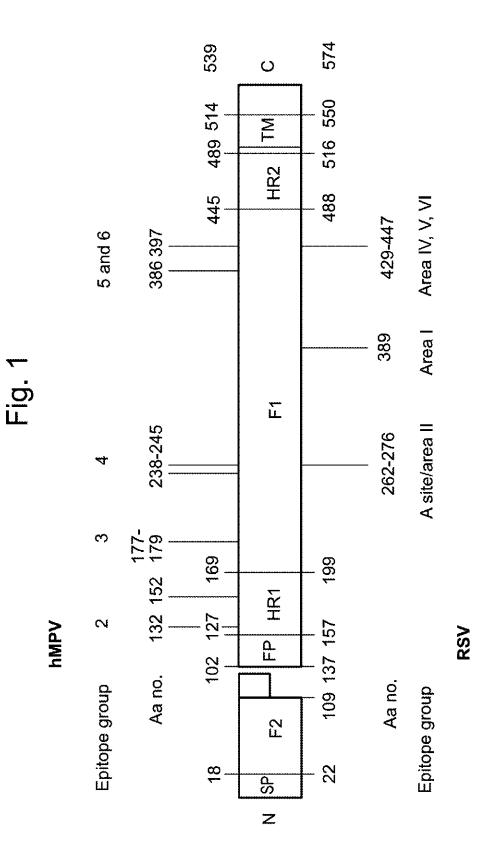
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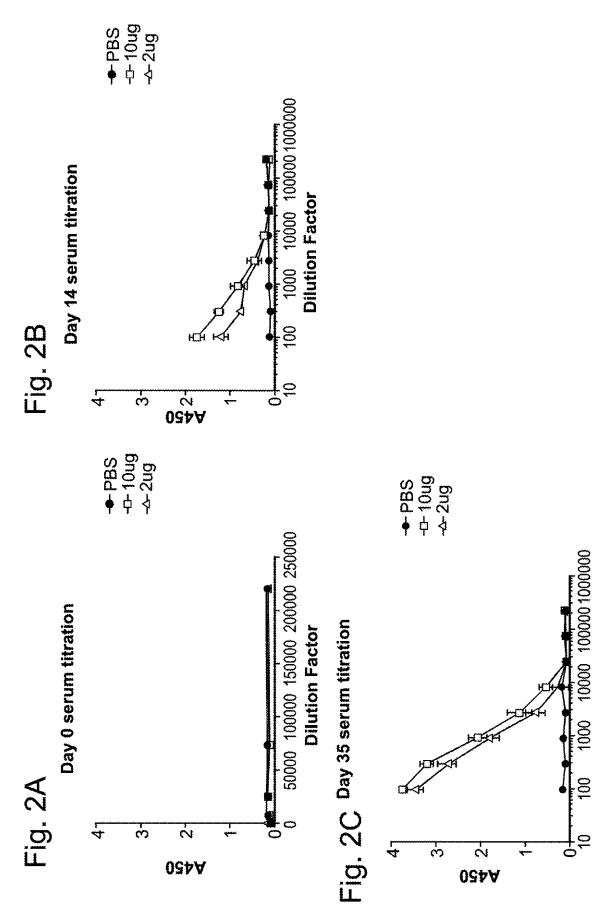
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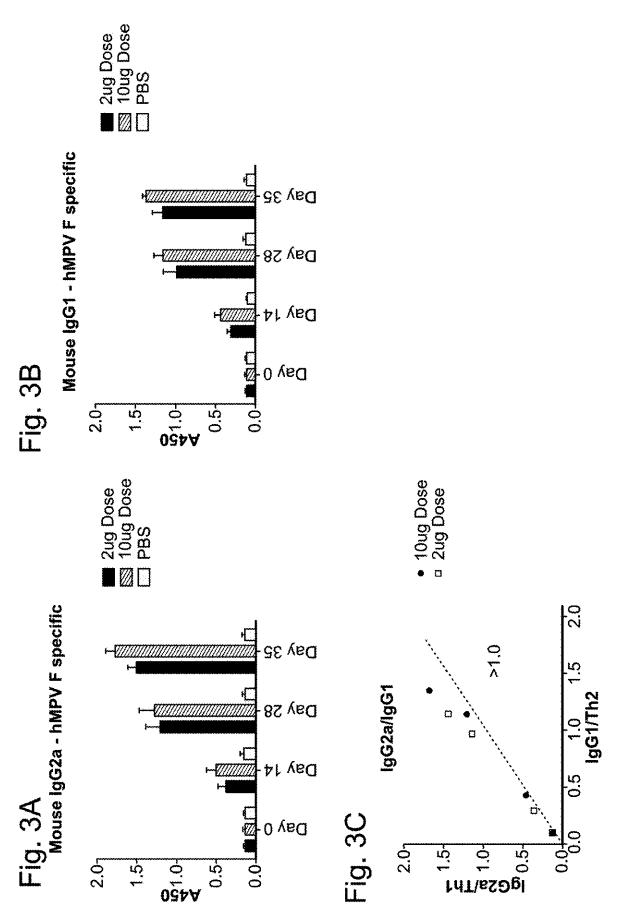
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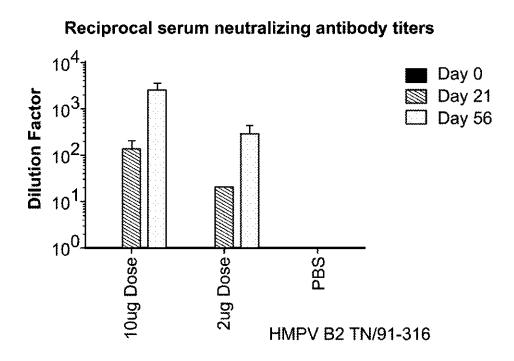
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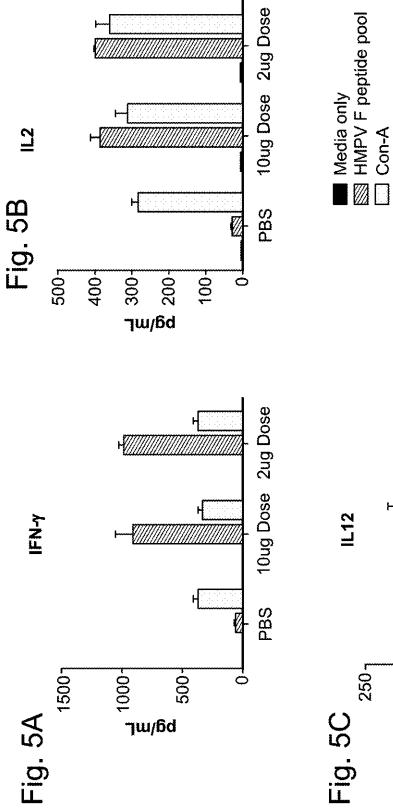


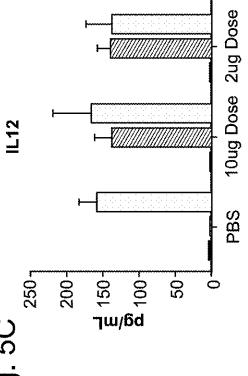
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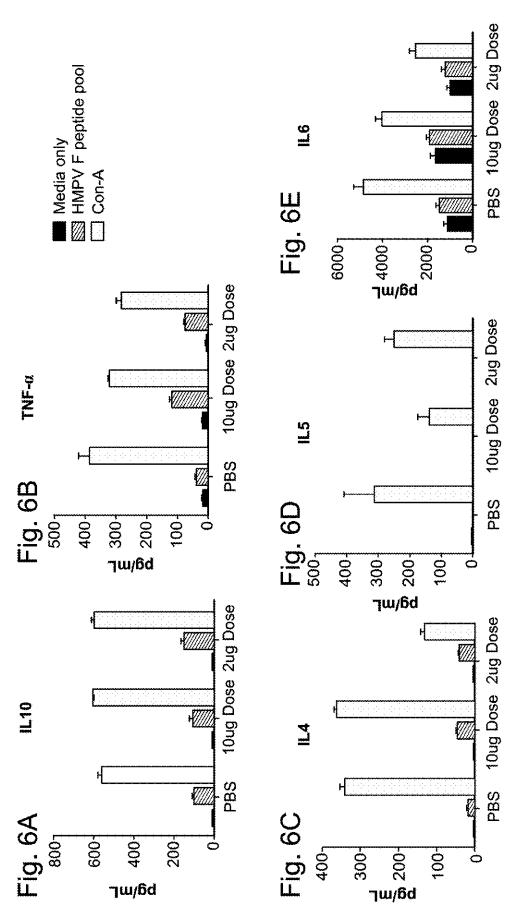


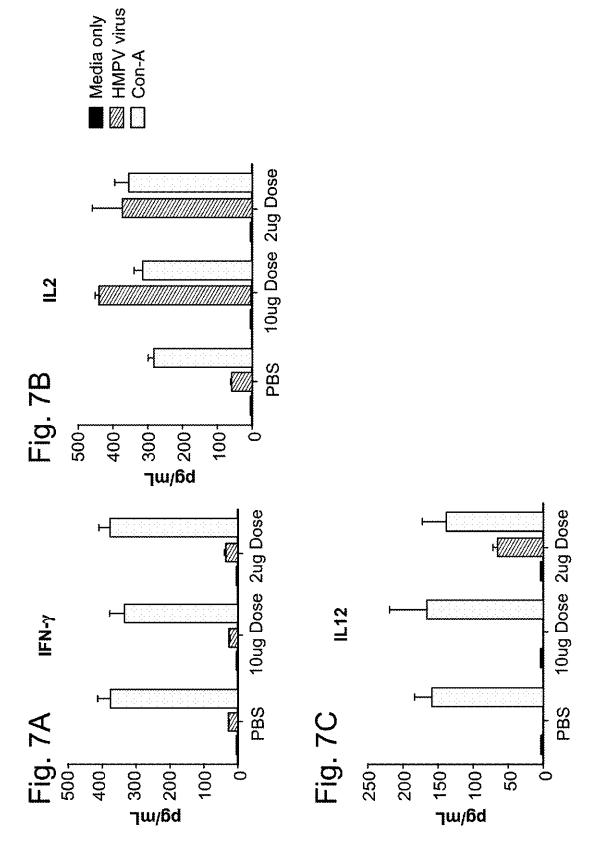


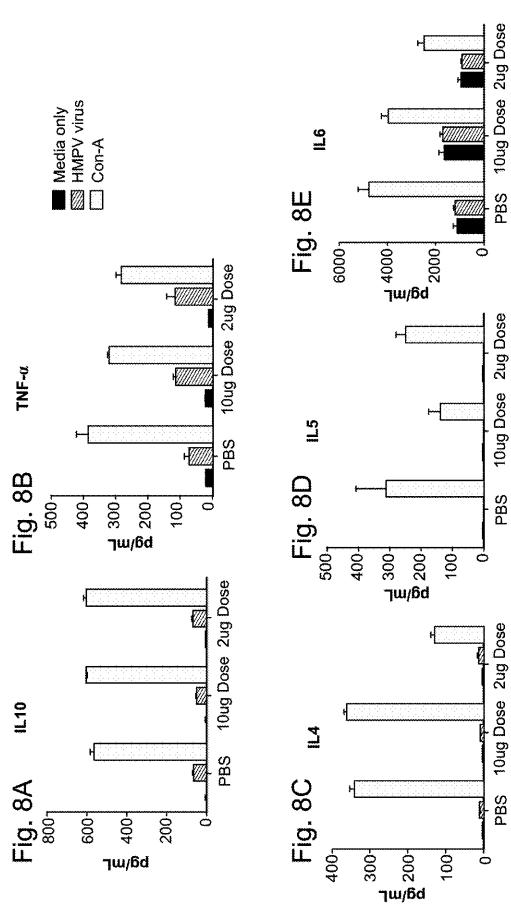


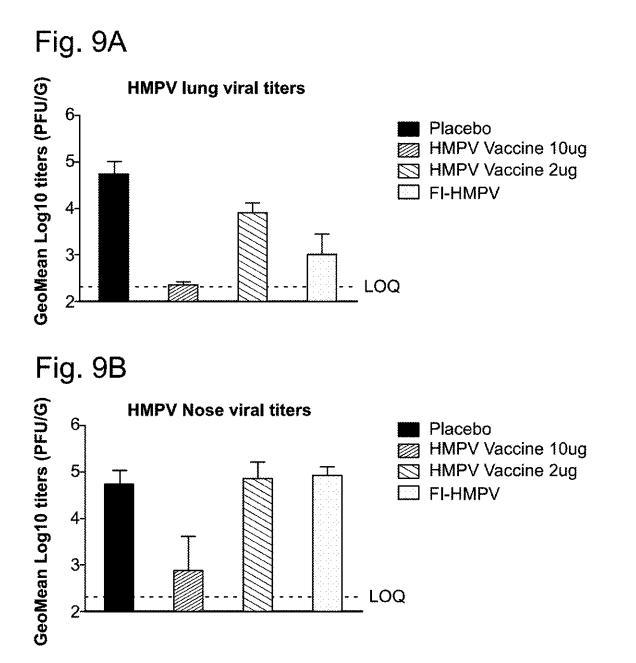


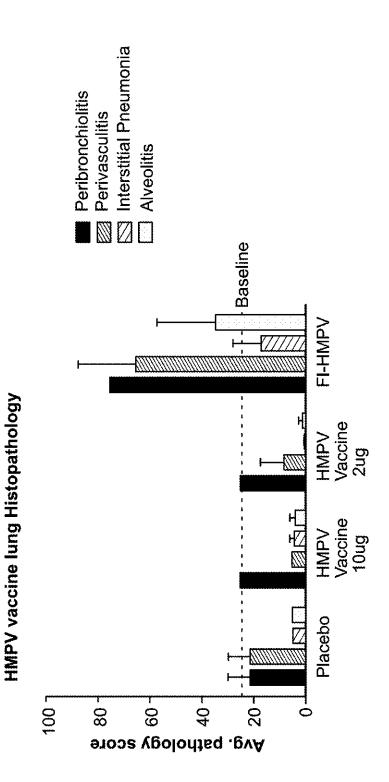


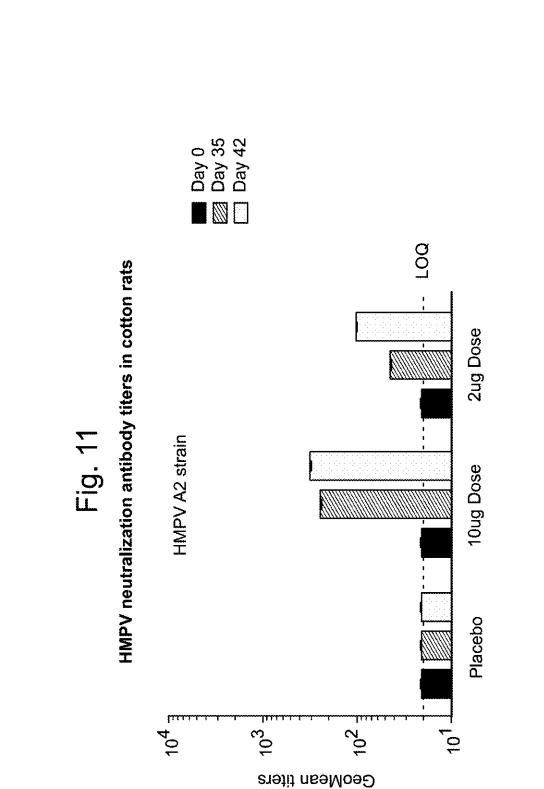


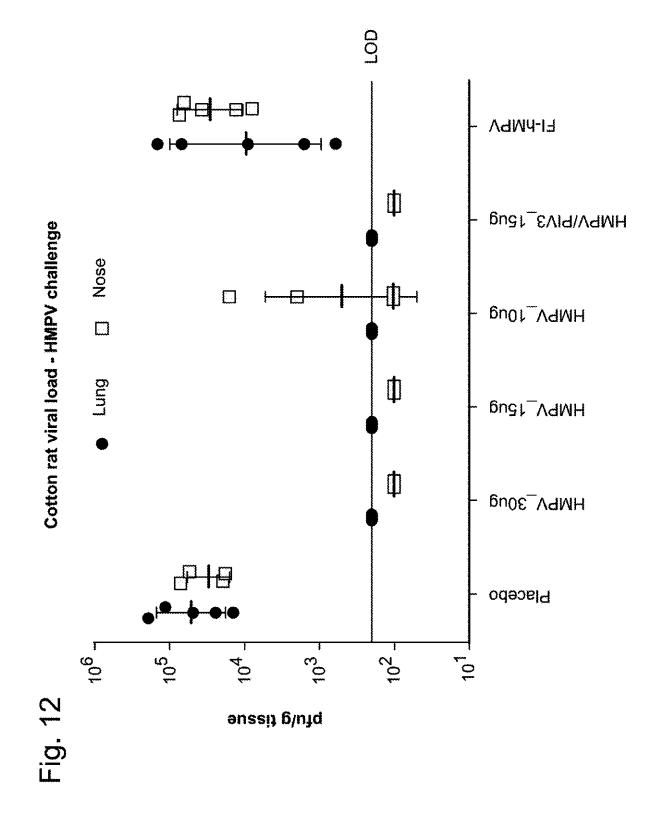


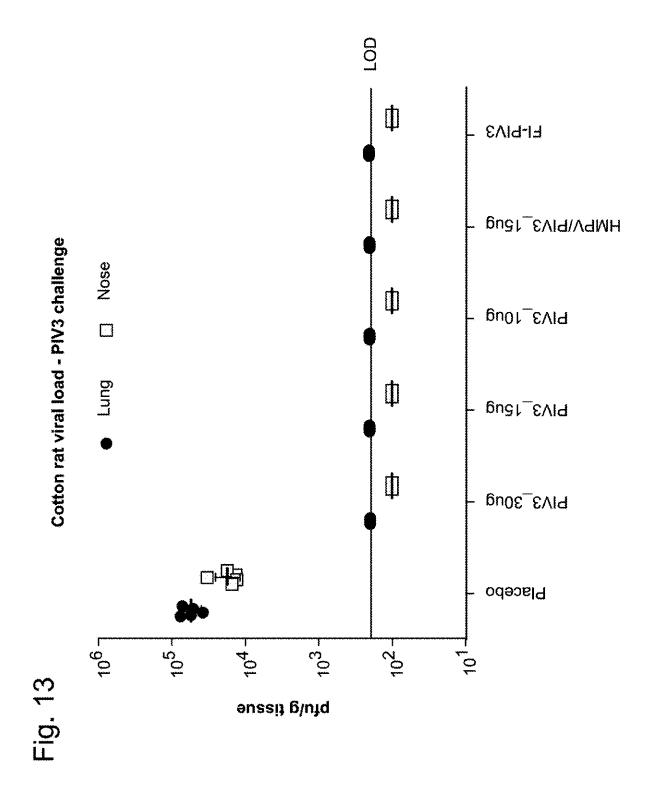


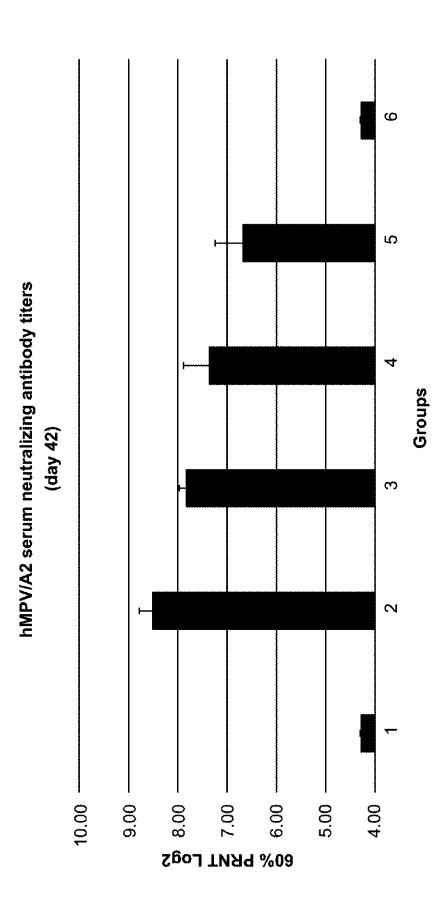


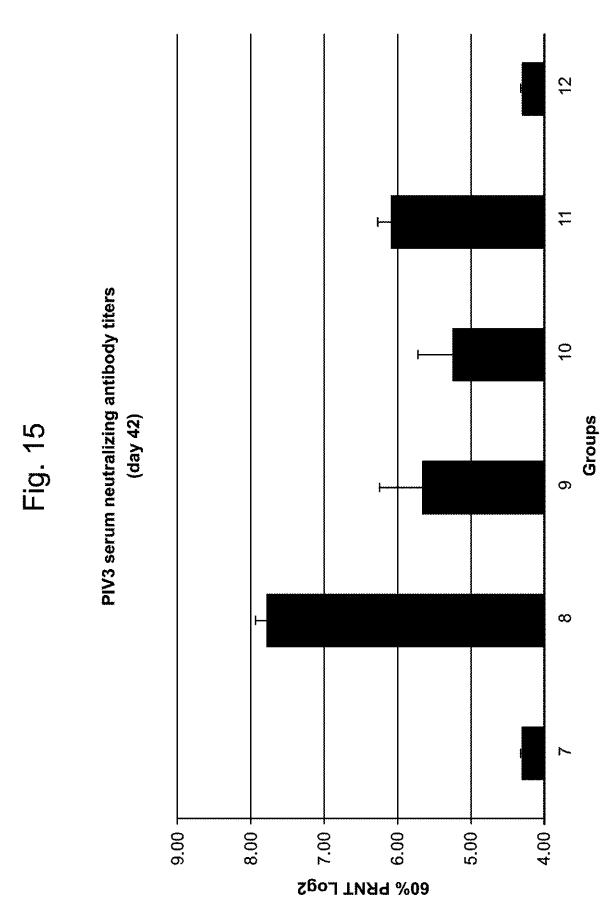




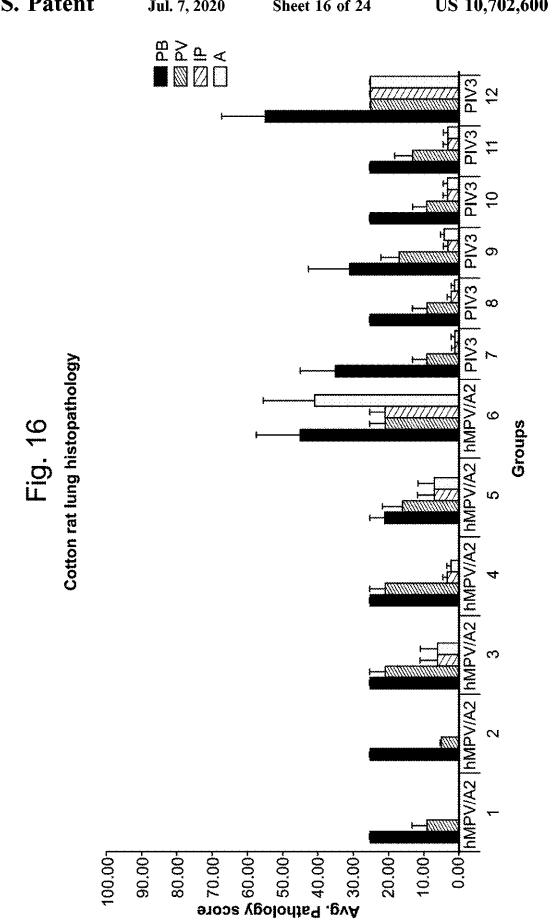








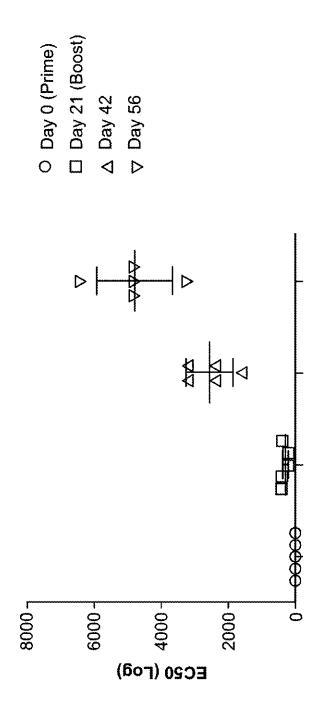
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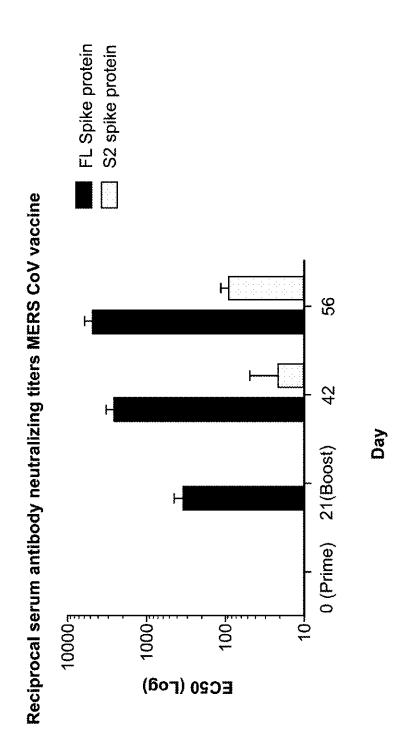






Reciprocal serum antibody neutralizing titers MERS CoV FL vaccine





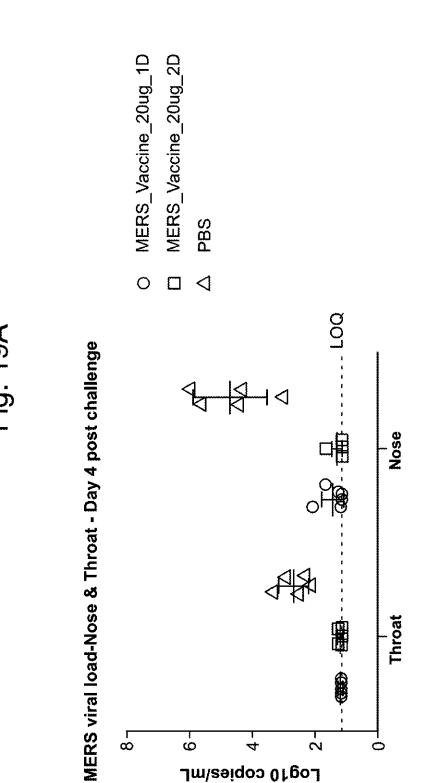


Fig. 19A

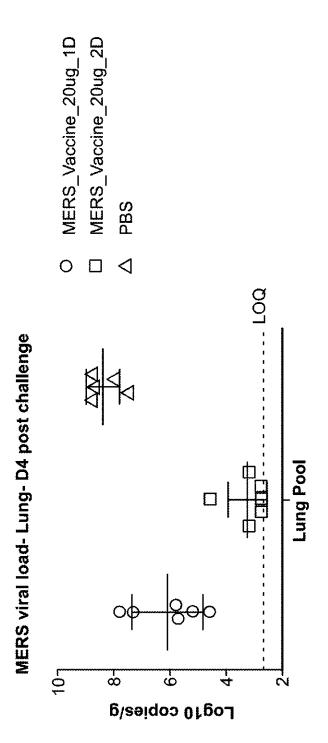
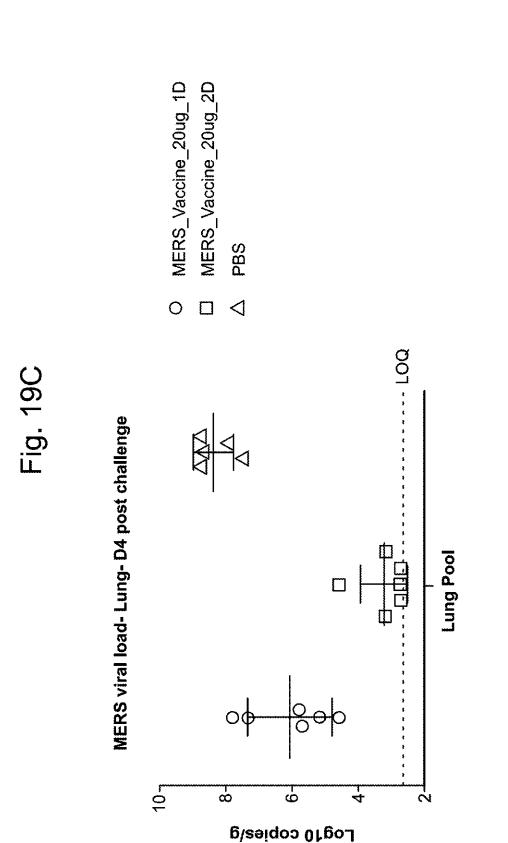
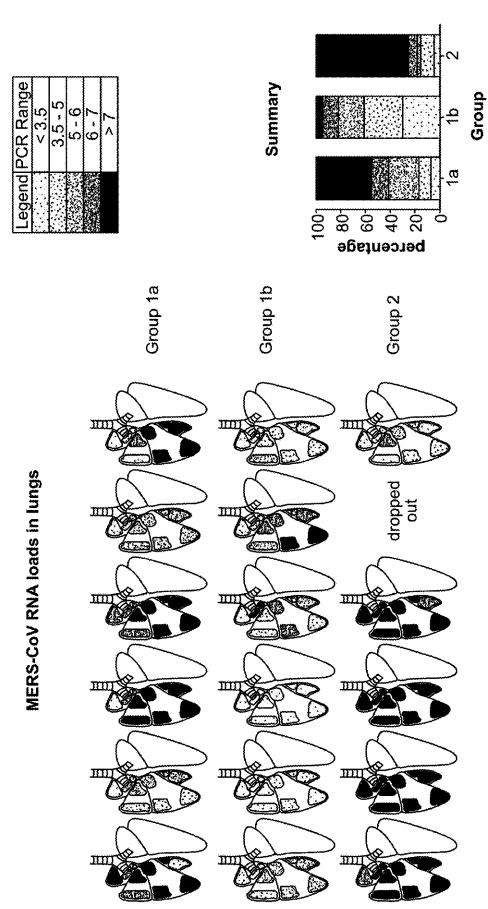
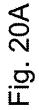


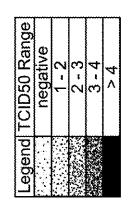
Fig. 19B

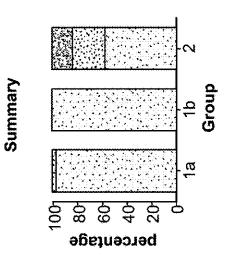


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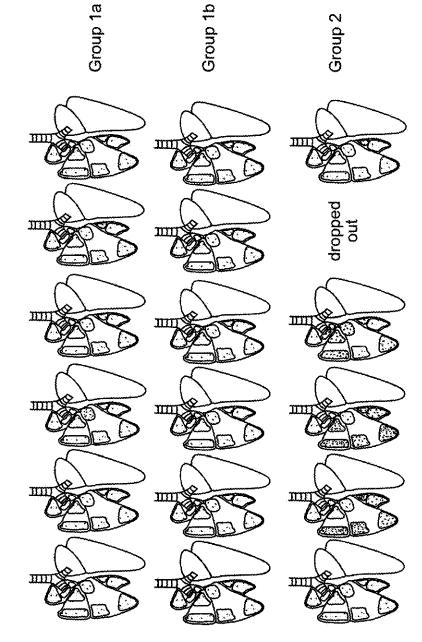






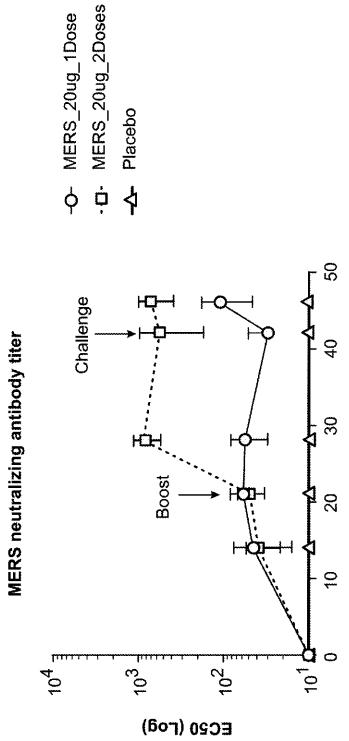


MERS-CoV replication in lungs





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BETACORONAVIRUS MRNA VACCINE

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. 5 No. 16/368,270, filed Mar. 28, 2019, which is a continuation of Ser. No. 16/040,981, filed Jul. 20, 2018, now U.S. Pat. No. 10,272,150, which is a continuation of U.S. application Ser. No. 15/674,599, filed Aug. 11, 2017, now U.S. Pat. No. 10,064,934, which is a continuation of International appli-10 cation number PCT/US2016/058327, filed Oct. 21, 2016, which claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application No. 62/244,802, filed Oct. 22, 2015, U.S. provisional application No. 62/247,297, filed Oct. 28, 2015, U.S. provisional application No. 62/244,946, filed 15 Oct. 22, 2015, U.S. provisional application No. 62/247,362, filed Oct. 28, 2015, U.S. provisional application No. 62/244, 813, filed Oct. 22, 2015, U.S. provisional application No. 62/247,394, filed Oct. 28, 2015, U.S. provisional application No. 62/244,837, filed Oct. 22, 2015, U.S. provisional appli- 20 cation No. 62/247,483, filed Oct. 28, 2015, and U.S. provisional application No. 62/245,031, filed Oct. 22, 2015, each of which is incorporated by reference herein in its entirety.

BACKGROUND

Respiratory disease is a medical term that encompasses pathological conditions affecting the organs and tissues that make gas exchange possible in higher organisms, and includes conditions of the upper respiratory tract, trachea, 30 bronchi, bronchioles, alveoli, pleura and pleural cavity, and the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting, such as the common cold, to life-threatening entities like bacterial pneumonia, pulmonary embolism, acute asthma and lung cancer. Respiratory 35 disease is a common and significant cause of illness and death around the world. In the US, approximately 1 billion "common colds" occur each year. Respiratory conditions are among the most frequent reasons for hospital stays among children. 40

The human metapneumovirus (hMPV) is a negativesense, single-stranded RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae and is closely related to the avian metapneumovirus (AMPV) subgroup C. It was isolated for the first time in 2001 in the Netherlands by using 45 the RAP-PCR (RNA arbitrarily primed PCR) technique for identification of unknown viruses growing in cultured cells. hPMV is second only to RSV as an important cause of viral lower respiratory tract illness (LRI) in young children. The seasonal epidemiology of hMPV appears to be similar to that 50 of RSV, but the incidence of infection and illness appears to be substantially lower.

Parainfluenza virus type 3 (PIV3), like hMPV, is also a negative-sense, single-stranded sense RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae 55 and is a major cause of ubiquitous acute respiratory infections of infancy and early childhood. Its incidence peaks around 4-12 months of age, and the virus is responsible for 3-10% of hospitalizations, mainly for bronchiolitis and pneumonia. PIV3 can be fatal, and in some instances is 60 associated with neurologic diseases, such as febrile seizures. It can also result in airway remodeling, a significant cause of morbidity. In developing regions of the world, infants and young children are at the highest risk of mortality, either from primary PIV3 viral infection or a secondary conse-65 quences, such as bacterial infections. Human parainfluenza viruses (hPIV) types 1, 2 and 3 (hPIV1, hPIV2 and hPIV3,

respectively), also like hMPV, are second only to RSV as important causes of viral LRI in young children.

RSV, too, is a negative-sense, single-stranded RNA virus of the genus Pneumovirinae and of the family Paramyxoviridae. Symptoms in adults typically resemble a sinus infection or the common cold, although the infection may be asymptomatic. In older adults (e.g., >60 years), RSV infection may progress to bronchiolitis or pneumonia. Symptoms in children are often more severe, including bronchiolitis and pneumonia. It is estimated that in the United States, most children are infected with RSV by the age of three. The RSV virion consists of an internal nucleocapsid comprised of the viral RNA bound to nucleoprotein (N), phosphoprotein (P), and large polymerase protein (L). The nucleocapsid is surrounded by matrix protein (M) and is encapsulated by a lipid bilayer into which the viral fusion (F) and attachment (G) proteins as well as the small hydrophobic protein (SH) are incorporated. The viral genome also encodes two nonstructural proteins (NS1 and NS2), which inhibit type I interferon activity as well as the M-2 protein.

The continuing health problems associated with hMPV, PIV3 and RSV are of concern internationally, reinforcing the importance of developing effective and safe vaccine candidates against these virus.

Despite decades of research, no vaccines currently exist (Sato and Wright, *Pediatr: Infect. Dis. J.* 2008; 27(10 Suppl): S123-5). Recombinant technology, however, has been used to target the formation of vaccines for hPIV-1, 2 and 3 serotypes, for example, and has taken the form of several live-attenuated intranasal vaccines. Two vaccines in particular were found to be immunogenic and well tolerated against hPIV-3 in phase I trials. hPIV1 and hPIV2 vaccine candidates remain less advanced (Durbin and Karron, Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2003; 37(12):1668-77).

Measles virus (MeV), like hMPV, PIV3 and RSV, is a negative-sense, single-stranded RNA virus that is the cause of measles, an infection of the respiratory system. MeV is of the genus Morbillivirus within the family Paramyxoviridae. Humans are the natural hosts of the virus; no animal reservoirs are known to exist. Symptoms of measles include fever, cough, runny nose, red eyes and a generalized, maculopapular, erythematous rash. The virus is highly contagious and is spread by coughing

In additional to hMPV, PIV, RSV and MeV, betacoronaviruses are known to cause respiratory illnesses. Betacoronaviruses (BetaCoVs) are one of four genera of coronaviruses of the subfamily Coronavirinae in the family Coronaviridae, of the order Nidovirales. They are enveloped, positive-sense, single-stranded RNA viruses of zoonotic origin. The coronavirus genera are each composed of varying viral lineages, with the betacoronavirus genus containing four such lineages. The BetaCoVs of the greatest clinical importance concerning humans are OC43 and HKU1 of the A lineage, SARS-CoV of the B lineage, and MERS-CoV of the C lineage. MERS-CoV is the first betacoronavirus belonging to lineage C that is known to infect humans.

The Middle East respiratory syndrome coronavirus (MERS-CoV), or EMC/2012 (HCoV-EMC/2012), initially referred to as novel coronavirus 2012 or simply novel coronavirus, was first reported in 2012 after genome sequencing of a virus isolated from sputum samples from a person who fell ill during a 2012 outbreak of a new flu. As of July 2015, MERS-CoV cases have been reported in over 21 countries. The outbreaks of MERS-CoV have raised

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serious concerns world-wide, reinforcing the importance of developing effective and safe vaccine candidates against MERS-CoV.

Severe acute respiratory syndrome (SARS) emerged in China in 2002 and spread to other countries before brought ⁵ under control. Because of a concern for reemergence or a deliberate release of the SARS coronavirus, vaccine development was initiated.

Deoxyribonucleic acid (DNA) vaccination is one technique used to stimulate humoral and cellular immune responses to foreign antigens, such as hMPV antigens and/or PIV antigens and/or RSV antigens. The direct injection of genetically engineered DNA (e.g., naked plasmid DNA) into a living host results in a small number of its cells directly producing an antigen, resulting in a protective immunological response. With this technique, however, comes potential problems, including the possibility of insertional mutagenesis, which could lead to the activation of oncogenes or the inhibition of tumor suppressor genes.

SUMMARY

Provided herein are ribonucleic acid (RNA) vaccines that build on the knowledge that RNA (e.g., messenger RNA 25 (mRNA)) can safely direct the body's cellular machinery to produce nearly any protein of interest, from native proteins to antibodies and other entirely novel protein constructs that can have therapeutic activity inside and outside of cells. The RNA (e.g., mRNA) vaccines of the present disclosure may 30 be used to induce a balanced immune response against hMPV, PIV, RSV, MeV, and/or BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), or any combination of two or more of the foregoing viruses, comprising 35 both cellular and humoral immunity, without risking the possibility of insertional mutagenesis, for example, hMPV, PIV, RSV, MeV, BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) and combinations thereof are 40 referred to herein as "respiratory viruses." Thus, the term "respiratory virus RNA vaccines" encompasses hMPV RNA vaccines, PIV RNA vaccines, RSV RNA vaccines, MeV RNA vaccines, BetaCoV RNA vaccines, and any combination of two or more of hMPV RNA vaccines, PIV RNA 45 vaccines, RSV RNA vaccines, MeV RNA vaccines, and BetaCoV RNA vaccines.

The RNA (e.g., mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. The RNA (e.g. 50 mRNA) vaccines may be utilized to treat and/or prevent a hMPV, PIV, RSV, MeV, a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1), or any combination of two or more of the foregoing viruses, of various geno- 55 types, strains, and isolates. The RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially available anti-viral therapeutic treatments. While not wishing to be bound by theory, it is believed that the RNA 60 (e.g., mRNA) vaccines, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger 65 unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

In some aspects the invention is a respiratory virus vaccine, comprising at least one RNA polynucleotide having an open reading frame encoding at least one respiratory virus antigenic polypeptide, formulated in a cationic lipid nanoparticle.

Surprisingly, in some aspects, it has also been shown that efficacy of mRNA vaccines can be significantly enhanced when combined with a flagellin adjuvant, in particular, when one or more antigen-encoding mRNAs is combined with an mRNA encoding flagellin.

RNA (e.g., mRNA) vaccines combined with the flagellin adjuvant (e.g., mRNA-encoded flagellin adjuvant) have superior properties in that they may produce much larger antibody titers and produce responses earlier than commer-15 cially available vaccine formulations. While not wishing to be bound by theory, it is believed that the RNA (e.g., mRNA) vaccines, for example, as mRNA polynucleotides, are better designed to produce the appropriate protein conformation upon translation, for both the antigen and the adjuvant, as the RNA (e.g., mRNA) vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured ex vivo and may trigger unwanted cellular responses, RNA (e.g., mRNA) vaccines are presented to the cellular system in a more native fashion.

Some embodiments of the present disclosure provide RNA (e.g., mRNA) vaccines that include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment thereof (e.g., an immunogenic fragment capable of inducing an immune response to the antigenic polypeptide) and at least one RNA (e.g., mRNA polynucleotide) having an open reading frame encoding a flagellin adjuvant.

In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is a flagellin protein. In some embodiments, at least one flagellin polypeptide (e.g., encoded flagellin polypeptide) is an immunogenic flagellin fragment. In some embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are encoded by a single RNA (e.g., mRNA) polynucleotide. In other embodiments, at least one flagellin polypeptide and at least one antigenic polypeptide are each encoded by a different RNA polynucleotide.

In some embodiments at least one flagellin polypeptide has at least 80%, at least 85%, at least 90%, or at least 95% identity to a flagellin polypeptide having a sequence identified by any one of SEQ ID NO: 54-56.

Provided herein, in some embodiments, is a ribonucleic acid (RNA) (e.g., mRNA) vaccine, comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides. Herein, use of the term "antigenic polypeptide" encompasses immunogenic fragments of the antigenic polypeptide (an immunogenic fragment that is induces (or is capable of inducing) an immune response to hMPV, PIV, RSV, MeV, or a BetaCoV), unless otherwise stated.

Also provided herein, in some embodiments, is a RNA (e.g., mRNA) vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63,

HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, linked to a signal peptide.

Further provided herein, in some embodiments, is a nucleic acid (e.g., DNA) encoding at least one (e.g., at least 5 2, 3, 4 or 5) hMPV, PIV, RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) RNA (e.g., mRNA) polynucleotide.

Further still, provided herein, in some embodiments, is a 10 method of inducing an immune response in a subject, the method comprising administering to the subject a vaccine comprising at least one (e.g., at least 2, 3, 4 or 5) RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one (e.g., at least 2, 3, 4 or 5) hMPV, PIV, 15 RSV, MeV, and/or a BetaCoV (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide, or any combination of two or more of the foregoing antigenic polypeptides. 20

hMPV/PIV3/RSV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3 or RSV antigenic polypeptide. In some embodiments, 25 at least one antigenic polypeptide is a hMPV, PIV3 or RSV polyprotein. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is Fusion (F) glycoprotein (e.g., 30 Fusion glycoprotein F0, F1 or F2) or an immunogenic fragment thereof. In some embodiments, at least one antigenic polypeptide is major surface glycoprotein G or an immunogenic fragment thereof and F glycoprotein or an immunogenic fragment thereof. In some embodiments, the 35 antigenic polypeptide is nucleoprotein (N) or an immunogenic fragment thereof, phosphoprotein (P) or an immunogenic fragment thereof, large polymerase protein (L) or an immunogenic fragment thereof, matrix protein (M) or an immunogenic fragment thereof, small hydrophobic protein 40 (SH) or an immunogenic fragment thereof nonstructural protein1 (NS1) or an immunogenic fragment thereof, or nonstructural protein 2 (NS2) and an immunogenic fragment thereof.

In some embodiments, at least one hMPV antigenic 45 polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4). In some embodiments, the amino acid sequence of the hMPV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% 50 (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 5-8 (Table 3; see also amino acid sequences of Table 4).

In some embodiments, at least one hMPV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 1-4 (Table 2). In some embodiments, at least one MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 4.4 (Table 2).

In some embodiments, at least one hMPV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 1-4 (Table 2). In some embodi-60 ments, at least one hMPV RNA (e.g., mRNA) polynucle-otide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 57-60 (Table 2).

In some embodiments, at least one antigenic polypeptide 65 is obtained from hMPV strain CAN98-75 (CAN75) or the hMPV strain CAN97-83 (CAN83).

In some embodiments, at least one PIV3 antigenic polypeptide comprises hemagglutinin-neuraminidase, Fusion (F) glycoprotein, matrix protein (M), nucleocapsid protein (N), viral replicase (L), non-structural V protein, or an immunogenic fragment thereof.

In some embodiments, at least one PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7). In some embodiments, the amino acid sequence of the PIV3 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

In some embodiments, at least one PIV3 antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

In some embodiments, at least one PIV3 RNA (e.g., 20 mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7). In some embodiments, at least one PIV3 RNA (e.g., mRNA) polynucleotide comprises a 25 nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 61-64 (Table 5).

In some embodiments, at least one antigenic polypeptide is obtained from PIV3 strain HPIV3/Homo sapiens/PER/ FLA4815/2008.

In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein G, glycoprotein F, or an immunogenic fragment thereof. In some embodiments, at least one RSV antigenic polypeptide comprises at least one antigenic polypeptide that comprises glycoprotein F and at least one or at least two antigenic polypeptide selected from G, M, N, P, L, SH, M2, NS1 and NS2.



In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide. In some embodiments, at least one antigenic polypeptide is a hemagglutinin (HA) protein or an immunogenic fragment thereof. The HA protein may be from MeV strain D3 or B8, for example. In some embodiments, at least one antigenic polypeptide is a Fusion (F) protein or an immunogenic fragment thereof. The F protein may be from MeV strain D3 or B8, for example. In some embodiments, a MeV RNA (e.g., mRNA) vaccines comprises a least one RNA polynucleotide encoding a HA protein and a F protein. The HA and F proteins may be from MeV strain D3 or B8, for example.

In some embodiments, at least one MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14). In some embodiments, the amino acid sequence of the MeV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 47-50 (Table 14).

In some embodiments, at least one MeV antigenic polypeptide is encoded by a nucleic acid sequence of SEQ ID NO: 35-46 (Table 13).

In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified

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by any one of SEQ ID NO: 35-46 (Table 13). In some embodiments, at least one MeV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 69-80 (Table 13).

In some embodiments, at least one antigenic polypeptide is obtained from MeV strain B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05, MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/ 3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, or MVi/Pennsylvania.USA/ 20.09.

BetaCoV

In some embodiments, a RNA (e.g., mRNA) vaccine comprises at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one Beta-CoV antigenic polypeptide. In some embodiments, the Beta-CoV is MERS-CoV. In some embodiments, the BetaCoV is SARS-CoV. In some embodiments, the BetaCoV is HCoV- 20 OC43. In some embodiments, the BetaCoV is HCoV-229E. In some embodiments, the BetaCoV is HCoV-NL63. In some embodiments, the BetaCoV is HCoV-HKU1. In some embodiments, at least one antigenic polypeptide is a betacoronavirus structural protein. For example, a betacorona- 25 virus structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, a betacoronavirus structural protein is a spike protein (S). In some embodiments, a betacoronavirus structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

BetaCoV RNA (e.g., mRNA) polynucleotides of the vaccines provided herein may encode viral protein components 35 of betacoronaviruses, for example, accessory proteins, replicase proteins and the like are encompassed by the present disclosure. RNA (e.g., mRNA) vaccines may include RNA polynucleotides encoding at least one accessory protein (e.g., protein 3, protein 4a, protein 4b, protein 5), at least one 40 is a SARS-CoV structural protein. For example, a SARSreplicase protein (e.g., protein 1a, protein 1b), or a combination of at least one accessory protein and at least one replicase protein. The present disclosure also encompasses RNA (e.g., mRNA) vaccines comprising RNA (e.g., mRNA) polynucleotides encoding an accessory protein and/or a 45 replicase protein in combination with at least one structural protein. Due to their surface expression properties, vaccines featuring RNA polynucleotides encoding structural proteins are believed to have preferred immunogenic activity and, hence, may be most suitable for use in the vaccines of the 50 present disclosure.

Some embodiments of the present disclosure provide betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1 or a combination thereof) vaccines that 55 include at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH, HCoV-HKU1) antigenic polypeptide. Also provided herein are 60 pan-betacoronavirus vaccines. Thus, a betacoronavirus vaccine comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding any one, two, three or four of MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1, for example, may be effec- 65 tive against any one of, any combination of, or all of, MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E,

HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1. Other betacoronaviruses are encompassed by the present disclosure.

In some embodiments, at least one antigenic polypeptide is a MERS-CoV structural protein. For example, a MERS-CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the MERS-CoV structural protein is a spike protein (S) (see, e.g., Coleman C M et al. Vaccine 2014; 32:3169-74, incorporated herein by reference). In some embodiments, the MERS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof (Li J et al. Viral Immunol 2013; 26(2):126-32; He Y et al. Biochem Biophys Res Commun 2004; 324(2):773-81, each of which is incorporated herein by reference).

In some embodiments, at least one MERS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11). In some embodiments, the amino acid sequence of the MERS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 24-28 or 33 (Table 11).

In some embodiments, at least one MERS-CoV antigenic polypeptide is encoded by a nucleic acid sequence identified by any one of SEQ ID NO: 20-23 (Table 10).

In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide is encoded by a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 20-23 (Table 10). In some embodiments, at least one MERS-CoV RNA (e.g., mRNA) polynucleotide comprises a nucleic acid sequence, or a fragment of a nucleotide sequence, identified by any one of SEQ ID NO: 65-68 (Table 10).

In some embodiments, at least one antigenic polypeptide is obtained from MERS-CoV strain Rivadh 14 2013, 2cEMC/2012, or Hasa_1_2013.

In some embodiments, at least one antigenic polypeptide CoV structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the SARS-CoV structural protein is a spike protein (S). In some embodiments, the SARS-CoV structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one SARS-CoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11). In some embodiments, the amino acid sequence of the SARS-CoV antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11).

In some embodiments, at least one antigenic polypeptide is a HCoV-OC43 structural protein. For example, a HCoV-OC43 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodiments, the HCoV-OC43 structural protein is a spike protein (S). In some embodiments, the HCoV-OC43 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-OC43 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 30 (Table 11). In some embodiments, the amino acid sequence of the HCoV-OC43 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 30 (Table 11).

In some embodiments, an antigenic polypeptide is a HCoV-HKU1 structural protein. For example, a HCoV-HKU1 structural protein may be spike protein (S), envelope protein (E), nucleocapsid protein (N), membrane protein (M) or an immunogenic fragment thereof. In some embodi-10 ments, the HCoV-HKU1 structural protein is a spike protein (S). In some embodiments, the HCoV-HKU1 structural protein is a S1 subunit or a S2 subunit of spike protein (S) or an immunogenic fragment thereof.

In some embodiments, at least one HCoV-HKU1 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11). In some embodiments, the amino acid sequence of the HCoV-HKU1 antigenic polypeptide is, or is a fragment of, or is a homolog or variant having at least 80% (e.g., 85%, 90%, 95%, 98%, 20 99%) identity to, the amino acid sequence identified by any one of SEQ ID NO: 31 (Table 11).

In some embodiments, an open reading frame of a RNA (e.g., mRNA) vaccine is codon-optimized. In some embodiments, at least one RNA polynucleotide encodes at least one 25 antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and is codon optimized mRNA.

In some embodiments, a RNA (e.g., mRNA) vaccine 30 further comprising an adjuvant.

Tables 4, 7, 12 and 15 provide National Center for Biotechnology Information (NCBI) accession numbers of interest. It should be understood that the phrase "an amino acid sequence of Tables 4, 7, 12 and 15" refers to an amino 35 acid sequence identified by one or more NCBI accession numbers listed in Tables 4, 7, 12 and 15. Each of the amino acid sequences, and variants having greater than 95% identity or greater than 98% identity to each of the amino acid sequences encompassed by the accession numbers of Tables 40 4, 7, 12 and 15 are included within the constructs (polynucleotides/polypeptides) of the present disclosure.

In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 45 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 50 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 75%, 85% or 95% identity to a wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence identified by any one of 55SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 50-80%, 60-80%, 40-80%, 30-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is 60 encoded by a nucleic acid having a sequence identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-85%, 50-85%, 60-85%, 30-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA 65 sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence

identified by any one of SEQ ID NO: 1-4, 9-12, 20-23, or 35-46 (Tables 2, 5, 10 and 13; see also nucleic acid sequences of Table 7) and having less than 40-90%, 50-90%, 60-90%, 30-90%, 70-90%, 75-90%, 80-90%, or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has less than 95%, 90%, 85%, 80% or 75% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and has 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80%, 30-85%, 40-85%, 50-805%, 60-85%, 70-85%, 75-85% or 78-85%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 75-90%, 80-90% or 85-90% identity to wild-type mRNA sequence.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15). In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15).

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide having 95%-99% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, or 47-50 (Tables 3, 6, 11 and 14; see also amino acid sequences of Tables 4, 7, 12 and 15) and having membrane fusion activity.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that attaches to cell receptors.

In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) that causes fusion of viral and cellular membranes.

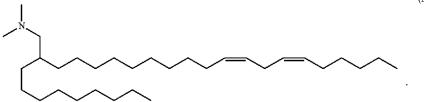
In some embodiments, at least one RNA polynucleotide encodes at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic

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a cationic lipid is selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)—N,N-dimethyl-2-nonylhenicosa-12,15-dien-1amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530).

In some embodiments, the lipid is (L608). In some embodiments, the lipid is

(L608)



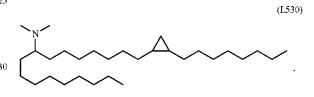
polypeptide, at least one RSV antigenic polypeptide, at least ²⁵ one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) ³⁰ that is responsible for binding of the virus to a cell being infected.

Some embodiments of the present disclosure provide a vaccine that includes at least one ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame 35 encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, 40 SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), at least one 5' terminal cap and at least one chemical modification, formulated within a lipid nanoparticle.

In some embodiments, a 5' terminal cap is 7mG(5')ppp (5')NlmpNp.

In some embodiments, at least one chemical modification is selected from pseudouridine, N1-methylpseudouridine, 2-thiouridine, N1-ethylpseudouridine, 4'-thiouridine, 50 5-methylcytosine, 5-methyluridine, 2-thio-1-methyl-1deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thiodihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thiopseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl- 55 pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, the chemical modification is in the 5-position of the uracil. In some embodiments, the chemical modification is a N1-methylpseudouridine. In 60 some embodiments, the chemical modification is a N1-ethylpseudouridine.

In some embodiments, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a noncationic lipid. In some embodiments, a cationic lipid is an 65 ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments,



In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), discussed below.

In some embodiments, a repiratory virus RNA (e.g., mRNA) vaccine is formulated in a lipid nanoparticle that comprises a compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122, described below.

Some embodiments of the present disclosure provide a vaccine that includes at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides), wherein at least 80% (e.g., 85%, 90%, 95%, 98%, 99%) of the uracil in the open reading frame have a chemical modification, optionally wherein the vaccine is formulated in a lipid nanoparticle (e.g., a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid).

In some embodiments, 100% of the uracil in the open reading frame have a chemical modification. In some embodiments, a chemical modification is in the 5-position of the uracil. In some embodiments, a chemical modification is a N1-methyl pseudouridine. In some embodiments, 100% of the uracil in the open reading frame have a N1-methyl pseudouridine in the 5-position of the uracil.

In some embodiments, an open reading frame of a RNA (e.g., mRNA) polynucleotide encodes at least two antigenic polypeptides (e.g., at least two hMPV antigenic polypeptides, at least two PIV3 antigenic polypeptides, at least two

RSV antigenic polypeptides, at least two MeV antigenic polypeptides, or at least two BetaCoV antigenic polypeptides, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the 5 foregoing antigenic polypeptides). In some embodiments, the open reading frame encodes at least five or at least ten antigenic polypeptides. In some embodiments, the open reading frame encodes at least 100 antigenic polypeptides. In some embodiments, the open reading frame encodes 10 2-100 antigenic polypeptides.

In some embodiments, a vaccine comprises at least two RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one 15 PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or 20 any combination of two or more of the foregoing antigenic polypeptides). In some embodiments, the vaccine comprises at least five or at least ten RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide or an immunogenic fragment 25 thereof. In some embodiments, the vaccine comprises at least 100 RNA (e.g., mRNA) polynucleotides, each having an open reading frame encoding at least one antigenic polypeptide. In some embodiments, the vaccine comprises 2-100 RNA (e.g., mRNA) polynucleotides, each having an 30 open reading frame encoding at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic 35 methods of inducing an antigen specific immune response in polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic 40 polypeptides) is fused to a signal peptide. In some embodiments, the signal peptide is selected from: a HulgGk signal peptide (METPAQLLFLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MDWTWIL-FLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis 45 PRM signal sequence (MLGSNSGQRVVFTILLLLVA-PAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTA-CAGA; SEQ ID NO: 19). 50

In some embodiments, the signal peptide is fused to the N-terminus of at least one antigenic polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of at least one antigenic polypeptide.

In some embodiments, at least one antigenic polypeptide 55 (e.g., at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, or at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, 60 HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides) comprises a mutated N-linked glycosylation site.

Also provided herein is a RNA (e.g., mRNA) vaccine of 65 any one of the foregoing paragraphs (e.g., a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a

BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing vaccines), formulated in a nanoparticle (e.g., a lipid nanoparticle).

In some embodiments, the nanoparticle has a mean diameter of 50-200 nm. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, the lipid nanoparticle comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid. In some embodiments, the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol. In some embodiments, the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

In some embodiments, a lipid nanoparticle comprises compounds of Formula (I) and/or Formula (II), as discussed below.

In some embodiments, a lipid nanoparticle comprises Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122, as discussed below.

In some embodiments, the nanoparticle has a polydispersity value of less than 0.4 (e.g., less than 0.3, 0.2 or 0.1).

In some embodiments, the nanoparticle has a net neutral charge at a neutral pH value.

In some embodiments, the respiratory virus vaccine is multivalent.

Some embodiments of the present disclosure provide a subject, comprising administering to the subject any of the RNA (e.g., mRNA) vaccine as provided herein in an amount effective to produce an antigen-specific immune response. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, an antigen-specific immune response comprises a T cell response or a B cell response.

In some embodiments, a method of producing an antigenspecific immune response comprises administering to a subject a single dose (no booster dose) of a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the RNA (e.g., mRNA) vaccine is a hMPV vaccine, a PIV3 vaccine, a RSV vaccine, a MeV vaccine, or a BetaCoV vaccine, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1 vaccines. In some embodiments, the RNA (e.g., mRNA) vaccine is a combination vaccine comprising a combination of any two or more of the foregoing vaccines.

In some embodiments, a method further comprises administering to the subject a second (booster) dose of a RNA (e.g., mRNA) vaccine. Additional doses of a RNA (e.g., mRNA) vaccine may be administered.

In some embodiments, the subjects exhibit a seroconversion rate of at least 80% (e.g., at least 85%, at least 90%, or at least 95%) following the first dose or the second (booster)

dose of the vaccine. Seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, a virus can be detected in blood tests for the antibody. During an infection or immunization, antigens enter the 5 blood, and the immune system begins to produce antibodies in response. Before seroconversion, the antigen itself may or may not be detectable, but antibodies are considered absent. During seroconversion, antibodies are present but not yet detectable. Any time after seroconversion, the antibodies can 10 be detected in the blood, indicating a prior or current infection.

In some embodiments, a RNA (e.g., mRNA) vaccine is administered to a subject by intradermal or intramuscular injection.

Some embodiments, of the present disclosure provide methods of inducing an antigen specific immune response in a subject, including administering to a subject a RNA (e.g., mRNA) vaccine in an effective amount to produce an antigen specific immune response in a subject. Antigen- 20 PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, specific immune responses in a subject may be determined, in some embodiments, by assaying for antibody titer (for titer of an antibody that binds to a hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic polypeptide) following administration to the subject of any of the RNA (e.g., mRNA) 25 vaccines of the present disclosure. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative 30 to a control.

In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the 35 subject is increased at least 5 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is 40 increased 2-10 times relative to a control.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, the control is an 45 anti-antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine (see, e.g., Ren J. et al. J of Gen. Virol. 2015; 96: 1515-1520), or wherein the control is an anti-antigenic polypeptide 50 antibody titer produced in a subject who has been administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a hMPV, 55 PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine (see, e.g., Cox R G et al., J Virol. 2014 June; 88(11): 6368-6379).

A RNA (e.g., mRNA) vaccine of the present disclosure is administered to a subject in an effective amount (an amount 60 effective to induce an immune response). In some embodiments, the effective amount is a dose equivalent to an at least 2-fold, at least 4-fold, at least 10-fold, at least 100-fold, at least 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV 65 protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an

anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, or a hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine. In some embodiments, the effective amount is a dose equivalent to 2-1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine, an inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV VLP vaccine.

In some embodiments, the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a virus-like particle (VLP) vaccine comprising structural proteins of hMPV, PIV3, RSV, MeV and/or BetaCoV.

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, the effective amount is a total dose of 25 µg to 1000 µg, or 50 µg to 1000 µg. In some embodiments, the effective amount is a total dose of $100 \,\mu g$. In some embodiments, the effective amount is a dose of 25 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 µg administered to the subject a total of two times.

In some embodiments, the efficacy (or effectiveness) of a RNA (e.g., mRNA) vaccine is greater than 60%. In some embodiments, the RNA (e.g., mRNA) polynucleotide of the vaccine at least one hMPV antigenic polypeptide, at least one PIV3 antigenic polypeptide, at least one RSV antigenic polypeptide, at least one MeV antigenic polypeptide, at least one BetaCoV antigenic polypeptide, e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1, or any combination of two or more of the foregoing antigenic polypeptides.

Vaccine efficacy may be assessed using standard analyses (see, e.g., Weinberg et al., J Infect Dis. 2010 Jun. 1; 201(11):1607-10). For example, vaccine efficacy may be measured by double-blind, randomized, clinical controlled trials. Vaccine efficacy may be expressed as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) study cohorts and can be calculated from the relative risk (RR) of disease among the vaccinated group with use of the following formulas:

Likewise, vaccine effectiveness may be assessed using standard analyses (see, e.g., Weinberg et al., J Infect Dis. 2010 Jun. 1; 201(11):1607-10). Vaccine effectiveness is an

Efficacy=(ARU-ARV)/ARU×100; and

Efficacy=(1-RR)×100.

assessment of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure can assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under natural field conditions rather than in a controlled clinical trial. Vaccine effectiveness is proportional to vaccine efficacy (potency) but is also affected by how well target groups in the population are immunized, as well as by other non-vaccine-related factors that influence the 'real-world' outcomes of hospitalizations, ambulatory visits, or costs. For example, a retrospective case control analysis may be used, in which the rates of vaccination among a set of infected cases and appropriate controls are compared. Vaccine effectiveness may be expressed as a 15 rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

Effectiveness=(1-OR)×100.

In some embodiments, the efficacy (or effectiveness) of a 20 RNA (e.g., mRNA) vaccine is at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for up to 2 years. In some embodiments, the vaccine immunizes the subject against hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses for more than 2 years, more than 3 years, more than 4 years, or for 5-10 years. 35

In some embodiments, the subject is about 5 years old or younger. For example, the subject may be between the ages of about 1 year and about 5 years (e.g., about 1, 2, 3, 5 or 5 years), or between the ages of about 6 months and about 1 year (e.g., about 6, 7, 8, 9, 10, 11 or 12 months). In some 40 embodiments, the subject is about 12 months or younger (e.g., 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 months or 1 month). In some embodiments, the subject is about 6 months or younger.

In some embodiments, the subject was born full term 45 (e.g., about 37-42 weeks). In some embodiments, the subject was born prematurely, for example, at about 36 weeks of gestation or earlier (e.g., about 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26 or 25 weeks). For example, the subject may have been born at about 32 weeks of gestation or earlier. In some 50 embodiments, the subject was born prematurely between about 32 weeks and about 36 weeks of gestation. In such subjects, a RNA (e.g., mRNA) vaccine may be administered later in life, for example, at the age of about 6 months to about 5 years, or older. 55

In some embodiments, the subject is pregnant (e.g., in the first, second or third trimester) when administered an RNA (e.g., mRNA) vaccine. Viruses such as hMPV, PIV3 and RSV causes infections of the lower respiratory tract, mainly in infants and young children. One-third of RSV related 60 deaths, for example, occur in the first year of life, with 99 percent of these deaths occurring in low-resource countries. It's so widespread in the United States that nearly all children become infected with the virus before their second birthdays. Thus, the present disclosure provides RNA (e.g., 65 mRNA) vaccines for maternal immunization to improve mother-to-child transmission of protection against the virus.

In some embodiments, the subject is a young adult between the ages of about 20 years and about 50 years (e.g., about 20, 25, 30, 35, 40, 45 or 50 years old).

In some embodiments, the subject is an elderly subject about 60 years old, about 70 years old, or older (e.g., about 60, 65, 70, 75, 80, 85 or 90 years old).

In some embodiments, the subject is has a chronic pulmonary disease (e.g., chronic obstructive pulmonary disease (COPD) or asthma). Two forms of COPD include chronic bronchitis, which involves a long-term cough with mucus, and emphysema, which involves damage to the lungs over time. Thus, a subject administered a RNA (e.g., mRNA) vaccine may have chronic bronchitis or emphysema.

In some embodiments, the subject has been exposed to hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; the subject is infected with hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses; or subject is at risk of infection by hMPV, PIV3, RSV, MeV, BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-NL63, HCoV-NL, HCoV-NL63, HCoV-229E, HCoV-NL63, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1), or any combination of two or more of the foregoing viruses.

In some embodiments, the subject is immunocompromised (has an impaired immune system, e.g., has an immune disorder or autoimmune disorder).

In some embodiments the nucleic acid vaccines described herein are chemically modified. In other embodiments the nucleic acid vaccines are unmodified.

Yet other aspects provide compositions for and methods of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first respiratory virus antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization ele-40 ment, and wherein an adjuvant is not coformulated or co-administered with the vaccine.

In other aspects the invention is a composition for or method of vaccinating a subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide wherein a dosage of between 10 µg/kg and 400 µg/kg of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 µg, 5-10 µg, 10-15 $\mu g,\,15\text{-}20\,\mu g,\,10\text{-}25\,\mu g,\,20\text{-}25\,\mu g,\,20\text{-}50\,\mu g,\,30\text{-}50\,\mu g,\,40\text{-}50$ $\mu g,\,40\text{-}60~\mu g,\,60\text{-}80~\mu g,\,60\text{-}100~\mu g,\,50\text{-}100~\mu g,\,80\text{-}120~\mu g,$ 40-120 µg, 40-150 µg, 50-150 µg, 50-200 µg, 80-200 µg, 100-200 µg, 120-250 µg, 150-250 µg, 180-280 µg, 200-300 μg, 50-300 μg, 80-300 μg, 100-300 μg, 40-300 μg, 50-350 55 µg, 100-350 µg, 200-350 µg, 300-350 µg, 320-400 µg, 40-380 µg, 40-100 µg, 100-400 µg, 200-400 µg, or 300-400 µg per dose. In some embodiments, the nucleic acid vaccine is administered to the subject by intradermal or intramuscular injection. In some embodiments, the nucleic acid vaccine is administered to the subject on day zero. In some embodiments, a second dose of the nucleic acid vaccine is administered to the subject on day twenty one.

In some embodiments, a dosage of 25 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 100 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some

embodiments, a dosage of 50 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 75 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some 5 embodiments, a dosage of 150 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, a dosage of 400 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some 10 embodiments, a dosage of 200 micrograms of the RNA polynucleotide is included in the nucleic acid vaccine administered to the subject. In some embodiments, the RNA polynucleotide accumulates at a 100 fold higher level in the local lymph node in comparison with the distal lymph node. 15 In other embodiments the nucleic acid vaccine is chemically modified and in other embodiments the nucleic acid vaccine is not chemically modified.

Aspects of the invention provide a nucleic acid vaccine comprising one or more RNA polynucleotides having an 20 open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and a pharmaceutically acceptable carrier or excipient, wherein an adjuvant is not included in the vaccine. In some embodiments, the stabilization element is 25 a histone stem-loop. In some embodiments, the stabilization element is a nucleic acid sequence having increased GC content relative to wild type sequence.

Aspects of the invention provide nucleic acid vaccines comprising one or more RNA polynucleotides having an 30 open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host, which confers an antibody titer superior to the criterion for seroprotection for the first antigen for an acceptable percentage of human 35 subjects. In some embodiments, the antibody titer produced by the mRNA vaccines of the invention is a neutralizing antibody titer. In some embodiments the neutralizing antibody titer is greater than a protein vaccine. In other embodiments the neutralizing antibody titer produced by the mRNA 40 vaccines of the invention is greater than an adjuvanted protein vaccine. In yet other embodiments the neutralizing antibody titer produced by the mRNA vaccines of the invention is 1,000-10,000, 1,200-10,000, 1,400-10,000, 1,500-10,000, 1,000-5,000, 1,000-4,000, 1,800-10,000, 45 2000-10,000, 2,000-5,000, 2,000-3,000, 2,000-4,000, 3,000-5.000, 3.000-4.000, or 2.000-2.500. A neutralization titer is typically expressed as the highest serum dilution required to achieve a 50% reduction in the number of plaques.

Also provided are nucleic acid vaccines comprising one 50 or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide is present in a formulation for in vivo administration to a host for eliciting a longer lasting high antibody titer than an antibody titer elicited by an mRNA vaccine 55 having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide. In some embodiments, the RNA polynucleotide is formulated to produce a neutralizing antibodies within one week of a single administration. In some embodiments, the adjuvant is 60 selected from a cationic peptide and an immunostimulatory nucleic acid. In some embodiments, the cationic peptide is protamine.

Aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame 65 comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encod-

ing a first antigenic polypeptide, wherein the RNA polynucleotide is present in the formulation for in vivo administration to a host such that the level of antigen expression in the host significantly exceeds a level of antigen expression produced by an mRNA vaccine having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Aspects of the invention also provide a unit of use vaccine, comprising between 10 ug and 400 ug of one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification or optionally no nucleotide modification, the open reading frame encoding a first antigenic polypeptide, and a pharmaceutically acceptable carrier or excipient, formulated for delivery to a human subject. In some embodiments, the vaccine further comprises a cationic lipid nanoparticle.

Aspects of the invention provide methods of creating, maintaining or restoring antigenic memory to a respiratory virus strain in an individual or population of individuals comprising administering to said individual or population an antigenic memory booster nucleic acid vaccine comprising (a) at least one RNA polynucleotide, said polynucleotide comprising at least one chemical modification or optionally no nucleotide modification and two or more codon-optimized open reading frames, said open reading frames encoding a set of reference antigenic polypeptides, and (b) optionally a pharmaceutically acceptable carrier or excipient. In some embodiments, the vaccine is administered to the individual via a route selected from the group consisting of intramuscular administration, intradermal administration and subcutaneous administration. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition. In some embodiments, the administering step comprises contacting a muscle tissue of the subject with a device suitable for injection of the composition in combination with electroporation.

Aspects of the invention provide methods of vaccinating a subject comprising administering to the subject a single dosage of between 25 ug/kg and 400 ug/kg of a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a first antigenic polypeptide in an effective amount to vaccinate the subject.

Other aspects provide nucleic acid vaccines comprising one or more RNA polynucleotides having an open reading frame comprising at least one chemical modification, the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified mRNA vaccine to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

Other aspects provide nucleic acid vaccines comprising an LNP formulated RNA polynucleotide having an open reading frame comprising no nucleotide modifications (unmodified), the open reading frame encoding a first antigenic polypeptide, wherein the vaccine has at least 10 fold less RNA polynucleotide than is required for an unmodified

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mRNA vaccine not formulated in a LNP to produce an equivalent antibody titer. In some embodiments, the RNA polynucleotide is present in a dosage of 25-100 micrograms.

The data presented in the Examples demonstrate significant enhanced immune responses using the formulations of 5 the invention. Both chemically modified and unmodified RNA vaccines are useful according to the invention. Surprisingly, in contrast to prior art reports that it was preferable to use chemically unmodified mRNA formulated in a carrier for the production of vaccines, it is described herein that 10 chemically modified mRNA-LNP vaccines required a much lower effective mRNA dose than unmodified mRNA, i.e., tenfold less than unmodified mRNA when formulated in carriers other than LNP. Both the chemically modified and unmodified RNA vaccines of the invention produce better 15 immune responses than mRNA vaccines formulated in a different lipid carrier.

In other aspects the invention encompasses a method of treating an elderly subject age 60 years or older comprising administering to the subject a nucleic acid vaccine compris- 20 ing one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of treating a young subject age 17 years or younger comprising 25 administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In other aspects the invention encompasses a method of 30 treating an adult subject comprising administering to the subject a nucleic acid vaccine comprising one or more RNA polynucleotides having an open reading frame encoding a respiratory virus antigenic polypeptide in an effective amount to vaccinate the subject.

In some aspects the invention is a method of vaccinating a subject with a combination vaccine including at least two nucleic acid sequences encoding respiratory antigens wherein the dosage for the vaccine is a combined therapeutic dosage wherein the dosage of each individual nucleic acid 40 encoding an antigen is a sub therapeutic dosage. In some embodiments, the combined dosage is 25 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 100 micrograms of the RNA polynucleotide in the 45 nucleic acid vaccine administered to the subject. In some embodiments the combined dosage is 50 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 75 micrograms of the RNA polynucleotide in the 50 nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 150 micrograms of the RNA polynucleotide in the nucleic acid vaccine administered to the subject. In some embodiments, the combined dosage is 400 micrograms of the RNA polynucleotide in the 55 nucleic acid vaccine administered to the subject. In some embodiments, the sub therapeutic dosage of each individual nucleic acid encoding an antigen is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 micrograms. In other embodiments the nucleic acid vaccine is chemically 60 modified and in other embodiments the nucleic acid vaccine is not chemically modified.

The RNA polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and includes at least one chemical modification. In other embodiments the RNA 65 polynucleotide is one of SEQ ID NO: 1-4, 9-12, 20-23, 35-46, 57-61, and 64-80 and does not include any nucleotide

modifications, or is unmodified. In yet other embodiments the at least one RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and includes at least one chemical modification. In other embodiments the RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 5-8, 12-13, 24-34, and 47-50 and does not include any nucleotide modifications, or is unmodified.

In preferred aspects, vaccines of the invention (e.g., LNP-encapsulated mRNA vaccines) produce prophylactically- and/or therapeutically-efficacious levels, concentrations and/or titers of antigen-specific antibodies in the blood or serum of a vaccinated subject. As defined herein, the term antibody titer refers to the amount of antigen-specific antibody produces in s subject, e.g., a human subject. In exemplary embodiments, antibody titer is expressed as the inverse of the greatest dilution (in a serial dilution) that still gives a positive result. In exemplary embodiments, antibody titer is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody titer is determined or measured by neutralization assay, e.g., by microneutralization assay. In certain aspects, antibody titer measurement is expressed as a ratio, such as 1:40, 1:100, etc. In exemplary embodiments of the invention, an efficacious vaccine produces an antibody titer of greater than 1:40, greater that 1:100, greater than 1:400, greater than 1:1000, greater than 1:2000, greater than 1:3000, greater than 1:4000, greater than 1:500, greater than 1:6000, greater than 1:7500, greater than 1:10000. In exemplary embodiments, the antibody titer is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the titer is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the titer is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary aspects of the invention, antigen-specific antibodies are measured in units of µg/ml or are measured in units of IU/L (International Units per liter) or mIU/ml (milli International Units per ml). In exemplary embodiments of the invention, an efficacious vaccine produces >0.5 µg/ml, >0.1 µg/ml, >0.2 µg/ml, >0.35 $\mu g/ml$, >0.5 $\mu g/ml$, >1 $\mu g/ml$, >2 $\mu g/ml$, >5 $\mu g/ml$ or >10 µg/ml. In exemplary embodiments of the invention, an efficacious vaccine produces >10 mIU/ml, >20 mIU/ml, >50 mIU/ml, >100 mIU/ml, >200 mIU/ml, >500 mIU/ml or >1000 mIU/ml. In exemplary embodiments, the antibody level or concentration is produced or reached by 10 days following vaccination, by 20 days following vaccination, by 30 days following vaccination, by 40 days following vaccination, or by 50 or more days following vaccination. In exemplary embodiments, the level or concentration is produced or reached following a single dose of vaccine administered to the subject. In other embodiments, the level or concentration is produced or reached following multiple doses, e.g., following a first and a second dose (e.g., a booster dose.) In exemplary embodiments, antibody level or concentration is determined or measured by enzyme-linked immunosorbent assay (ELISA). In exemplary embodiments, antibody level or concentration is determined or measured by neutralization assay, e.g., by microneutralization assay.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, 15

and advantages of the disclosure will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the disclosure, as illustrated in the accompanying drawings in which like reference characters refer to 10the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

FIG. 1 shows a schematic of one example of a RNA (e.g. mRNA) vaccine construct of the present disclosure. The construct depicts a human metapneumovirus and human respiratory syncytial virus full length fusion protein obtained from wild-type strains (The Journal of General Virology. 2008; 89(Pt 12):3113-3118, incorporated herein by refer- 20 ence).

FIGS. 2A-2C are graphs showing the levels of anti-hMPV fusion protein-specific antibodies in the serum of mice immunized with hMPV mRNA vaccines on day 0 (FIG. 2A), day 14 (FIG. 2B) and day 35 (FIG. 2C) post immunization. 25 The mice were immunized with a single dose $(2 \mu g \text{ or } 10 \mu g)$ on day 0 and were given a boost dose (2 µg or 10 µg) on day 21. hMPV fusion protein-specific antibodies were detected at up to 1:10000 dilution of serum on day 35 for both doses.

FIGS. 3A-3C are graphs showing the result of IgG 30 isotyping in the serum of mice immunized with hMPV mRNA vaccines. The levels of hMPV fusion protein-specific IgG2a (FIG. 3A) and IgG1 (FIG. 3B) antibodies in the serum are measured by ELISA. FIG. 3C shows that hMPV fusion protein mRNA vaccine induced a mixed Th1/Th2 cytokine 35 response with a Th1 bias.

FIG. 4 is a graph showing in vitro neutralization of a hMPV B2 strain (TN/91-316) using the sera of mice immunized with a mRNA vaccine encoding hMPV fusion protein. Mouse serum obtained from mice receiving a 10 µg or a 2 40 titers in cotton rats that received different dosages of PIV µg dose contained hMPV-neutralizing antibodies.

FIGS. 5A-5C are graphs showing a Th1 cytokine response induced by a hMPV fusion peptide pool (15-mers-50 (overlap)) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a 45 negative control and Concanavalin A (ConA, a positive control for splenocyte stimulation) was included. The cytokines tested included IFN-y (FIG. 5A), IL-2 (FIG. 5B) and IL12 (FIG. 5C).

FIGS. 6A-6E are graphs showing the Th2 cytokine 50 response induced by a hMPV fusion peptide pool (15-mers-50) in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. Virus-free media was used as a negative control and Concanavalin A was also included. The cytokines tested included IL-10 (FIG. 6A), TNF-a (FIG. 55 immunization. 6B), IL4 (FIG. 6C), IL-5 (FIG. 6D) and IL-6 (FIG. 6E).

FIGS. 7A-7C are graphs showing the Th1 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with hMPV mRNA vaccines. Virusfree media was used as a negative control and Concanavalin 60 A was included. The cytokines tested included IFN-y (FIG. 7A), IL-2 (FIG. 7B) and IL12 (FIG. 7C).

FIGS. 8A-8E are graphs showing the Th2 response induced by inactivated hMPV virus in splenocytes isolated from mice immunized with the hMPV mRNA vaccines. 65 Virus-free media was used as a negative control and Concanavalin A was included. The cytokines tested include

IL-10 (FIG. 8A), TNF-a (FIG. 8B), IL4 (FIG. 8C), IL-5 (FIG. 8D) and IL-6 (FIG. 8E).

FIGS. 9A-9B are graphs showing the results of cotton rat challenge experiments. Two different doses of the hMPV mRNA vaccines were used (2 µg or 10 µg doses) to immunize the cotton rats before challenge. The hMPV mRNA vaccines reduced the viral titer in the lung and nose of the cotton rat, with the 10 µg dose being more effective in reducing viral titer. Use of a 10 µg dose resulted in 100% protection in the lung and a ~2 log reduction in nose viral titer. Use of a 2 µg dose resulted in a 1 log reduction in lung vital titer and no reduction in nose viral titer. The vaccine was administered on Day 0, and a boost was administered on Day 21.

FIG. 10 is a graph showing the lung histopathology of cotton rats that received hMPV mRNA vaccines. Pathology associated with vaccine-enhanced disease was not observed in immunized groups.

FIG. 11 is a graph showing hMPV neutralization antibody titers in cotton rats that received hMPV mRNA vaccines (2 µg or 10 µg doses) on days 35 and 42 post immunization.

FIG. 12 is a graph showing the lung and nose viral load in cotton rats challenged with a hMPV/A2 strain after immunization with the indicated mRNA vaccines (hMPV mRNA vaccine or hMPV/PIV mRNA combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. 13 is a graph showing the lung and nose viral load in cotton rats challenged with PIV3 strain after immunization with indicated mRNA vaccines (PIV mRNA vaccine or hMPV/PIV combination vaccine). Vaccinated cotton rats showed reduced lung and nose viral loads after challenge, compared to control.

FIG. 14 is a graph showing hMPV neutralizing antibody titers in cotton rats that received different dosages of hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. 15 is a graph showing PIV3 neutralizing antibody mRNA vaccines or hMPV/PIV combination mRNA vaccines on day 42 post immunization. The dosages of the vaccine are indicated in Table 9.

FIG. 16 is a graph showing the lung histopathology score of cotton rats immunized with hMPV mRNA vaccines, PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines as indicated in Table 9. Low occurrence of alevolitis and interstitial pneumonia was observed, indicating no antibody-dependent enhancement (ADE) of hMPV associated diseases.

FIG. 17 is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with betacoronavirus mRNA vaccine encoding the MERS-CoV fulllength Spike protein, on days 0, 21, 42, and 56 post

FIG. 18 is a graph showing the reciprocal MERS-CoV neutralizing antibody titers in mice immunized with betacoronavirus mRNA vaccine encoding either the MERS-CoV full-length Spike protein, or the S2 subunit of the Spike protein. The full length spike protein induced a stronger immune response compared to the S2 subunit alone.

FIGS. 19A-19C are graphs showing the viral load in the nose and throat, the bronchoalveolar lavage (BAL), or the lungs of New Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with one 20 µg-dose (on day 0) or two 20 µg-doses (on day 0 and 21) of MERS-CoV mRNA vaccine encoding the full-length Spike protein before challenge. FIG. **19**A shows that two doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits. FIG. **19**B shows that two doses of ⁵ MERS-CoV mRNA vaccine resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits. FIG. **19**C show one dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two doses of MERS-CoV mRNA vaccine resulted in an over 4 log ¹⁰ reduction of viral load in the lungs of the New Zealand white rabbits.

FIGS. 20A-20B are images and graphs showing viral load or replicating virus detected by PCR in the lungs of New 15 Zealand white rabbits 4 days post challenge with MERS-CoV. The New Zealand white rabbits were immunized with a single 20 µg dose (on day 0, Group 1a) of MERS-CoV mRNA vaccine encoding the full-length Spike protein, two 20 µg doses (on day 0 and 21, Group 1b) of MERS-CoV 20 mRNA vaccine encoding the full-length Spike protein, or placebo (Group 2) before challenge. FIG. 20A shows that two doses of 20 µg a MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits. FIG. 20B shows that the group of New 25 Zealand white rabbits that received 2 doses of 20 µg MERS-CoV mRNA vaccine did not have any detectable replicating MERS-CoV virus in their lungs.

FIG. **21** is a graph showing the MERS-CoV neutralizing antibody titers in New Zealand white rabbits immunized ³⁰ with MERS-CoV mRNA vaccine encoding the full-length Spike protein. Immunization of the in New Zealand white rabbits were carried out as described in FIGS. **21A-21C**. The results show that two doses of 20 μ g MERS-CoV mRNA vaccine induced a significant amount of neutralizing antibodies against MERS-CoV (EC₅₀ between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer is 3-5 fold better than any other vaccines tested in the same model.

DETAILED DESCRIPTION

The present disclosure provides, in some embodiments, vaccines that comprise RNA (e.g., mRNA) polynucleotides encoding a human metapneumovirus (hMPV) antigenic 45 polypeptide, a parainfluenza virus type 3 (PIV3) antigenic polypeptide, a respiratory syncytial virus (RSV) antigenic polypeptide, a measles virus (MeV) antigenic polypeptide, or a betacoronavirus antigenic polypeptide (e.g., Middle East respiratory syndrome coronavirus (MERS-CoV), 50 SARS-CoV, human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH (New Haven) and HCoV-HKU1) (see, e.g., Esper F. et al. Emerging Infectious Diseases, 12(5), 2006; and Pyrc K. et al. Journal of Virology, 81(7):3051-57, 2007, the contents of each of 55 which is here incorporated by reference in their entirety). The present disclosure also provides, in some embodiments, combination vaccines that comprise at least one RNA (e.g., mRNA) polynucleotide encoding at least two antigenic polypeptides selected from hMPV antigenic polypeptides, 60 PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides and BetaCoV antigenic polypeptides. Also provided herein are methods of administering the RNA (e.g., mRNA) vaccines, methods of producing the RNA (e.g., mRNA) vaccines, compositions (e.g., pharma- 65 ceutical compositions) comprising the RNA (e.g., mRNA) vaccines, and nucleic acids (e.g., DNA) encoding the RNA

(e.g., mRNA) vaccines. In some embodiments, a RNA (e.g., mRNA) vaccine comprises an adjuvant, such as a flagellin adjuvant, as provided herein.

The RNA (e.g., mRNA) vaccines (e.g., hMPV, PIV3, RSV, MeV, BetaCoV RNA vaccines and combinations thereof), in some embodiments, may be used to induce a balanced immune response, comprising both cellular and humoral immunity, without many of the risks associated with DNA vaccination.

The entire contents of International Application No. PCT/ US2015/02740 is incorporated herein by reference.

Human Metapneumovirus (hMPV)

hMPV shares substantial homology with respiratory syncytial virus (RSV) in its surface glycoproteins. hMPV fusion protein (F) is related to other paramyxovirus fusion proteins and appears to have homologous regions that may have similar functions. The hMPV fusion protein amino acid sequence contains features characteristic of other paramyxovirus F proteins, including a putative cleavage site and potential N-linked glycosylation sites. Paramyxovirus fusion proteins are synthesized as inactive precursors (F0) that are cleaved by host cell proteases into the biologically fusion-active F1 and F2 domains (see, e.g., Cseke G. et al. Journal of Virology 2007; 81(2):698-707, incorporated herein by reference). hMPV has one putative cleavage site, in contrast to the two sites established for RSV F, and only shares 34% amino acid sequence identity with RSV F. F2 is extracellular and disulfide linked to F1. Fusion proteins are type I glycoproteins existing as trimers, with two 4-3 heptad repeat domains at the N- and C-terminal regions of the protein (HR1 and HR2), which form coiled-coil alphahelices. These coiled coils become apposed in an antiparallel fashion when the protein undergoes a conformational change into the fusogenic state. There is a hydrophobic fusion peptide N proximal to the N-terminal heptad repeat, which is thought to insert into the target cell membrane, while the association of the heptad repeats brings the trans-40 membrane domain into close proximity, inducing membrane fusion (see, e.g., Baker, K A et al. Mol. Cell 1999; 3:309-319). This mechanism has been proposed for a number of different viruses, including RSV, influenza virus, and human immunodeficiency virus. Fusion proteins are major antigenic determinants for all known paramyxoviruses and for other viruses that possess similar fusion proteins such as human immunodeficiency virus, influenza virus, and Ebola virus.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV fusion protein (F). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a hMPV F protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV glycoprotein (G). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV matrix protein (M). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV phosphoprotein (P). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV nucleoprotein (N). In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding hMPV SH protein (SH).

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, M protein, P protein, N protein and SH protein.

In some embodiments, a hMPV vaccine of the present 5 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a hMPV vaccine of the 10 present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a 15 hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and SH protein.

In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide 20 encoding G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly- 25 nucleotide encoding G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and SH protein.

In some embodiments, a hMPV vaccine of the present 30 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a 35 hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a 35 hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a hMPV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and SH pro- 40 tein.

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV antigenic polypeptide identified by any one of SEQ ID NO: 5-8 (Table 3; see also 45 amino acid sequences of Table 4).

A hMPV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 1-4 (Table 2).

The present disclosure is not limited by a particular strain of hMPV. The strain of hMPV used in a vaccine may be any strain of hMPV. Non-limiting examples of strains of hMPV for use as provide herein include the CAN98-75 (CAN75) and the CAN97-83 (CAN83) hMPV strains (Skiadopoulos 55 M H et al. *J Virol.* 20014; 78(13)6927-37, incorporated herein by reference), a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General Virology* 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference), a hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5), a hMPV isolate NL/1/99 (e.g., SEQ ID NO: 2 and 6), or a hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7).

In some embodiments, at least one hMPV antigenic 65 polypeptide is obtained from a hMPV A1, A2, B1 or B2 strain (see, e.g., de Graaf M et al. *The Journal of General*

Virology 2008; 89:975-83; Peret T C T et al. *The Journal of Infectious Disease* 2002; 185:1660-63, incorporated herein by reference). In some embodiments, at least one antigenic polypeptide is obtained from the CAN98-75 (CAN75) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from the CAN97-83 (CAN83) hMPV strain. In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate TN/92-4 (e.g., SEQ ID NO: 1 and 5). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate NL/1/ 99 (e.g., SEQ ID NO: 2 and 6). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate NL/1/ 91 (e.g., SEQ ID NO: 2 and 6). In some embodiments, at least one antigenic polypeptide is obtained from hMPV isolate PER/CFI0497/2010/B (e.g., SEQ ID NO: 3 and 7). In some embodiments, hMPV vaccines comprise RNA

(e.g., mRNA) polynucleotides encoding a hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV F protein and having F protein activity.

A protein is considered to have F protein activity if, for example, the protein acts to fuse the viral envelope and host cell plasma membrane, mediates viral entry into a host cell via an interaction with arginine-glycine-aspartate RGDbinding integrins, or a combination thereof (see, e.g., Cox R G et al. *J Virol.* 2012; 88(22):12148-60, incorporated herein by reference).

In some embodiments, hMPV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding hMPV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with hMPV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPVinduced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

Human Parainfluenza Virus Type 3 (PIV3)

Parainfluenza viruses belong to the family Paramyxoviridae. These are enveloped viruses with a negative-sense single-stranded RNA genome. Parainfluenza viruses belong to the subfamily Paramyxoviridae, which is subdivided into three genera: Respirovirus (PIV-1, PIV-3, and Sendai virus (SeV)), Rubulavirus (PIV-2, PIV-4 and mumps virus) and Morbillivirus (measles virus, rinderpest virus and canine distemper virus (CDV)). Their genome, a ~15 500 nucleotide-long negative-sense RNA molecule, encodes two envelope glycoproteins, the hemagglutinin-neuraminidase (HN), the fusion protein (F or F0), which is cleaved into F1 and F2 subunits, a matrix protein (M), a nucleocapsid protein (N) and several nonstructural proteins including the viral replicase (L). All parainfluenza viruses, except for PIV-1, express a non-structural V protein that blocks IFN signaling in the infected cell and acts therefore as a virulence factor (see, e.g., Nishio M et al. J Virol. 2008; 82(13):6130-38).

PIV3 hemagglutinin-neuraminidase (HN), a structural protein, is found on the viral envelope, where it is necessary for attachment and cell entry. It recognizes and binds to sialic acid-containing receptors on the host cell's surface. As a neuroaminidase, HN removes sialic acid from virus particles, preventing self-aggregation of the virus, and promoting the efficient spread of the virus. Furthermore, HN promotes the activity of the fusion (F or F0) protein, contributing to the penetration of the host cell's surface.

PIV3 fusion protein (PIV3 F) is located on the viral envelope, where it facilitates the viral fusion and cell entry. The F protein is initially inactive, but proteolytic cleavage leads to its active forms, F1 and F2, which are linked by disulfide bonds. This occurs when the HN protein binds its

receptor on the host cell's surface. During early phases of infection, the F glycoprotein mediates penetration of the host cell by fusion of the viral envelope to the plasma membrane. In later stages of the infection, the F protein facilitates the fusion of the infected cells with neighboring uninfected cells, which leads to the formation of a syncytium and spread of the infection.

PIV3 matrix protein (M) is found within the viral envelope and assists with viral assembly. It interacts with the nucleocapsid and envelope glycoproteins, where it facilitates the budding of progeny viruses through its interactions with specific sites on the cytoplasmic tail of the viral glycoproteins and nucleocapsid. It also plays a role in transporting viral components to the budding site.

PIV3 phosphoprotein (P) and PIV3 large polymerase protein (L) are found in the nucleocapsid where they form part of the RNA polymerase complex. The L protein, a viral RNA-dependent RNA polymerase, facilitates genomic transcription, while the host cell's ribosomes translate the viral 20 mRNA into viral proteins.

PIV3 V is a non-structural protein that blocks IFN signaling in the infected cell, therefore acting as a virulence factor.

PIV3 nucleoprotein (N) encapsidates the genome in a 25 ratio of 1 N per 6 ribonucleotides, protecting it from nucleases. The nucleocapsid (NC) has a helical structure.

The encapsidated genomic RNA is termed the NC and serves as template for transcription and replication. During replication, encapsidation by PIV3 N is coupled to RNA 30 synthesis and all replicative products are resistant to nucleases. PIV3 N homo-multimerizes to form the nucleocapsid and binds to viral genomic RNA. PIV3 N binds the P protein and thereby positions the polymerase on the template.

In some embodiments, a PIV3 vaccine of the present 35 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 fusion protein (F). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding a F1 or F2 subunit of a PIV3 F protein. In some embodiments, a PIV3 vaccine of 40 the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 hemagglutinin-neuraminidase (HN) (see, e.g., van Wyke Coelingh K L et al. J Virol. 1987; 61(5):1473-77, incorporated herein by reference). In some embodiments, a PIV3 vaccine of the present disclosure 45 comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 matrix protein (M). In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 phosphoprotein (P). In some embodiments, a PIV3 vaccine of the present dis- 50 closure comprises a RNA (e.g., mRNA) polynucleotide encoding PIV3 nucleoprotein (N).

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein, M protein, P protein, and N 55 protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and HN protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA 60 (e.g., mRNA) polynucleotide encoding F protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure 65 comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HN protein and N protein.

In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and M protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, HN protein and P protein. In some embodiments, a 15 PIV3 vaccine of the present disclosure comprises a RNA

(e.g., mRNA) polynucleotide encoding F protein, HN protein and N protein.

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one PIV3 antigenic polypeptide identified by any one of SEQ ID NO: 12-13 (Table 6; see also amino acid sequences of Table 7).

A PIV3 vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 9-12 (Table 5; see also nucleic acid sequences of Table 7).

The present disclosure is not limited by a particular strain of PIV3. The strain of PIV3 used in a vaccine may be any strain of PIV3. A non-limiting example of a strain of PIV3 for use as provide herein includes HPIV3/Homo sapiens/ PER/FLA4815/2008.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 F protein and having F protein activity.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 hemagglutinin-neuraminidase (HN) and having hemagglutininneuraminidase activity.

A protein is considered to have hemagglutinin-neuraminidase activity if, for example, it is capable of both receptor binding and receptor cleaving. Such proteins are major surface glycoproteins that have functional sites for cell attachment and for neuraminidase activity. They are able to cause red blood cells to agglutinate and to cleave the glycosidic linkages of neuraminic acids, so they have the potential to both bind a potential host cell and then release the cell if necessary, for example, to prevent self-aggregation of the virus.

In some embodiments, PIV3 vaccines comprise RNA (e.g., mRNA) polynucleotides encoding PIV3 antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with PIV3 HN, F (e.g., F, F1 or F2), M, N, L or V and having HN, F (e.g., F, F1 or F2), M, N, L or V activity, respectively. Respiratory Syncytial Virus (RSV)

RSV is a negative-sense, single-stranded RNA virus of the genus Pneumovirinae. The virus is present in at least two antigenic subgroups, known as Group A and Group B, primarily resulting from differences in the surface G glycoproteins. Two RSV surface glycoproteins—G and F—mediate attachment with and attachment to cells of the respiratory epithelium. F surface glycoproteins mediate coalescence of neighboring cells. This results in the forma-

tion of syncytial cells. RSV is the most common cause of bronchiolitis. Most infected adults develop mild cold-like symptoms such as congestion, low-grade fever, and wheezing. Infants and small children may suffer more severe symptoms such as bronchiolitis and pneumonia. The disease 5 may be transmitted among humans via contact with respiratory secretions.

The genome of RSV encodes at least three surface glycoproteins, including F, G, and SH, four nucleocapsid proteins, including L, P, N, and M2, and one matrix protein, M. 10 Glycoprotein F directs viral penetration by fusion between the virion and the host membrane. Glycoprotein G is a type II transmembrane glycoprotein and is the major attachment protein. SH is a short integral membrane protein. Matrix protein M is found in the inner layer of the lipid bilayer and 15 assists virion formation. Nucleocapsid proteins L, P, N, and M2 modulate replication and transcription of the RSV genome. It is thought that glycoprotein G tethers and stabilizes the virus particle at the surface of bronchial epithelial cells, while glycoprotein F interacts with cellular gly- 20 cosaminoglycans to mediate fusion and delivery of the RSV virion contents into the host cell (Krzyzaniak M A et al. PLoS Pathog 2013; 9(4)).

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide 25 encoding F protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding L protein. In some 30 embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding N protein. In some embodiments, a 35 PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M2 protein. In some embodiments, a PIV3 vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein, L protein, P protein, N protein, M2 protein and M protein.

In some embodiments, a RSV vaccine of the present 45 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and G protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and L protein. In some embodiments, a RSV vaccine of the present 50 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and N protein. In some embodiments, a RSV vaccine of the present 55 disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and P 65 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide

encoding G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding G protein and M protein.

In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and L protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and P protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and N protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M2 protein. In some embodiments, a RSV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein, G protein and M protein.

The present disclosure is not limited by a particular strain of RSV. The strain of RSV used in a vaccine may be any strain of RSV.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding a RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV F protein and having F protein activity.

In some embodiments, RSV vaccines comprise RNA (e.g., mRNA) polynucleotides encoding RSV antigenic polypeptides having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with RSV G protein and having G protein activity.

A protein is considered to have G protein activity if, for example, the protein acts to modulate (e.g., inhibit) hMPVinduced cellular (immune) responses (see, e.g., Bao X et al. *PLoS Pathog.* 2008; 4(5):e1000077, incorporated herein by reference).

40 Measles Virus (MeV) Molecular epidemiologic investigations and virologic surveillance contribute notably to the control and prevention of measles. Nearly half of measlesrelated deaths worldwide occur in India, yet virologic surveillance data are incomplete for many regions of the 45 country. Previous studies have documented the presence of measles virus genotypes D4, D7, and D8 in India, and genotypes D5, D9, D11, H1, and G3 have been detected in neighboring countries. Recently, MeV genotype B3 was detected in India (Kuttiatt V S et al. *Emerg Infect Dis.* 2014; 50 20(10): 1764-66).

The glycoprotein complex of paramyxoviruses mediates receptor binding and membrane fusion. In particular, the MeV fusion (F) protein executes membrane fusion, after receptor binding by the hemagglutinin (HA) protein (Muhlebach M D et al. Journal of Virology 2008; 82(22):11437-45). The MeV P gene codes for three proteins: P, an essential polymerase cofactor, and V and C, which have multiple functions but are not strictly required for viral propagation in cultured cells. V shares the amino-terminal domain with 60 P but has a zinc-binding carboxyl-terminal domain, whereas C is translated from an overlapping reading frame. The MeV C protein is an infectivity factor. During replication, the P protein binds incoming monomeric nucleocapsid (N) proteins with its amino-terminal domain and positions them for assembly into the nascent ribonucleocapsid. The P protein amino-terminal domain is natively unfolded (Deveaux P et al. Journal of Virology 2004; 78(21): 11632-40).

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein. In some embodiments, a ⁵ MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding V protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide 15 encoding HA protein, F protein, P protein, V protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and F protein. In some embodiments, ²⁰ a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and V protein. In some embodiments, ²⁵ a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and V protein. In some embodiments, ²⁵ a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein and C protein.

some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encod- 30 ing F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding F 35 protein and C protein.

In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and P protein. In some embodiments, a MeV vaccine of the present disclosure 40 comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and V protein. In some embodiments, a MeV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding HA protein, F protein and C protein. 45

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV HA protein and having MeV HA protein activity.

In some embodiments, MeV vaccines comprise RNA (e.g., mRNA) encoding a MeV antigenic polypeptide having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with MeV F protein and having MeV F protein activity.

A protein is considered to have HA protein activity if the protein mediates receptor binding and/or membrane fusion. MeV F protein executes membrane fusion, after receptor binding by the MeV HA protein.

A MeV vaccine may comprise, for example, at least one 60 RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MeV antigenic polypeptide identified by any one of SEQ ID NO: 47-50 (Table 14; see also amino acid sequences of Table 15).

A MeV vaccine may comprise, for example, at least one 65 RNA (e.g., mRNA) polynucleotide identified by any one of SEQ ID NO: 37, 40, 43, 46 (Table 13).

A MeV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 35, 36, 38, 39, 41, 42, 44 and 45 (Table 13).

The present disclosure is not limited by a particular strain of MeV. The strain of MeV used in a vaccine may be any strain of MeV. Non-limiting examples of strains of MeV for use as provide herein include B3/B3.1, C2, D4, D6, D7, D8, G3, H1, Moraten, Rubeovax, MVi/New Jersey.USA/45.05,

MVi/Texas.USA/4.07, AIK-C, MVi/New York.USA/26.09/ 3, MVi/California.USA/16.03, MVi/Virginia.USA/15.09, MVi/California.USA/8.04, and MVi/Pennsylvania.USA/ 20.09.

MeV proteins may be from MeV genotype D4, D5, D7, D8, D9, D11, H1, G3 or B3. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype D8. In some embodiments, a MeV HA protein or a MeV F protein is from MeV genotype B3.

Betacoronaviruses (BetaCoV)

MERS-CoV. MERS-CoV is a positive-sense, singlestranded RNA virus of the genus Betacoronavirus. The genomes are phylogenetically classified into two clades, clade A and clade B. It has a strong tropism for non-ciliated bronchial epithelial cells, evades the innate immune response and antagonizes interferon (IFN) production in infected cells. Dipeptyl peptidase 4 (DDP4, also known as CD26) has been identified as a functional cellular receptor for MERS-CoV. Its enzymatic activity is not required for infection, although its amino acid sequence is highly conserved across species and is expressed in the human bronchial epithelium and kidneys. Most infected individuals develop severe acute respiratory illnesses, including fever, cough, and shortness of breath, and the virus can be fatal. The disease may be transmitted among humans, generally among those in close contact.

The genome of MERS-CoV encodes at least four unique accessory proteins, such as 3, 4a, 4b and 5, two replicase proteins (open reading frame 1a and 1b), and four major structural proteins, including spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins (Almazan F et al. MBio 2013; 4(5):e00650-13). The accessory proteins play nonessential roles in MERS-CoV replication, but they are likely structural proteins or interferon antagonists, modulating in vivo replication efficiency and/or pathogenesis, as in the case of SARS-CoV (Almazan F et al. MBio 2013; 4(5):e00650-13; Totura A L et al. Curr Opin Virol 2012; 2(3):264-75; Scobey T et al. Proc Natl Acad Sci USA 2013; 110(40):16157-62). The other proteins of MERS-CoV maintain different functions in virus replication. The E protein, for example, involves in virulence, and deleting the E-coding gene results in replication-competent and propagation-defective viruses or attenuated viruses (Almazan F et al. MBio 2013; 4(5):e00650-13). The S protein is particularly essential in mediating virus binding to cells expressing 55 receptor dipeptidyl peptidase-4 (DPP4) through receptorbinding domain (RBD) in the S1 subunit, whereas the S2 subunit subsequently mediates virus entry via fusion of the virus and target cell membranes (Li F. J Virol 2015; 89(4): 1954-64; Raj V S et al. Nature 2013; 495(7440):251-4).

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S1 subunit of the S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding the S2 subunit of the S protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding N protein. In 5 some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly- 10 nucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E 15 protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly- 20 nucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein 25 and M protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a 30 RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a MERS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one MERS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 24-38 or 33 (Table 11; see also amino acid sequences of Table 12). 40

A MERS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide encoded by a nucleic acid (e.g., DNA) identified by any one of SEQ ID NO: 20-23 (Table 10).

The present disclosure is not limited by a particular strain 45 of MERS-CoV. The strain of MERS-CoV used in a vaccine may be any strain of MERS-CoV. Non-limiting examples of strains of MERS-CoV for use as provide herein include Riyadh_14_2013, and 2cEMC/2012, Hasa_1_2013.

SARS-CoV. The genome of SARS-CoV includes of a 50 single, positive-strand RNA that is approximately 29,700 nucleotides long. The overall genome organization of SARS-CoV is similar to that of other coronaviruses. The reference genome includes 13 genes, which encode at least 14 proteins. Two large overlapping reading frames (ORFs) 55 encompass 71% of the genome. The remainder has 12 potential ORFs, including genes for structural proteins S (spike), E (small envelope), M (membrane), and N (nucleocapsid). Other potential ORFs code for unique putative SARS-CoV-specific polypeptides that lack obvious 60 sequence similarity to known proteins. A detailed analysis of the SARS-CoV genome has been published in J Mol Biol 2003; 331: 991-1004.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) poly- 65 nucleotide encoding S protein (S, S1 and/or S2), E protein, N protein and M protein.

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In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and E protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2) and M protein.

In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and M protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), E protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding S protein (S, S1 and/or S2), M protein and N protein. In some embodiments, a SARS-CoV vaccine of the present disclosure comprises a RNA (e.g., mRNA) polynucleotide encoding E protein, M protein and N protein.

A SARS-CoV vaccine may comprise, for example, at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one SARS-CoV antigenic polypeptide identified by any one of SEQ ID NO: 29, 32 or 34 (Table 11; see also amino acid sequences of Table 12).

The present disclosure is not limited by a particular strain of SARS-CoV. The strain of SARS-CoV used in a vaccine may be any strain of SARS-CoV.

HCoV-OC43.

Human coronavirus OC43 is an enveloped, positivesense, single-stranded RNA virus in the species Betacoro-35 navirus-1 (genus Betacoronavirus, subfamily Coronavirinae, family Coronaviridae, order Nidovirales). Four HCoV-OC43 genotypes (A to D), have been identified with genotype D most likely arising from recombination. The complete genome sequencing of two genotype C and D strains and bootscan analysis shows recombination events between genotypes B and C in the generation of genotype D. Of 29 strains identified, none belong to the more ancient genotype A. Along with HCoV-229E, a species in the Alphacoronavirus genus, HCoV-OC43 are among the known viruses that cause the common cold. Both viruses can cause severe lower respiratory tract infections, including pneumonia in infants, the elderly, and immunocompromised individuals such as those undergoing chemotherapy and those with HIV-AIDS.

HCoV-HKU1.

Human coronavirus HKU1 (HCoV-H KU 1) is a positivesense, single-stranded RNA virus with the HE gene, which distinguishes it as a group 2, or betacoronavirus. It was discovered in January 2005 in two patients in Hong Kong. The genome of HCoV-HKU1 is a 29,926-nucleotide, polyadenylated RNA. The GC content is 32%, the lowest among all known coronaviruses. The genome organization is the same as that of other group II coronaviruses, with the characteristic gene order 1a, 1b, HE, S, E, M, and N. Furthermore, accessory protein genes are present between the S and E genes (ORF4) and at the position of the N gene (ORF8). The TRS is presumably located within the AAUC-UAAAC sequence, which precedes each ORF except E. As in sialodacryoadenitis virus and mouse hepatitis virus (MHV), translation of the E protein possibly occurs via an internal ribosomal entry site. The 3' untranslated region contains a predicted stem-loop structure immediately down-

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stream of the N ORF (nucleotide position 29647 to 29711). Further downstream, a pseudoknot structure is present at nucleotide position 29708 to 29760. Both RNA structures are conserved in group II coronaviruses and are critical for virus replication.

HCoV-NL63.

The RNA genome of human coronavirus NL63 (HCoV-NL63) is 27,553 nucleotides, with a poly(A) tail (FIG. 1). With a GC content of 34%, HCoV-NL63 has one of the lowest GC contents of the coronaviruses, for which GC 10 content ranges from 32 to 42%. Untranslated regions of 286 and 287 nucleotides are present at the 5' and 3' termini, respectively. Genes predicted to encode the S, E, M, and N proteins are found in the 3' part of the HCoV-NL63 genome. The HE gene, which is present in some group II coronavi- 15 ruses, is absent, and there is only a single, monocistronic accessory protein ORF (ORF3) located between the S and E genes. Subgenomic mRNAs are generated for all ORFs (S, ORF3, E, M, and N), and the core sequence of the TRS of HCoV-NL63 is defined as AACUAAA. This sequence is 20 situated upstream of every ORF except for the E ORF, which contains the suboptimal core sequence AACUAUA. Interestingly, a 13-nucleotide sequence with perfect homology to the leader sequence is situated upstream of the suboptimal E TRS. Annealing of this 13-nucleotide sequence to the leader 25 sequence may act as a compensatory mechanism for the disturbed leader-TRS/body-TRS interaction.

HCoV-229E.

Human coronavirus 229E (HCoV-229E) is a singlestranded, positive-sense, RNA virus species in the Alpha- 30 coronavirus genus of the subfamily Coronavirinae, in the family Coronaviridae, of the order Nidovirales. Along with Human coronavirus OC43, it is responsible for the common cold. HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two 35 viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is 40 vaccine comprises a RNA (e.g., mRNA) polynucleotide associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of 45 infection differs (HCoV-NL63 and HCoV-229E are two of the four human coronaviruses that circulate worldwide. These two viruses are unique in their relationship towards each other. Phylogenetically, the viruses are more closely related to each other than to any other human coronavirus, 50 yet they only share 65% sequence identity. Moreover, the viruses use different receptors to enter their target cell. HCoV-NL63 is associated with croup in children, whereas all signs suggest that the virus probably causes the common cold in healthy adults. HCoV-229E is a proven common cold 55 virus in healthy adults, so it is probable that both viruses induce comparable symptoms in adults, even though their mode of infection differs (Dijkman R. et al. J Formos Med Assoc. 2009 April; 108(4):270-9, the contents of which is incorporated herein by reference in their entirety). Combination Vaccines

Embodiments of the present disclosure also provide combination RNA (e.g., mRNA) vaccines. A "combination RNA (e.g., mRNA) vaccine" of the present disclosure refers to a vaccine comprising at least one (e.g., at least 2, 3, 4, or 5) 65 RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a combination of any two or more (or all of)

antigenic polypeptides selected from hMPV antigenic polypeptides, PIV3 antigenic polypeptides, RSV antigenic polypeptides, MeV antigenic polypeptides, and BetaCoV antigenic polypeptides (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide, and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a PIV3 antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide and a BetaCoV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) encoding a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, 60 HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, 10 SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1). encoding a RS polypeptide and a BetaCoV 10 HCoV-HKU1). encoding a RS polypeptide and a BetaCoV 10 HCoV-NL63, 10 HCoV-NL (HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic 15 polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) 20 vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, 25 HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a RSV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) 35 vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a PIV3 antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and 40 HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, 50 HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a hMPV antigenic polypeptide, a MeV antigenic 55 polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) 60 vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a MeV antigenic polypeptide.

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide 65 encoding a PIV3 antigenic polypeptide, a RSV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g.,

selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

In some embodiments, a combination RNA (e.g., mRNA) vaccine comprises a RNA (e.g., mRNA) polynucleotide encoding a RSV antigenic polypeptide, a MeV antigenic polypeptide and a BetaCoV antigenic polypeptide (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1).

Other combination respiratory virus RNA (e.g., mRNA) vaccines are encompassed by the present disclosure.

It has been discovered that the mRNA vaccines described herein are superior to current vaccines in several ways. First, the lipid nanoparticle (LNP) delivery is superior to other formulations including a protamine base approach described in the literature and no additional adjuvants are to be necessary. The use of LNPs enables the effective delivery of chemically modified or unmodified mRNA vaccines. Additionally it has been demonstrated herein that both modified and unmodified LNP formulated mRNA vaccines were superior to conventional vaccines by a significant degree. In some embodiments the mRNA vaccines of the invention are superior to conventional vaccines by a factor of at least 10 fold, 20 fold, 40 fold, 50 fold, 100 fold, 500 fold or 1,000 fold.

Although attempts have been made to produce functional RNA vaccines, including mRNA vaccines and self-replicating RNA vaccines, the therapeutic efficacy of these RNA vaccines have not yet been fully established. Quite surprisingly, the inventors have discovered, according to aspects of the invention a class of formulations for delivering mRNA vaccines in vivo that results in significantly enhanced, and in many respects synergistic, immune responses including enhanced antigen generation and functional antibody production with neutralization capability. These results can be achieved even when significantly lower doses of the mRNA are administered in comparison with mRNA doses used in other classes of lipid based formulations. The formulations of the invention have demonstrated significant unexpected in vivo immune responses sufficient to establish the efficacy of functional mRNA vaccines as prophylactic and therapeutic agents. Additionally, self-replicating RNA vaccines rely on viral replication pathways to deliver enough RNA to a cell to produce an immunogenic response. The formulations of the invention do not require viral replication to produce enough protein to result in a strong immune response. Thus, the mRNA of the invention are not self-replicating RNA and do not include components necessary for viral replication.

The invention involves, in some aspects, the surprising finding that lipid nanoparticle (LNP) formulations significantly enhance the effectiveness of mRNA vaccines, including chemically modified and unmodified mRNA vaccines. The efficacy of mRNA vaccines formulated in LNP was examined in vivo using several distinct antigens. The results presented herein demonstrate the unexpected superior efficacy of the mRNA vaccines formulated in LNP over other commercially available vaccines.

In addition to providing an enhanced immune response, the formulations of the invention generate a more rapid immune response with fewer doses of antigen than other vaccines tested. The mRNA-LNP formulations of the invention also produce quantitatively and qualitatively better immune responses than vaccines formulated in a different carriers.

The data described herein demonstrate that the formulations of the invention produced significant unexpected

improvements over existing antigen vaccines. Additionally, the mRNA-LNP formulations of the invention are superior to other vaccines even when the dose of mRNA is lower than other vaccines. Mice immunized with either 10 μ g or 2 μ g doses of an hMPV fusion protein mRNA LNP vaccine or a 5 PIV3 mRNA LNP vaccine produced neutralizing antibodies which for instance, successfully neutralized the hMPV B2 virus. A 10 µg dose of mRNA vaccine protected 100% of mice from lethal challenge and drastically reduced the viral titer after challenge (~2 log reduction). 10

Two 20 µg doses of MERS-CoV mRNA LNP vaccine significantly reduced viral load and induced significant amount of neutralizing antibodies against MERS-CoV (ECso between 500-1000). The MERS-CoV mRNA vaccine induced antibody titer was 3-5 fold better than any other 15 vaccines tested in the same model.

The LNP used in the studies described herein has been used previously to deliver siRNA in various animal models as well as in humans. In view of the observations made in association with the siRNA delivery of LNP formulations. 20 the fact that LNP is useful in vaccines is quite surprising. It has been observed that therapeutic delivery of siRNA formulated in LNP causes an undesirable inflammatory response associated with a transient IgM response, typically leading to a reduction in antigen production and a compro- 25 1-100, 2-50 or 2-100 antigenic polypeptides. mised immune response. In contrast to the findings observed with siRNA, the LNP-mRNA formulations of the invention are demonstrated herein to generate enhanced IgG levels, sufficient for prophylactic and therapeutic methods rather than transient IgM responses.

Nucleic Acids/Polynucleotides

Respiratory virus vaccines, as provided herein, comprise at least one (one or more) ribonucleic acid (RNA) (e.g., mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide selected from 35 hMPV, PIV3, RSV, MeV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides. The term "nucleic acid" includes any compound and/or substance that comprises a polymer of 40 nucleotides (nucleotide monomer). These polymers are referred to as polynucleotides. Thus, the terms "nucleic acid" and "polynucleotide" are used interchangeably.

Nucleic acids may be or may include, for example, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), 45 threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β -D-ribo configuration, α -LNA having an α -L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 50 2'-amino- α -LNA having a 2'-amino functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or chimeras or combinations thereof.

In some embodiments, polynucleotides of the present disclosure function as messenger RNA (mRNA). "Messen- 55 rally-occurring or wild-type mRNA sequence encoding a ger RNA" (mRNA) refers to any polynucleotide that encodes a (at least one) polypeptide (a naturally-occurring, non-naturally-occurring, or modified polymer of amino acids) and can be translated to produce the encoded polypeptide in vitro, in vivo, in situ or ex vivo. The skilled artisan 60 will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite "T"s in a representative DNA sequence but where the sequence represents RNA (e.g., mRNA), the "T"s would be substituted for "U"s. Thus, any of the RNA polynucleotides 65 encoded by a DNA identified by a particular sequence identification number may also comprise the corresponding

RNA (e.g., mRNA) sequence encoded by the DNA, where each "T" of the DNA sequence is substituted with "U."

The basic components of an mRNA molecule typically include at least one coding region, a 5' untranslated region (UTR), a 3' UTR, a 5' cap and a poly-A tail. Polynucleotides of the present disclosure may function as mRNA but can be distinguished from wild-type mRNA in their functional and/or structural design features, which serve to overcome existing problems of effective polypeptide expression using nucleic-acid based therapeutics.

In some embodiments, a RNA polynucleotide of an RNA (e.g., mRNA) vaccine encodes 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9 or 9-10 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 antigenic polypeptides. In some embodiments, a RNA (e.g., mRNA) polynucleotide of a respiratory virus vaccine encodes at least 100 or at least 200 antigenic polypeptides. In some embodiments, a RNA polynucleotide of an respiratory virus vaccine encodes 1-10, 5-15, 10-20, 15-25, 20-30, 25-35, 30-40, 35-45, 40-50, 1-50,

Polynucleotides of the present disclosure, in some embodiments, are codon optimized. Codon optimization methods are known in the art and may be used as provided herein. Codon optimization, in some embodiments, may be used to match codon frequencies in target and host organisms to ensure proper folding; bias GC content to increase mRNA stability or reduce secondary structures; minimize tandem repeat codons or base runs that may impair gene construction or expression; customize transcriptional and translational control regions; insert or remove protein trafficking sequences; remove/add post translation modification sites in encoded protein (e.g. glycosylation sites); add, remove or shuffle protein domains; insert or delete restriction sites; modify ribosome binding sites and mRNA degradation sites; adjust translational rates to allow the various domains of the protein to fold properly; or to reduce or eliminate problem secondary structures within the polynucleotide. Codon optimization tools, algorithms and services are known in the art-non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park Calif.) and/or proprietary methods. In some embodiments, the open reading frame (ORF) sequence is optimized using optimization algorithms.

In some embodiments, a codon optimized sequence shares less than 95% sequence identity, less than 90% sequence identity, less than 85% sequence identity, less than 80% sequence identity, or less than 75% sequence identity to a naturally-occurring or wild-type sequence (e.g., a natupolypeptide or protein of interest (e.g., an antigenic protein or antigenic polypeptide)).

In some embodiments, a codon-optimized sequence shares between 65% and 85% (e.g., between about 67% and about 85%, or between about 67% and about 80%) sequence identity to a naturally-occurring sequence or a wild-type sequence (e.g., a naturally-occurring or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)). In some embodiments, a codon-optimized sequence shares between 65% and 75%, or about 80% sequence identity to a naturally-occurring sequence or wild-type sequence (e.g., a naturally-occurring

or wild-type mRNA sequence encoding a polypeptide or protein of interest (e.g., an antigenic protein or polypeptide)).

In some embodiments a codon-optimized RNA (e.g., mRNA) may, for instance, be one in which the levels of G/C are enhanced. The G/C-content of nucleic acid molecules may influence the stability of the RNA. RNA having an increased amount of guanine (G) and/or cytosine (C) residues may be functionally more stable than nucleic acids containing a large amount of adenine (A) and thymine (T) or 10 uracil (U) nucleotides. WO02/098443 discloses a pharmaceutical composition containing an mRNA stabilized by sequence modifications in the translated region. Due to the degeneracy of the genetic code, the modifications work by substituting existing codons for those that promote greater 15 RNA stability without changing the resulting amino acid. The approach is limited to coding regions of the RNA. Antigens/Antigenic Polypeptides

In some embodiments, an antigenic polypeptide (e.g., a hMPV, PIV3, RSV, MeV or BetaCoV antigenic polypeptide) 20 is longer than 25 amino acids and shorter than 50 amino acids. Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a 25 single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. Polypeptides may also comprise single chain polypeptides or multichain polypeptides, such as antibodies or insulin, and may be associated or linked to each other. Most commonly, disulfide linkages are 30 found in multichain polypeptides. The term "polypeptide" may also apply to amino acid polymers in which at least one amino acid residue is an artificial chemical analogue of a corresponding naturally-occurring amino acid.

A "polypeptide variant" is a molecule that differs in its 35 amino acid sequence relative to a native sequence or a reference sequence. Amino acid sequence variants may possess substitutions, deletions, insertions, or a combination of any two or three of the foregoing, at certain positions within the amino acid sequence, as compared to a native 40 sequence or a reference sequence. Ordinarily, variants possess at least 50% identity to a native sequence or a reference sequence. In some embodiments, variants share at least 80% identity or at least 90% identity with a native sequence or a reference sequence.

In some embodiments "variant mimics" are provided. A "variant mimic" contains at least one amino acid that would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoroserine. Alternatively, variant mimics may result in deacti- 50 vation or in an inactivated product containing the mimic. For example, phenylalanine may act as an inactivating substitution for tyrosine, or alanine may act as an inactivating substitution for serine.

evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is important for reliable prediction of gene function in newly sequenced genomes.

"Analogs" is meant to include polypeptide variants that differ by one or more amino acid alterations, for example, substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

The present disclosure provides several types of compositions that are polynucleotide or polypeptide based, includ-

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ing variants and derivatives. These include, for example, substitutional, insertional, deletion and covalent variants and derivatives. The term "derivative" is synonymous with the term "variant" and generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or a starting molecule.

As such, polynucleotides encoding peptides or polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference sequences, in particular the polypeptide sequences disclosed herein, are included within the scope of this disclosure. For example, sequence tags or amino acids, such as one or more lysines, can be added to peptide sequences (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide detection, purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal residues or N-terminal residues) alternatively may be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence that is soluble, or linked to a solid support.

"Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. Substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more (e.g., 3, 4 or 5) amino acids have been substituted in the same molecule.

As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of nonconservative substitutions include the substitution of a nonpolar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

"Features" when referring to polypeptide or polynucle-"Orthologs" refers to genes in different species that 55 otide are defined as distinct amino acid sequence-based or nucleotide-based components of a molecule respectively. Features of the polypeptides encoded by the polynucleotides include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, ter-60 mini and any combination(s) thereof.

As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

As used herein when referring to polypeptides the terms "site" as it pertains to amino acid based embodiments is used

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synonymously with "amino acid residue" and "amino acid side chain." As used herein when referring to polynucleotides the terms "site" as it pertains to nucleotide based embodiments is used synonymously with "nucleotide." A site represents a position within a peptide or polypeptide or 5 polynucleotide that may be modified, manipulated, altered, derivatized or varied within the polypeptide-based or polynucleotide-based molecules.

As used herein the terms "termini" or "terminus" when referring to polypeptides or polynucleotides refers to an 10 extremity of a polypeptide or polynucleotide respectively. Such extremity is not limited only to the first or final site of the polypeptide or polynucleotide but may include additional amino acids or nucleotides in the terminal regions. Polypeptide-based molecules may be characterized as hav- 15 ing both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent 20 forces (multimers, oligomers). These proteins have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino 30 acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein having a length of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or longer than 100 amino acids. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 (contiguous) 35 amino acids that are 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical to any of the sequences described herein can be utilized in accordance with the disclosure. In some embodiments, a polypeptide includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences pro- 40 vided herein or referenced herein. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 amino acids that are greater than 80%, 90%, 95%, or 100% identical to any of the sequences described herein, wherein the protein has a stretch of 5, 10, 15, 20, 25, or 30 amino 45 acids that are less than 80%, 75%, 70%, 65% to 60% identical to any of the sequences described herein can be utilized in accordance with the disclosure.

Polypeptide or polynucleotide molecules of the present disclosure may share a certain degree of sequence similarity 50 or identity with the reference molecules (e.g., reference polypeptides or reference polynucleotides), for example, with art-described molecules (e.g., engineered or designed molecules or wild-type molecules). The term "identity," as known in the art, refers to a relationship between the 55 sequences of two or more polypeptides or polynucleotides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between two sequences as determined by the number of matches between strings of two or more amino acid residues 60 or nucleic acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (e.g., "algorithms"). Identity of related peptides can be readily 65 calculated by known methods. "% identity" as it applies to polypeptide or polynucleotide sequences is defined as the

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percentage of residues (amino acid residues or nucleic acid residues) in the candidate amino acid or nucleic acid sequence that are identical with the residues in the amino acid sequence or nucleic acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity. Methods and computer programs for the alignment are well known in the art. Identity depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation. Generally, variants of a particular polynucleotide or polypeptide have at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, et al. (1997)." Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," Nucleic Acids Res. 25:3389-3402). Another popular local alignment technique is based on the Smith-Waterman algorithm (Smith, T. F. & Waterman, M. S. (1981) "Identification of common molecular subsequences." J. Mol. Biol. 147:195-197). A general global alignment technique based on dynamic programming is the Needleman-Wunsch algorithm (Needleman, S. B. & Wunsch, C. D. (1970) "A general method applicable to the search for similarities in the amino acid sequences of two proteins." J. Mol. Biol. 48:443-453). More recently, a Fast Optimal Global Sequence Alignment Algorithm (FOGSAA) was developed that purportedly produces global alignment of nucleotide and protein sequences faster than other optimal global alignment methods, including the Needleman-Wunsch algorithm. Other tools are described herein, specifically in the definition of "identity" below.

As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, e.g. between nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Polymeric molecules (e.g. nucleic acid molecules (e.g. DNA molecules and/or RNA molecules) and/or polypeptide molecules) that share a threshold level of similarity or identity determined by alignment of matching residues are termed homologous. Homology is a qualitative term that describes a relationship between molecules and can be based upon the quantitative similarity or identity. Similarity or identity is a quantitative term that defines the degree of sequence match between two compared sequences. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). Two polynucleotide sequences are considered homologous if the polypeptides they encode are at least 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4-5 uniquely specified amino acids. Two protein sequences are considered homologous if the proteins are at least 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least 20 amino acids.

Homology implies that the compared sequences diverged in evolution from a common origin. The term "homolog" refers to a first amino acid sequence or nucleic acid sequence (e.g., gene (DNA or RNA) or protein sequence) that is related to a second amino acid sequence or nucleic acid 5 sequence by descent from a common ancestral sequence. The term "homolog" may apply to the relationship between genes and/or proteins separated by the event of speciation or to the relationship between genes and/or proteins separated by the event of genetic duplication. "Orthologs" are genes 10 (or proteins) in different species that evolved from a common ancestral gene (or protein) by speciation. Typically, orthologs retain the same function in the course of evolution. "Paralogs" are genes (or proteins) related by duplication within a genome. Orthologs retain the same function in the 15 course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.

The term "identity" refers to the overall relatedness between polymeric molecules, for example, between polynucleotide molecules (e.g. DNA molecules and/or RNA 20 molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleic acid sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second 25 nucleic acid sequences for optimal alignment and nonidentical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, 30 at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the 35 molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the 40 two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleic acid sequences can be determined using methods such as those described in 45 Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis 50 of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity 55 between two nucleic acid sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM 120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The 60 percent identity between two nucleic acid sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those 65 disclosed in Carillo, H., and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference.

Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., et al., *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. et al., *J. Molec. Biol.*, 215, 403 (1990)).

Multiprotein and Multicomponent Vaccines

The present disclosure encompasses respiratory virus vaccines comprising multiple RNA (e.g., mRNA) polynucleotides, each encoding a single antigenic polypeptide, as well as respiratory virus vaccines comprising a single RNA polynucleotide encoding more than one antigenic polypeptide (e.g., as a fusion polypeptide). Thus, a vaccine composition comprising a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a first antigenic polypeptide and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a second antigenic polypeptide encompasses (a) vaccines that comprise a first RNA polynucleotide encoding a first antigenic polypeptide and a second RNA polynucleotide encoding a second antigenic polypeptide, and (b) vaccines that comprise a single RNA polynucleotide encoding a first and second antigenic polypeptide (e.g., as a fusion polypeptide). RNA (e.g., mRNA) vaccines of the present disclosure, in some embodiments, comprise 2-10 (e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10), or more, RNA polynucleotides having an open reading frame, each of which encodes a different antigenic polypeptide (or a single RNA polynucleotide encoding 2-10, or more, different antigenic polypeptides). The antigenic polypeptides may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides.

In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral capsid protein, a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral premembrane/membrane protein, and a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral envelope protein. In some embodiments, a respiratory virus vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral fusion (F) protein and a RNA polynucleotide having an open reading frame encoding a viral major surface glycoprotein (G protein). In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral F protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a viral G protein. In some embodiments, a vaccine comprises a RNA (e.g., mRNA) polynucleotide having an open reading frame encoding a HN protein.

In some embodiments, a multicomponent vaccine comprises at least one RNA (e.g., mRNA) polynucleotide encoding at least one antigenic polypeptide fused to a signal peptide (e.g., any one of SEQ ID NO: 15-19). The signal peptide may be fused at the N-terminus or the C-terminus of an antigenic polypeptide. An antigenic polypeptide fused to a signal peptide may be selected from hMPV, PIV3, RSV, MEV and BetaCoV (e.g., selected from MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and HCoV-HKU1) antigenic polypeptides. Signal Peptides

In some embodiments, antigenic polypeptides encoded by respiratory virus RNA (e.g., mRNA) polynucleotides comprise a signal peptide. Signal peptides, comprising the

N-terminal 15-60 amino acids of proteins, are typically needed for the translocation across the membrane on the secretory pathway and, thus, universally control the entry of most proteins both in eukaryotes and prokaryotes to the secretory pathway. Signal peptides generally include three 5 regions: an N-terminal region of differing length, which usually comprises positively charged amino acids; a hydrophobic region; and a short carboxy-terminal peptide region. In eukaryotes, the signal peptide of a nascent precursor protein (pre-protein) directs the ribosome to the rough 10 endoplasmic reticulum (ER) membrane and initiates the transport of the growing peptide chain across it for processing. ER processing produces mature proteins, wherein the signal peptide is cleaved from precursor proteins, typically by a ER-resident signal peptidase of the host cell, or they 15 remain uncleaved and function as a membrane anchor. A signal peptide may also facilitate the targeting of the protein to the cell membrane. The signal peptide, however, is not responsible for the final destination of the mature protein. Secretory proteins devoid of additional address tags in their 20 sequence are by default secreted to the external environment. During recent years, a more advanced view of signal peptides has evolved, showing that the functions and immunodominance of certain signal peptides are much more versatile than previously anticipated.

Respiratory virus vaccines of the present disclosure may comprise, for example, RNA (e.g., mRNA) polynucleotides encoding an artificial signal peptide, wherein the signal peptide coding sequence is operably linked to and is in frame with the coding sequence of the antigenic polypeptide. Thus, 30 respiratory virus vaccines of the present disclosure, in some embodiments, produce an antigenic polypeptide comprising an antigenic polypeptide (e.g., hMPV, PIV3, RSV, MeV or BetaCoV) fused to a signal peptide. In some embodiments, a signal peptide is fused to the N-terminus of the antigenic 35 polypeptide. In some embodiments, a signal peptide is fused to the C-terminus of the antigenic polypeptide.

In some embodiments, the signal peptide fused to the antigenic polypeptide is an artificial signal peptide. In some embodiments, an artificial signal peptide fused to the anti- 40 genic polypeptide encoded by the RNA (e.g., mRNA) vaccine is obtained from an immunoglobulin protein, e.g., an IgE signal peptide or an IgG signal peptide. In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine is an Ig 45 heavy chain epsilon-1 signal peptide (IgE HC SP) having the sequence of: MDWTWILFLVAAATRVHS (SEQ ID NO: 16). In some embodiments, a signal peptide fused to the antigenic polypeptide encoded by the (e.g., mRNA) RNA (e.g., mRNA) vaccine is an IgGk chain V-III region HAH 50 signal peptide (IgGk SP) having the sequence of MET-PAQLLFLLLWLPDTTG (SEQ ID NO: 15). In some embodiments, the signal peptide is selected from: Japanese encephalitis PRM signal sequence (MLGSNSGQRV-VFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal 55 sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVS-LAIVTACAGA; SEQ ID NO: 19).

In some embodiments, the antigenic polypeptide encoded by a RNA (e.g., mRNA) vaccine comprises an amino acid 60 sequence identified by any one of SEQ ID NO: 5-8, 12-13, 24-34, 47-50 or 54-56 (Tables 3, 6, 11, 14 or 17; see also amino acid sequences of Tables 4, 7, 12 or 15) fused to a signal peptide identified by any one of SEQ ID NO: 15-19 (Table 8). The examples disclosed herein are not meant to be 65 limiting and any signal peptide that is known in the art to facilitate targeting of a protein to ER for processing and/or

targeting of a protein to the cell membrane may be used in accordance with the present disclosure.

A signal peptide may have a length of 15-60 amino acids. For example, a signal peptide may have a length of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60 amino acids. In some embodiments, a signal peptide has a length of 20-60, 25-60, 30-60, 35-60, 40-60, 45-60, 50-60, 55-60, 15-55, 20-55, 25-55, 30-55, 35-55, 40-55, 45-55, 50-55, 15-50, 20-50, 25-50, 30-50, 35-50, 40-50, 45-50, 15-45, 20-45, 25-45, 30-45, 35-45, 40-45, 15-40, 20-40, 25-40, 30-40, 35-40, 15-35, 20-35, 25-35, 30-35, 15-30, 20-30, 25-30, 15-25, 20-25, or 15-20 amino acids.

A signal peptide is typically cleaved from the nascent polypeptide at the cleavage junction during ER processing. The mature antigenic polypeptide produce by a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure typically does not comprise a signal peptide.

Chemical Modifications

Respiratory virus vaccines of the present disclosure, in some embodiments, comprise at least RNA (e.g. mRNA) polynucleotide having an open reading frame encoding at least one antigenic polypeptide that comprises at least one 25 chemical modification.

The terms "chemical modification" and "chemically modified" refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribonucleosides or deoxyribnucleosides in at least one of their position, pattern, percent or population. Generally, these terms do not refer to the ribonucleotide modifications in naturally occurring 5'-terminal mRNA cap moieties. With respect to a polypeptide, the term "modification" refers to a modification relative to the canonical set 20 amino acids. Polypeptides, as provided herein, are also considered "modified" of they contain amino acid substitutions, insertions or a combination of substitutions and insertions.

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise various (more than one) different modifications. In some embodiments, a particular region of a polynucleotide contains one, two or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified RNA polynucleotide (e.g., a modified mRNA polynucleotide), introduced to a cell or organism, exhibits reduced degradation in the cell or organism, respectively, relative to an unmodified polynucleotide (e.g., a modified mRNA polynucleotide), introduced into a cell or organism, may exhibit reduced immunogenicity in the cell or organism, respectively (e.g., a reduced innate response).

Modifications of polynucleotides include, without limitation, those described herein. Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) may comprise modifications that are naturally-occurring, non-naturally-occurring or the polynucleotide may comprise a combination of naturally-occurring and non-naturally-occurring modifications. Polynucleotides may include any useful modification, for example, of a sugar, a nucleobase, or an internucleoside linkage (e.g., to a linking phosphate, to a phosphodiester linkage or to the phosphodiester backbone).

Polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides), in some embodiments, comprise non-natural modified nucleotides that are introduced during synthesis or post-synthesis of the polynucleotides to achieve desired functions or properties. The modifications may be present on an internucleotide linkages, purine or pyrimidine

bases, or sugars. The modification may be introduced with chemical synthesis or with a polymerase enzyme at the terminal of a chain or anywhere else in the chain. Any of the regions of a polynucleotide may be chemically modified.

The present disclosure provides for modified nucleosides 5 and nucleotides of a polynucleotide (e.g., RNA polynucleotides, such as mRNA polynucleotides). A "nucleoside" refers to a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a 10 derivative thereof (also referred to herein as "nucleobase"). A nucleotide" refers to a nucleoside, including a phosphate group. Modified nucleotides may by synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or 15 non-natural nucleosides. Polynucleotides may comprise a region or regions of linked nucleosides. Such regions may have variable backbone linkages. The linkages may be standard phosphdioester linkages, in which case the polynucleotides would comprise regions of nucleotides. 20

Modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrange-25 ment of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide 30 inosine and adenine, cytosine or uracil. Any combination of base/sugar or linker may be incorporated into polynucleotides of the present disclosure.

Modifications of polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) that are useful in the 35 vaccines of the present disclosure include, but are not limited to the following: 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-N6-methyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-glycinylcarbamoyladenosine; N6-isopentenyladenosine; 40 N6-methyladenosine; N6-threonylcarbamoyladenosine; 1,2'-O-dimethyladenosine; 1-methyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine; 2'-O- 45 methyladenosine; 2'-O-ribosyladenosine (phosphate); Isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; N6,2'-O-dimethyladenosine; N6,2'-O-dimethyladenosine; N6,N6,2'-O-trimethyladenosine; N6,N6-dimethyladenosine; N6-acetyladenosine; 50 N6-hydroxynorvalylcarbamoyladenosine; N6-methyl-N6threonylcarbamoyladenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyl-adenosine; N6, N6 (dimethyl)adenine; N6-cishydroxy-isopentenyl-adenosine; α -thio-adenosine; 2 55 (amino)adenine; 2 (aminopropyl)adenine; 2 (methylthio) N6 (isopentenyl)adenine; 2-(alkyl)adenine; 2-(aminoalkyl)adenine; 2-(aminopropyl)adenine; 2-(halo)adenine; 2-(halo) adenine; 2-(propyl)adenine; 2'-Amino-2'-deoxy-ATP; 2'-Azido-2'-deoxy-ATP; 2'-Deoxy-2'-a-aminoadenosine TP; 60 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; (deaza)adenine; 8 (alkenyl)adenine; 8 (alkynyl)adenine; 8 (amino)adenine; 8 (thioalkyl)adenine; 8-(alkenyl)adenine; 8-(alkyl)adenine; 8-(alkynyl)adenine; 8-(amino)adenine; 65 8-(halo)adenine; 8-(hydroxyl)adenine; 8-(thioalkyl)adenine; 8-(thiol)adenine; 8-azido-adenosine; aza adenine; deaza

adenine; N6 (methyl)adenine; N6-(isopentyl)adenine; 7-deaza-8-aza-adenosine; 7-methyladenine; 1-Deazaadenosine TP; 2'Fluoro-N6-Bz-deoxyadenosine TP; 2'-OMe-2-Amino-ATP; 2'O-methyl-N6-Bz-deoxyadenosine TP; 2'-a-Ethynyladenosine TP; 2-aminoadenine; 2-Aminoadenosine TP; 2-Amino-ATP; 2'-a-Trifluoromethyladenosine TP; 2-Azidoadenosine TP; 2'-b-Ethynyladenosine TP; 2-Bromoadenosine TP; 2'-b-Trifluoromethyladenosine TP: 2-Chloroadenosine TP; 2'-Deoxy-2', 2'-difluoroadenosine TP; 2'-Deoxy-2'-a-mercaptoadenosine TP; 2'-Deoxy-2'-athiomethoxyadenosine TP; 2'-Deoxy-2'-b-aminoadenosine TP; 2'-Deoxy-2'-b-azidoadenosine TP; 2'-Deoxy-2'-b-bromoadenosine TP; 2'-Deoxy-2'-b-chloroadenosine TP; 2'-Deoxy-2'-b-fluoroadenosine TP; 2'-Deoxy-2'-b-iodoadenosine TP; 2'-Deoxy-2'-b-mercaptoadenosine TP; 2'-Deoxy-2'-bthiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-lodoadenosine TP; 2-Mercaptoadenosine TP; 2-methoxy-adenine; 2-methylthio-adenine; 2-Trifluoromethyladenosine TP; 3-Deaza-3-bromoadenosine TP; 3-Deaza-3-chloroadenosine TP: 3-Deaza-3-fluoroadenosine TP: 3-Deaza-3-iodoadenosine TP; 3-Deazaadenosine TP; 4'-Azidoadenosine TP; 4'-Carbocyclic adenosine TP; 4'-Ethynyladenosine TP; 5'-Homo-adenosine TP; 8-Aza-ATP; 8-bromo-adenosine TP; 8-Trifluoromethyladenosine TP; 9-Deazaadenosine TP; 2-aminopurine; 7-deaza-2,6-diaminopurine; 7-deaza-8-aza-2,6-diaminopurine; 7-deaza-8-aza-2-aminopurine; 2,6-diaminopurine; 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine; 2-thiocytidine; 3-methylcytidine; 5-formylcytidine; 5-hydroxymethylcytidine; 5-methylcytidine; N4-acetylcytidine; 2'-O-methylcytidine; 2'-O-methylcytidine; 5,2'-O-dimethylcytidine; 5-formyl-2'-O-methylcytidine; Lysidine; N4,2'-O-dimethylcytidine; N4-acetyl-2'-O-methylcytidine; N4-methylcytidine; N4,N4-Dimethyl-2'-OMe-Cytidine TP; 4-methylcytidine; 5-aza-cytidine; Pseudo-iso-cytidine; pyrrolo-cytidine; α-thio-cytidine; 2-(thio)cytosine; 2'-Amino-2'-deoxy-CTP; 2'-Azido-2'-deoxy-CTP; 2'-Deoxy-2'-aaminocytidine TP; 2'-Deoxy-2'-a-azidocytidine TP; 3 (deaza) 5 (aza)cytosine; 3 (methyl)cytosine; 3-(alkyl)cytosine; 3-(deaza) 5 (aza)cytosine; 3-(methyl)cytidine; 4,2'-Odimethylcytidine; 5 (halo)cytosine; 5 (methyl)cytosine; 5 (propynyl)cytosine; 5 (trifluoromethyl)cytosine; 5-(alkyl) cytosine; 5-(alkynyl)cytosine; 5-(halo)cytosine; 5-(propynyl)cytosine; 5-(trifluoromethyl)cytosine; 5-bromo-cytidine; 5-iodo-cytidine; 5-propynyl cytosine; 6-(azo)cytosine; 6-aza-cytidine; aza cytosine; deaza cytosine; N4 (acetyl) cytosine; 1-methyl-1-deaza-pseudoisocytidine; 1-methylpseudoisocvtidine; 2-methoxy-5-methyl-cytidine: 2-methoxy-cytidine; 2-thio-5-methyl-cytidine; 4-methoxy-1-methyl-pseudoisocytidine; 4-methoxy-pseudoisocytidine; 4-thio-1-methyl-1-deaza-pseudoisocytidine; 4-thio-1methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-azazebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromo-vinyl)cytidine TP; 2,2'-anhydro-cytidine TP hydrochloride; 2'Fluor-N4-Bz-cytidine TP; 2'Fluoro-N4-Acetyl-cytidine TP; 2'-O-Methyl-N4-Acetyl-cytidine TP; 2'O-methyl-N4-Bz-cytidine TP; 2'-a-Ethynylcytidine TP; 2'-a-Trifluoromethylcytidine TP; 2'-b-Ethynylcytidine TP; 2'-b-Trifluoromethylcytidine TP; 2'-Deoxy-2', 2'-difluorocytidine TP; 2'-Deoxy-2'-a-mercaptocytidine TP; 2'-Deoxy-2'-a-thiomethoxycytidine TP; 2'-Deoxy-2'-b-aminocytidine TP; 2'-Deoxy-2'-b-azidocytidine TP; 2'-Deoxy-2'-b-bromocytidine TP; 2'-Deoxy-2'-bchlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-Deoxy-2'-b-mercaptocytidine TP; 2'-Deoxy-2'-b-thiomethoxycytidine TP; 2'-O-Methyl-5-(1-propynyl)cytidine TP; 3'-Ethynylcytidine TP; 4'-Azidocytidine TP; 4'-Carbocyclic cytidine TP; 4'-Ethynylcytidine

methyluridine;

TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2thiocytidine TP; 5-(4-Amino-phenyl)-2-thiocytidine TP; 5-Aminoallyl-CTP; 5-Cyanocytidine TP; 5-Ethynylara-cytidine TP; 5-Ethynylcytidine TP; 5'-Homo-cytidine TP; 5-Methoxycytidine TP; 5-Trifluoromethyl-Cytidine TP; 5 N4-Amino-cytidine TP; N4-Benzoyl-cytidine TP; Pseudoisocytidine; 7-methylguanosine; N2,2'-O-dimethylguanosine; N2-methylguanosine; Wyosine; 1,2'-O-dimethylguanosine; 1-methylguanosine; 2'-O-methylguanosine; 2'-O-ribosylguanosine (phosphate); 2'-O-methylguanosine; 10 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7deazaguanosine; 7-cyano-7-deazaguanosine; Archaeosine; Methylwyosine; N2,7-dimethylguanosine; N2,N2,2'-Otrimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thio- 15 7-deaza-guanosine; 8-oxo-guanosine; guanosine; N1-methyl-guanosine; α -thio-guanosine; 2 (propyl)guanine; 2-(alkyl)guanine; 2'-Amino-2'-deoxy-GTP; 2'-Azido-2'-deoxy-GTP; 2'-Deoxy-2'-a-aminoguanosine TP; 2'-Deoxy-2'a-azidoguanosine TP; 6 (methyl)guanine; 6-(alkyl)guanine; 20 6-(methyl)guanine; 6-methyl-guanosine; 7 (alkyl)guanine; 7 (deaza)guanine; 7 (methyl)guanine; 7-(alkyl)guanine; 7-(deaza)guanine; 7-(methyl)guanine; 8 (alkyl)guanine; 8 (alkynyl)guanine; 8 (halo)guanine; 8 (thioalkyl)guanine; 8-(alkenyl)guanine; 8-(alkyl)guanine; 8-(alkynyl)guanine; 25 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine; deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl- 30 7-deaza-8-aza-guanosine; guanosine; 7-methyl-8-oxoguanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP: 2'Fluoro-N2-isobutylguanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-Trifluoromethylguanosine TP; 35 2'-b-Ethynylguanosine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2', 2'-difluoroguanosine TP; 2'-Deoxy-2'-amercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-bazidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 40 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP; 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 45 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deazaguanosine TP: N2-isobutyl-guanosine TP: 1-methylinosine; 1,2'-O-dimethylinosine; 2'-O-methylinosine; Inosine: 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; 50 allyamino-thymidine; aza thymidine; deaza thymidine; deoxy-thymidine; 2'-O-methyluridine; 2-thiouridine; 3-methyluridine; 5-carboxymethyluridine; 5-hydroxyuridine; 5-methyluridine; 5-taurinomethyl-2-thiouridine; 5-taurinomethyluridine; Dihydrouridine; Pseudouridine; (3-(3- 55 amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5carboxypropyl)pseudouridine; 1-methylpseduouridine; 1-methyl-pseudouridine; 2'-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2'-O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2'-O-dimethy- 60 luridine; 3-Methyl-pseudo-Uridine TP; 4-thiouridine; 5-(carboxyhydroxymethyl)uridine; 5-(carboxyhydroxymethyl)uridine methyl ester; 5,2'-O-dimethyluridine; 5,6-dihydro-uridine; 5-aminomethyl-2-thiouridine; 5-carbamoylmethyl-2'-O-methyluridine; 5-carbamoylmethyluridine; 65 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2'-O-

5-carboxymethylaminomethyl-2-thiouri-

5-carboxymethylaminomethyl-2-thiouridine; dine; 5-carboxymethylaminomethyluridine; 5-carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP: 5-methoxycarbonylmethyl-2'-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid-Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methylpseudo-uridine; uridine 5-oxyacetic acid; uridine 5-oxyacetic acid methyl ester; 3-(3-Amino-3-carboxypropyl)-Uridine TP; 5-(iso-Pentenylaminomethyl)-2-thiouridine TP; 5-(iso-Pentenylaminomethyl)-2'-O-methyluridine TP; 5-(iso-Pentenylaminomethyl)uridine TP; 5-propynyl uracil; α -thio-uridine; 1 (aminoalkylamino-carbonylethylenyl)-2 (thio)-pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminoalkylaminocarbo-(thio)pseudouracil: nvlethvlenvl)-4 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethvlenvl)-pseudouracil; 1 substituted 2(thio)-pseudouracil; 1 substituted 2,4-(dithio)pseudouracil; 1 substituted 4 (thio) pseudouracil; 1 substituted pseudouracil; 1-(aminoalkylamino-carbonylethylenyl)-2-(thio)-pseudouracil; 1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP; 1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-UTP; 1-Methyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio)psuedouracil; 2' methyl, 2'amino, 2' azido, 2'fluro-guanosine; 2'-Amino-2'-deoxy-UTP; 2'-Azido-2'-deoxy-UTP; 2'-Azido-deoxyuridine TP; 2'-O-methylpseudouridine; 2' deoxy uridine; 2' fluorouridine; 2'-Deoxy-2'-a-aminouridine TP; 2'-Deoxy-2'-a-azidouridine TP; 2-methylpseudouridine; 3 (3 amino-3 carboxypropyl)uracil; 4 (thio)pseudouracil; 4-(thio)pseudouracil; 4-(thio)uracil; 4-thiouracil; 5 (1,3-diazole-1-alkyl)uracil; 5 (2-aminopropyl)uracil; 5 (aminoalkyl)uracil; 5 (dimethylaminoalkyl)uracil; 5 (guanidiniumalkyl)uracil; 5 (methoxycarbonylmethyl)-2-(thio)uracil; 5 (methoxycarbonyl-methyl)uracil; 5 (methyl) 2 (thio)uracil; 5 (methyl) 2,4 (dithio)uracil; 5 (methyl) 4 (thio)uracil; 5 (methylaminomethyl)-2 (thio)uracil; 5 (methylaminomethyl)-2,4 (dithio)uracil; 5 (methylaminomethyl)-4 (thio) uracil; 5 (propynyl)uracil; 5 (trifluoromethyl)uracil; 5-(2aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; (dithio)pseudouracil; 5-(alkyl)-4 5-(alkyl)-2,4 (thio) pseudouracil; 5-(alkyl)pseudouracil; 5-(alkyl)uracil; 5-(alkynyl)uracil; 5-(allylamino)uracil; 5-(cyanoalkyl)uracil; 5-(dialkylaminoalkyl)uracil; 5-(dimethylaminoalkyl) uracil; 5-(guanidiniumalkyl)uracil; 5-(halo)uracil; 5-(1,3-diazole-1-alkyl)uracil; 5-(methoxy)uracil; 5-(methoxycarbonylmethyl)-2-(thio)uracil; 5-(methoxycarbonyl-methyl)uracil; 5-(methyl) 2(thio)uracil; 5-(methyl) 2,4 (dithio)uracil; 5-(methyl) 4 (thio)uracil; 5-(methyl)-2-(thio)pseudouracil; 5-(methyl)-2,4 (dithio)pseudouracil; 5-(methyl)-4 (thio)pseudouracil; 5-(methyl)pseudouracil; 5-(methylaminomethyl)-2 (thio)uracil; 5-(methylaminomethyl)-2,4(dithio)uracil; 5-(methylaminomethyl)-4-(thio) uracil: 5-(propynyl)uracil; 5-(trifluoromethyl)uracil; 5-aminoallyl-uridine; 5-bromo-uridine; 5-iodo-uridine;

5-uracil; 6 (azo)uracil; 6-(azo)uracil; 6-aza-uridine; allyamino-uracil; aza uracil; deaza uracil; N3 (methyl)uracil; Pseudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thiopseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1deaza-pseudouridine; 1-propynyl-uridine; 1-taurinomethyl-1-methyl-uridine; 1-taurinomethyl-4-thio-uridine; 1-taurinomethyl-pseudouridine; 2-methoxy-4-thio-pseudouridine; 2-thio-1-methyl-1-deaza-pseudouridine; 2-thio-1methyl-pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihy- 5 dropseudouridine; 2-thio-dihydrouridine; 2-thio-4-methoxy-2-thio-pseudouridine; pseudouridine; 4-methoxy-pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine; Dihydropseudouridine; (±) 1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-Hy- 10 droxypropyl)pseudouridine TP; (2S)-1-(2-Hydroxypropyl) pseudouridine TP; (E)-5-(2-Bromo-vinyl)ara-uridine TP; (E)-5-(2-Bromo-vinyl)uridine TP; (Z)-5-(2-Bromo-vinyl) ara-uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-(2,2,3,3,3-Pentafluoropro- 15 pyl)pseudouridine TP; 1-(2,2-Diethoxyethyl)pseudouridine TP; 1-(2,4,6-Trimethylbenzyl)pseudouridine TP; 1-(2,4,6-Trimethyl-benzyl)pseudo-UTP; 1-(2,4,6-Trimethyl-phenyl) pseudo-UTP; 1-(2-Amino-2-carboxyethyl)pseudo-UTP; 1-(2-Amino-ethyl)pseudo-UTP; 1-(2-Hvdroxvethvl) 20 pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine TP; 1-(3,4-Bis-trifluoromethoxybenzyl)pseudouridine TP; 1-(3, 4-Dimethoxybenzyl)pseudouridine TP; 1-(3-Amino-3-carboxypropyl)pseudo-UTP; 1-(3-Amino-propyl)pseudo-UTP; 1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP; 1-(4- 25 Amino-4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl) pseudo-UTP; 1-(4-Amino-butyl)pseudo-UTP; 1-(4-Aminophenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl) pseudouridine TP; 1-(4-Fluorobenzyl)pseudouridine TP; 30 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonylbenzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxyphenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl) 35 pseudouridine TP; 1-(4-Nitro-benzyl)pseudo-UTP; 1(4-Nitro-phenyl)pseudo-UTP; 1-(4-Thiomethoxybenzyl) pseudouridine TP; 1-(4-Trifluoromethoxybenzyl) pseudouridine TP: 1-(4-Trifluoromethylbenzyl) pseudouridine TP; 1-(5-Amino-pentyl)pseudo-UTP; 1-(6- 40 Amino-hexyl)pseudo-UTP; 1,6-Dimethyl-pseudo-UTP; 1-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)propionyl]pseudouridine TP; 1-{3-[2-(2-Aminoethoxy)ethoxy]-propionyl}pseudouridine TP; 1-Acetylpseudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6- 45 (2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkvl-6-homoallvlpseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylpseudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpseudouridine TP; 1-Benzyloxymethylpseudouridine TP; 50 1-Benzyl-pseudo-UTP; 1-Biotinyl-PEG2-pseudouridine TP; 1-Biotinylpseudouridine TP; 1-Butyl-pseudo-UTP; 1-Cyanomethylpseudouridine TP; 1-Cyclobutylmethyl-pseudo-UTP; 1-Cyclobutyl-pseudo-UTP; 1-Cycloheptylmethylpseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 55 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP: 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctylpseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 60 1-Hexyl-pseudo-UTP; 1-Homoallylpseudouridine TP; 1-Hydroxymethylpseudouridine TP; 1-iso-propyl-pseudo-UTP; 1-Me-2-thio-pseudo-UTP; 1-Me-4-thio-pseudo-UTP; 1-Me-alpha-thio-pseudo-UTP; 1-Methanesulfonylmethylpseudouridine TP; 1-Methoxymethylpseudouridine TP; 65 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomor56

pholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl) pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6azido-pseudo-UTP; 1-Methyl-6-bromo-pseudo-UTP; 1-Methyl-6-butyl-pseudo-UTP; 1-Methyl-6-chloro-pseudo-UTP; 1-Methyl-6-cyano-pseudo-UTP; 1-Methyl-6-dimethylamino-pseudo-UTP; 1-Methyl-6-ethoxy-pseudo-UTP; 1-Methyl-6-ethylcarboxylate-pseudo-UTP; 1-Methyl-6-1-Methyl-6-fluoro-pseudo-UTP; ethyl-pseudo-UTP; 1-Methyl-6-formyl-pseudo-UTP; 1-Methyl-6-hydroxyamino-pseudo-UTP; 1-Methyl-6-hydroxy-pseudo-UTP; 1-Methyl-6-iodo-pseudo-UTP; 1-Methyl-6-iso-propyl-pseudo-UTP; 1-Methyl-6-methoxy-pseudo-UTP; 1-Methyl-6-methylamino-pseudo-UTP; 1-Methyl-6-phenylpseudo-UTP; 1-Methyl-6-propyl-pseudo-UTP; 1-Methyl-6tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxypseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpseudouridine TP; 1-Pentyl-pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; TP; 1-Propyl-pseudo-UTP; 1-Propargylpseudouridine 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-Trifluoroacetylpseudouridine TP; 1-Trifluoromethyl-pseudo-UTP; 1-Vinylpseudouridine TP; 2,2'-anhydro-uridine TP: 2'-bromo-deoxyuridine TP; 2'-F-5-Methyl-2'-deoxy-UTP; 2'-OMe-5-Me-UTP; 2'-OMe-pseudo-UTP; 2'-a-Ethynyluridine TP; 2'-a-Trifluoromethyluridine TP; 2'-b-Ethynyluridine TP; 2'-b-Trifluoromethyluridine TP; 2'-Deoxy-2', 2'-difluorouridine TP; 2'-Deoxy-2'-a-mercaptouridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-bbromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptouridine TP; 2'-Deoxy-2'-b-thiomethoxyuridine TP; 2-methoxy-4-thio-uridine; 2-methoxyuridine; 2'-O-Methyl-5-(1-propynyl)uridine TP; 3-Alkyl-pseudo-UTP; 4'-Azidouridine TP; 4'-Carbocyclic uridine TP; 4'-Ethynyluridine TP; 5-(1-Propynyl)ara-uridine TP; 5-(2-Furanyl)uridine TP; 5-Cyanouridine TP; 5-Dimethylaminouridine TP; 5'-Homo-uridine TP; 5-iodo-2'fluoro-deoxyuridine TP; 5-Phenylethynyluridine TP; 5-Trideuteromethyl-6-deuterouridine TP; 5-Trifluoromethyl-Uridine TP; 5-Vinylarauridine TP; 6-(2,2,2-Trifluoroethyl)pseudo-UTP; 6-(4-Morpholino)-pseudo-UTP; 6-(4-Thiomorpholino)-pseudo-UTP; 6-(Substituted-Phenyl)pseudo-UTP; 6-Amino-pseudo-UTP; 6-Azido-pseudo-UTP; 6-Bromo-pseudo-UTP; 6-Butyl-pseudo-UTP; 6-Chloropseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylaminopseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylatepseudo-UTP; 6-Ethyl-pseudo-UTP; 6-Fluoro-pseudo-UTP; 6-Formyl-pseudo-UTP; 6-Hydroxyamino-pseudo-UTP; 6-Hydroxy-pseudo-UTP; 6-Iodo-pseudo-UTP; 6-iso-Propyl-pseudo-UTP; 6-Methoxy-pseudo-UTP; 6-Methylamino-pseudo-UTP; 6-Methyl-pseudo-UTP; 6-Phenylpseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxypseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thiopseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudou-1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)ridine ΤP ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2 (2-ethoxy)-ethoxy]-ethoxy]-ethoxy]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2ethoxy)-ethoxy}] propionic acid; Pseudouridine TP 1-methylphosphonic acid; Pseudouridine TP 1-methylphosphonic

acid diethyl ester; Pseudo-UTP-N1-3-propionic acid; Pseudo-UTP-N1-4-butanoic acid; Pseudo-UTP-N1-5-pentanoic acid; Pseudo-UTP-N1-6-hexanoic acid; Pseudo-UTP-N1-7-heptanoic acid; Pseudo-UTP-N1-methyl-p-benzoic acid; Pseudo-UTP-N1-p-benzoic acid; Wybutosine; 5 Hvdroxywybutosine: Isowyosine: Peroxywybutosine: undermodified hydroxywybutosine; 4-demethylwyosine; 2,6-(diamino)purine; 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl: 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl; 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 1,3,5-(triaza)-2,6-(dioxa)-naphthalene;2 (amino)purine;2,4,5-(trimethyl)phenyl;2' methyl, 2'amino, 2'azido, 2'fluro-cytidine;2' methyl, 2' amino, 2'azido, 2'fluro-adenine;2'methyl, 2'amino, 2' azido, 2'flurouridine;2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 15 2-aza-inosinyl; 2'-azido-2'-deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl) isocarbostyrilyl; 3-(methyl)isocarbostyrilyl; 4-(fluoro)-6- 20 4-(methyl)benzimidazole; (methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyrilyl; 5-nitroindole; 6-(aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin- 25 2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-7-(aminoalkylhydroxy)-1,3-3-(aza)-phenoxazin-1-yl; (diaza)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1, 3-(diaza)-2-(oxo)-phenthiazin-1-yl;

7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1yl; 7-(aza)indolyl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazinl-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl;

7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phe- 35 noxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl;

7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-(propynyl)isocarbostyrilyl; 7-(propynyl)isocar- 40 bostyrilyl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl; 7-substituted 9-(methyl)-imidizopyridinyl; Aminoindolyl; Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimi-45 din-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine; Imidizopyridinyl; Inosinyl; Isocarbostyrilyl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthale- 50 nyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; 06-substituted purines; O-alkylated derivative; ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Oxoformycin para- 55 TP: (aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3yl; para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Pentacenyl; Phenanthracenyl; Phenyl; propynyl-7-(aza)indolyl; Pyrenyl; pyridopyrimidin-3-yl; pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl; pyrrolo-pyrimidin-2- 60 on-3-yl; Pyrrolopyrimidinyl; Pyrrolopyrizinyl; Stilbenzyl; substituted 1,2,4-triazoles; Tetracenyl; Tubercidine; Xanthine; Xanthosine-5'-TP; 2-thio-zebularine; 5-aza-2-thio-zebularine; 7-deaza-2-amino-purine; pyridin-4-one ribonucleoside; 2-Amino-riboside-TP; Formycin A TP; 65 Formycin B TP; Pyrrolosine TP; 2'-OH-ara-adenosine TP; 2'-OH-ara-cytidine TP; 2'-OH-ara-uridine TP; 2'-OH-ara-

guanosine TP; 5-(2-carbomethoxyvinyl)uridine TP; and N6-(19-Amino-pentaoxanonadecyl)adenosine TP.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of pseudouridine (ψ), N1-methylpseudouridine (m¹ ψ), N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcyto sine. 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxypseudouridine, 4-thio-1-methyl-pseudouridine, 4-thiopseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine. In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) include a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, modified nucleobases in polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are selected from the group consisting of 1-methyl-pseudouridine ($m^1\psi$), 5-methoxy-uridine (mo^5U), 5-methyl-cytidine (m^5C), pseudouridine (ψ), α -thio-guanosine and α -thio-adenosine. In some embodiments, polynucleotides includes a combination of at least two (e.g., 2, 3, 4 or more) of the aforementioned modified nucleobases.

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise pseudouridine (v) and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methylpseudouridine $(m^1\psi)$. In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 1-methyl-pseudouridine $(m^{1}\psi)$ and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine (s²U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2-thiouridine and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise methoxy-uridine (mo⁵U). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 5-methoxy-uridine (mo⁵U) and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-O-methyl uridine. In some embodiments polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise 2'-Omethyl uridine and 5-methyl-cytidine (m⁵C). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m⁶A). In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) comprise N6-methyl-adenosine (m⁶A) and 5-methyl-cytidine (m⁵C).

In some embodiments, polynucleotides (e.g., RNA polynucleotides, such as mRNA polynucleotides) are uniformly modified (e.g., fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with 5-methyl-cytidine ($m^{s}C$), meaning that all cytosine residues in the mRNA sequence are replaced with 5-methyl-cytidine ($m^{s}C$).

Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified residue such as those set forth above.

Exemplary nucleobases and nucleosides having a modi-5 fied cytosine include N4-acetyl-cytidine (ac4C), 5-methylcytidine (m5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm5C), 1-methyl-pseudoisocytidine, 2-thio-cytidine (s2C), and 2-thio-5-methyl-cytidine.

In some embodiments, a modified nucleobase is a modified uridine. Exemplary nucleobases and In some embodiments, a modified nucleobase is a modified cytosine. nucleosides having a modified uridine include 5-cyano uridine, and 4'-thio uridine.

In some embodiments, a modified nucleobase is a modi-15 fied adenine. Exemplary nucleobases and nucleosides having a modified adenine include 7-deaza-adenine, 1-methyladenosine (m1A), 2-methyl-adenine (m2A), and N6-methyladenosine (m6A).

In some embodiments, a modified nucleobase is a modi- 20 fied guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deazaguanosine, 7-cyano-7-deaza-guanosine (preQO), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine 25 (m7G), 1-methyl-guanosine (mIG), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine.

The polynucleotides of the present disclosure may be partially or fully modified along the entire length of the molecule. For example, one or more or all or a given type of 30 nucleotide (e.g., purine or pyrimidine, or any one or more or all of A, G, U, C) may be uniformly modified in a polynucleotide of the disclosure, or in a given predetermined sequence region thereof (e.g., in the mRNA including or excluding the polyA tail). In some embodiments, all nucleo-35 tides X in a polynucleotide of the present disclosure (or in a given sequence region thereof) are modified nucleotides, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C. 40

The polynucleotide may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e., any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 45 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 50 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 55 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%). Any remaining percentage is accounted for by the presence of unmodified A, G, U, or C.

The polynucleotides may contain at a minimum 1% and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 5% modified nucleotides, at least 10% modified nucleotides, at least 25% modified nucleotides, at least 50% modified nucleotides, at least 80% 65 modified nucleotides, or at least 90% modified nucleotides. For example, the polynucleotides may contain a modified

pyrimidine such as a modified uracil or cytosine. In some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the uracil in the polynucleotide is replaced with a modified uracil (e.g., a 5-substituted uracil). The modified uracil can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures). n some embodiments, at least 5%, at least 10%, at least 25%, at least 50%, at least 80%, at least 90% or 100% of the cytosine in the polynucleotide is replaced with a modified cytosine (e.g., a 5-substituted cytosine). The modified cytosine can be replaced by a compound having a single unique structure, or can be replaced by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures).

Thus, in some embodiments, the RNA (e.g., mRNA) vaccines comprise a 5'UTR element, an optionally codon optimized open reading frame, and a 3'UTR element, a poly(A) sequence and/or a polyadenylation signal wherein the RNA is not chemically modified.

In some embodiments, the modified nucleobase is a modified uracil. Exemplary nucleobases and nucleosides having a modified uracil include pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho⁵U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridineor 5-bromo-uridine), 3-methyl-uridine (m³U), 5-methoxy-uridine (mo⁵U), uridine 5-oxyacetic acid (cmo^{5}U) , uridine 5-oxyacetic acid methyl ester (mcmo⁵U), 5-carboxymethyl-uridine $(cm^{2}U),$ 1-carboxymethylpseudouridine, 5-carboxyhydroxymethyl-uridine (chm⁵U), 5-carboxyhydroxymethyl-uridine methyl ester (mchm⁵U), 5-methoxycarbonylmethyl-uridine (mcm⁵U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm⁵s²U), 5-aminomethyl-2-thio-uridine (nm^5s^2U) , 5-methylaminomethyl-uridine (mnm⁵U), 5-methylaminomethyl-2-thio-uridine $(mnm^5s^2U),$ 5-methylaminomethyl-2-seleno-uridine (mnm⁵se²U), 5-carbamoylmethyl-uridine (ncm⁵U), 5-carboxymethylaminomethyl-uridine (cmnm⁵U), 5-carboxymethylaminomethyl-2-thio-uridine (cmnm⁵s²U), 5-propynyluridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine ($\tau m^5 U$), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2thio-uridine(m⁵s²U), 1-taurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m⁵U, i.e., having the nucleobase deoxythymine), 1-methyl-pseudouridine ($m^1\psi$), 5-methyl-2-thiouridine (m5s²U), 1-methyl-4-thio-pseudouridine (m¹s⁴ ψ), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine $(m^{3}\psi)$, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deazapseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m⁵D), 2-thio-dihydrouri-2-thio-dihydropseudouridine, 2-methoxy-uridine, dine. 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine. 3-(3-amino-3-carboxypropyl)uridine (acp³U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine (inm⁵U), $(acp^{3}\psi),$ 5-(isopentenylaminomethyl)uridine 5-(isopentenylaminomethyl)-2-thio-uridine $(inm^5s^2U),$ 60 α-thio-uridine, 2'-O-methyl-uridine (Um), 5,2'-O-dimethyluridine (msUm), 2'-O-methyl-pseudouridine (Wm), 2-thio-2'-O-methyl-uridine (s²Um), 5-methoxycarbonylmethyl-2'-O-methyl-uridine (mcm⁵Um), 5-carbamoylmethyl-2'-O-

D-methyl-uridine (mcm⁻Um), 5-carbamoyimethyl-2'-O-methyl-uridine (ncm⁵Um), 5-carboxymethylaminomethyl 2'-O-methyl-uridine (cmnm⁵Um), 3,2'-O-dimethyl-uridine (m³Um), and 5-(isopentenylaminomethyl)-2'-O-methyl-uridine (inm⁵Um), 1-thio-uridine, deoxythymidine, 2'-F-ara-

uridine, 2'-F-uridine, 2'-OH-ara-uridine, 5-(2-carbomethoxyvinyl) uridine, and 5-[3-(1-E-propenylamino)] uridine.

In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides 5 having a modified cytosine include 5-aza-cytidine, 6-azacytidine, pseudoisocytidine, 3-methyl-cytidine $(m^{3}C),$ N4-acetyl-cytidine (ac^4C) , 5-formyl-cytidine (f⁵C), N4-methyl-cytidine (m⁴C), 5-methyl-cytidine $(m^{5}C),$ 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl- 10 cytidine (hm⁵C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s²C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-4-thio-1-methyl-1-deaza-1-methyl-pseudoisocytidine, pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, 15 zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k₂C), α -thio-cytidine, 2'-O-methyl-cytidine (Cm), 5.2'-O- 20 dimethyl-cytidine (m⁵Cm), N4-acetyl-2'-O-methyl-cytidine (ac⁴Cm), N4,2'-O-dimethyl-cytidine (m⁴Cm), 5-formyl-2'-O-methyl-cytidine (f^sCm), N4,N4,2'-O-trimethyl-cytidine (m⁴2Cm), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine. 25

In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 2-amino-purine, 2, 6-diaminopurine, 2-amino-6-halo-purine (e.g., 2-amino-6chloro-purine), 6-halo-purine (e.g., 6-chloro-purine), 30 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-ad-7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, enine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m¹A), 2-methyl-adenine (m²A), N6-methyl-adenosine 35 2-methylthio-N6-methyl-adenosine (ms^2m^6A) , $(m^{6}A),$ N6-isopentenyl-adenosine (i⁶A), 2-methylthio-N6-isopentenyl-adenosine (ms²i⁶A), N6-(cis-hydroxyisopentenyl)adenosine (io⁶A), 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine (ms²io⁶A), N6-glycinylcarbamoyl-adenosine 40 (g⁶A), N6-threonylcarbamoyl-adenosine (t⁶A), N6-methyl-N6-threonylcarbamoyl-adenosine (m6t6A), 2-methylthio-N6-threonylcarbamoyl-adenosine (ms²g⁶A), N6,N6-dimethyl-adenosine (m⁶2A), N6-hydroxynorvalylcarbamoyl- $(hn^6A),$ 2-methylthio-N6- 45 adenosine $(ms^2hn^6A),$ hydroxynorvalylcarbamoyl-adenosine N6-acetyl-adenosine (ac⁶A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α-thio-adenosine, 2'-O-N6,2'-O-dimethyl-adenosine methyl-adenosine (Am), (m⁶Am), N6,N6,2'-O-trimethyl-adenosine (m⁶2Am), 1,2'- 50 O-dimethyl-adenosine (m¹Am), 2'-O-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1-thio-adenosine, 8-azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino-pentaoxanonadecv1)-adenosine.

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methylinosine (m¹I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybu- 60 tosine (yW), peroxywybutosine (o₂yW), hydroxywybutosine (OhyW), undermodified hydroxywybutosine (OhyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7-deaza-guanosine (preQ₀), 7-aminomethyl-7- 65 deaza-guanosine (preQ₁), archaeosine (G⁺), 7-deaza-8-azaguanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine,

6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine 6-thio-7-methyl-guanosine, $(m^{7}G),$ 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (mG). N2-methyl-guanosine (m^2G) , N2,N2-dimethyl-guanosine (m²2G), N2,7-dimethyl-guanosine (m^{2,7}G), N2, N2,7-dimethyl-guanosine (m^{2,2,7}G), 8-oxo-guanosine, 7-methyl-8oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, a-thioguanosine, 2'-O-methyl-guanosine (Gm), N2-methyl-2'-Omethyl-guanosine (m²Gm), N2,N2-dimethyl-2'-O-methylguanosine (m²2Gm), 1-methyl-2'-O-methyl-guanosine (mGm), N2,7-dimethyl-2'-O-methyl-guanosine (m²'7Gm), 2'-O-methyl-inosine (Im), 1,2'-O-dimethyl-inosine (m¹Im), 2'-O-ribosylguanosine (phosphate) (Gr(p)), 1-thio-guanosine, 06-methyl-guanosine, 2'-F-ara-guanosine, and 2'-Fguanosine.

N-Linked Glycosylation Site Mutants

N-linked glycans of viral proteins play important roles in modulating the immune response. Glycans can be important for maintaining the appropriate antigenic conformations, shielding potential neutralization epitopes, and may alter the proteolytic susceptibility of proteins. Some viruses have putative N-linked glycosylation sites. Deletion or modification of an N-linked glycosylation site may enhance the immune response. Thus, the present disclosure provides, in some embodiments, RNA (e.g., mRNA) vaccines comprising nucleic acids (e.g., mRNA) encoding antigenic polypeptides that comprise a deletion or modification at one or more N-linked glycosylation sites.

In Vitro Transcription of RNA (e.g., mRNA)

Respiratory virus vaccines of the present disclosure comprise at least one RNA polynucleotide, such as a mRNA (e.g., modified mRNA). mRNA, for example, is transcribed in vitro from template DNA, referred to as an "in vitro transcription template." In some embodiments, an in vitro transcription template encodes a 5' untranslated (UTR) region, contains an open reading frame, and encodes a 3' UTR and a polyA tail. The particular nucleic acid sequence composition and length of an in vitro transcription template will depend on the mRNA encoded by the template.

A "5' untranslated region" (5'UTR) refers to a region of an mRNA that is directly upstream (i.e., 5') from the start codon (i.e., the first codon of an mRNA transcript translated by a ribosome) that does not encode a polypeptide.

A "3' untranslated region" (3'UTR) refers to a region of an mRNA that is directly downstream (i.e., 3') from the stop codon (i.e., the codon of an mRNA transcript that signals a termination of translation) that does not encode a polypeptide.

An "open reading frame" is a continuous stretch of DNA beginning with a start codon (e.g., methionine (ATG)), and ending with a stop codon (e.g., TAA, TAG or TGA) and encodes a polypeptide.

A "polyA tail" is a region of mRNA that is downstream,
e.g., directly downstream (i.e., 3'), from the 3' UTR that contains multiple, consecutive adenosine monophosphates. A polyA tail may contain 10 to 300 adenosine monophosphates. For example, a polyA tail may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290 or 300 adenosine monophosphates. In some embodiments, a polyA tail contains 50 to 250 adenosine monophosphates. In a relevant biological setting (e.g., in cells, in vivo) the poly(A) tail functions to protect mRNA from enzymatic 65 degradation, e.g., in the cytoplasm, and aids in transcription termination, export of the mRNA from the nucleus and translation.

In some embodiments, a polynucleotide includes 200 to 3,000 nucleotides. For example, a polynucleotide may include 200 to 500, 200 to 1000, 200 to 1500, 200 to 3000, 500 to 1000, 500 to 1500, 500 to 2000, 500 to 3000, 1000 to 1500, 1000 to 2000, 1000 to 3000, 1500 to 3000, or 2000 5 to 3000 nucleotides.

Flagellin Adjuvants

Flagellin is an approximately 500 amino acid monomeric protein that polymerizes to form the flagella associated with bacterial motion. Flagellin is expressed by a variety of 10 flagellated bacteria (Salmonella typhimurium for example) as well as non-flagellated bacteria (such as Escherichia coli). Sensing of flagellin by cells of the innate immune system (dendritic cells, macrophages, etc.) is mediated by the Tolllike receptor 5 (TLR5) as well as by Nod-like receptors 15 (NLRs) Ipaf and Naip5. TLRs and NLRs have been identified as playing a role in the activation of innate immune response and adaptive immune response. As such, flagellin provides an adjuvant effect in a vaccine.

The nucleotide and amino acid sequences encoding 20 known flagellin polypeptides are publicly available in the NCBI GenBank database. The flagellin sequences from S.

Typhimurium, H. Pylori, V. Cholera, S. marcesens, S. flexneri, T. Pallidum, L. pneumophila, B. burgdorferei, C. difficile, R. meliloti, A. tumefaciens, R. lupini, B. clar- 25 ridgeiae, P. Mirabilis, B. subtilus, L. monocytogenes, P. aeruginosa, and E. coli, among others are known.

A flagellin polypeptide, as used herein, refers to a full length flagellin protein, immunogenic fragments thereof, and peptides having at least 50% sequence identify to a 30 flagellin protein or immunogenic fragments thereof. Exemplary flagellin proteins include flagellin from Salmonella typhi (UniPro Entry number: Q56086), Salmonella typhimu-(A0A0C9DG09), rium Salmonella enteritidis (AOAOC9BAB7), and Salmonella choleraesuis (Q6V2X8), 35 includes at least two separate RNA polynucleotides, one and SEQ ID NO: 54-56 (Table 17). In some embodiments, the flagellin polypeptide has at least 60%, 70%, 75%, 80%, 90%, 95%, 97%, 98%, or 99% sequence identify to a flagellin protein or immunogenic fragments thereof.

In some embodiments, the flagellin polypeptide is an 40 immunogenic fragment. An immunogenic fragment is a portion of a flagellin protein that provokes an immune response. In some embodiments, the immune response is a TLR5 immune response. An example of an immunogenic fragment is a flagellin protein in which all or a portion of a hinge region has been deleted or replaced with other amino acids. For example, an antigenic polypeptide may be inserted in the hinge region. Hinge regions are the hypervariable regions of a flagellin. Hinge regions of a flagellin are also referred to as "D3 domain or region, "propeller 50 domain or region," "hypervariable domain or region" and "variable domain or region." "At least a portion of a hinge region," as used herein, refers to any part of the hinge region of the flagellin, or the entirety of the hinge region. In other embodiments an immunogenic fragment of flagellin is a 20, 55 25, 30, 35, or 40 amino acid C-terminal fragment of flagel-

The flagellin monomer is formed by domains D0 through D3. D0 and D1, which form the stem, are composed of tandem long alpha helices and are highly conserved among 60 different bacteria. The D1 domain includes several stretches of amino acids that are useful for TLR5 activation. The entire D1 domain or one or more of the active regions within the domain are immunogenic fragments of flagellin. Examples of immunogenic regions within the D1 domain 65 include residues 88-114 and residues 411-431 (in Salmonella typhimurium FliC flagellin. Within the 13 amino acids

in the 88-100 region, at least 6 substitutions are permitted between Salmonella flagellin and other flagellins that still preserve TLR5 activation. Thus, immunogenic fragments of flagellin include flagellin like sequences that activate TLR5 and contain a 13 amino acid motif that is 53% or more identical to the Salmonella sequence in 88-100 of FliC (LQRVRELAVQSAN; SEQ ID NO: 84).

In some embodiments, the RNA (e.g., mRNA) vaccine includes an RNA that encodes a fusion protein of flagellin and one or more antigenic polypeptides. A "fusion protein" as used herein, refers to a linking of two components of the construct. In some embodiments, a carboxy-terminus of the antigenic polypeptide is fused or linked to an amino terminus of the flagellin polypeptide. In other embodiments, an amino-terminus of the antigenic polypeptide is fused or linked to a carboxy-terminus of the flagellin polypeptide. The fusion protein may include, for example, one, two, three, four, five, six or more flagellin polypeptides linked to one, two, three, four, five, six or more antigenic polypeptides. When two or more flagellin polypeptides and/or two or more antigenic polypeptides are linked such a construct may be referred to as a "multimer."

Each of the components of a fusion protein may be directly linked to one another or they may be connected through a linker. For instance, the linker may be an amino acid linker. The amino acid linker encoded for by the RNA (e.g., mRNA) vaccine to link the components of the fusion protein may include, for instance, at least one member selected from the group consisting of a lysine residue, a glutamic acid residue, a serine residue and an arginine residue. In some embodiments the linker is 1-30, 1-25, 1-25, 5-10, 5, 15, or 5-20 amino acids in length.

In other embodiments the RNA (e.g., mRNA) vaccine encoding one or more antigenic polypeptides and the other encoding the flagellin polypeptide. The at least two RNA polynucleotides may be co-formulated in a carrier such as a lipid nanoparticle.

Broad Spectrum RNA (e.g., mRNA) Vaccines

There may be situations where persons are at risk for infection with more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). RNA (e.g., mRNA) therapeutic vaccines are particularly amenable to combination vaccination approaches due to a number of factors including, but not limited to, speed of manufacture, ability to rapidly tailor vaccines to accommodate perceived geographical threat, and the like. Moreover, because the vaccines utilize the human body to produce the antigenic protein, the vaccines are amenable to the production of larger, more complex antigenic proteins, allowing for proper folding, surface expression, antigen presentation, etc. in the human subject. To protect against more than one strain of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1), a combination vaccine can be administered that includes RNA (e.g., mRNA) encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a first respiratory virus and further includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a second respiratory virus. RNA (e.g., mRNA) can be co-formulated, for example, in a single lipid nanoparticle (LNP) or can be formulated in separate LNPs for co-administration.

Methods of Treatment

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention and/or treatment of respiratory diseases/infections in humans and other mammals. Respiratory virus RNA (e.g. 5 mRNA) vaccines can be used as therapeutic or prophylactic agents, alone or in combination with other vaccine(s). They may be used in medicine to prevent and/or treat respiratory disease/infection. In exemplary aspects, the RNA (e.g., mRNA) vaccines of the present disclosure are used to 10 provide prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). Prophylactic protection from hMPV, PIV3, RSV, MeV and/or BetaCoV (including 15 MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) can be achieved following administration of a RNA (e.g., mRNA) vaccine of the present disclosure. Respiratory virus RNA (e.g., mRNA) vaccines of the present disclosure may 20 be used to treat or prevent viral "co-infections" containing two or more respiratory infections. Vaccines can be administered once, twice, three times, four times or more, but it is likely sufficient to administer the vaccine once (optionally followed by a single booster). It is possible, although less 25 desirable, to administer the vaccine to an infected individual to achieve a therapeutic response. Dosing may need to be adjusted accordingly.

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including 30 MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in aspects of the present disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA 35 (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide thereof, thereby 40 inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, 45 wherein anti-antigenic polypeptide antibody titer in the subject is increased following vaccination relative to antiantigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV 50 (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1). An "anti-antigenic polypeptide antibody" is a serum antibody the binds specifically to the antigenic polypeptide.

In some embodiments, a RNA (e.g., mRNA) vaccine 55 (e.g., a hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1 RNA vaccine) capable of eliciting an immune response is administered intramuscularly via a composition including a 60 compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) (e.g., Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122).

A prophylactically effective dose is a therapeutically effective dose that prevents infection with the virus at a 65 clinically acceptable level. In some embodiments the therapeutically effective dose is a dose listed in a package insert

for the vaccine. A traditional vaccine, as used herein, refers to a vaccine other than the RNA (e.g., mRNA) vaccines of the present disclosure. For instance, a traditional vaccine includes but is not limited to live/attenuated microorganism vaccines, killed/inactivated microorganism vaccines, subunit vaccines, protein antigen vaccines, DNA vaccines, VLP vaccines, etc. In exemplary embodiments, a traditional vaccine is a vaccine that has achieved regulatory approval and/or is registered by a national drug regulatory body, for example the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log to 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log, 2 log, 3 log, 5 log or 10 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

A method of eliciting an immune response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) is provided in other aspects of the disclosure. The method involves administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 10-100 times, or 100-1000 times, the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, 5

HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine.

In some embodiments the immune response is assessed by determining [protein] antibody titer in the subject.

Some aspects of the present disclosure provide a method of eliciting an immune response in a subject against a In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated 10with a traditional vaccine at 2, 3, 4, 5, 10, 50, 100 times the dosage level relative to the hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) RNA (e.g., mRNA) vaccine by admin-15 istering to the subject a respiratory virus RNA (e.g., mRNA) vaccine comprising at least one RNA (e.g., mRNA) polynucleotide having an open reading frame encoding at least one hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, 20 mRNA) vaccine is provided based, at least in part, on the HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) antigenic polypeptide, thereby inducing in the subject an immune response specific to the antigenic polypeptide or an immunogenic fragment thereof, wherein the immune response in the subject is induced 2 days to 10 weeks earlier 25 relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the hMPV, PIV3, RSV, MeV and/or Beta-CoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or 30 HCoV-HKU1). In some embodiments, the immune response in the subject is induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine at 2 times to 100 times the dosage level relative to the RNA (e.g., mRNA) vaccine.

In some embodiments, the immune response in the subject is induced 2 days earlier, or 3 days earlier, relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

In some embodiments the immune response in the subject 40 is induced 1 week, 2 weeks, 3 weeks, 5 weeks, or 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine.

Also provided herein is a method of eliciting an immune 45 response in a subject against hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1) by administering to the subject a respiratory virus RNA (e.g., mRNA) vaccine having an open 50 reading frame encoding a first antigenic polypeptide, wherein the RNA polynucleotide does not include a stabilization element, and wherein an adjuvant is not co-formulated or co-administered with the vaccine.

Therapeutic and Prophylactic Compositions

Provided herein are compositions (e.g., pharmaceutical compositions), methods, kits and reagents for prevention, treatment or diagnosis of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH 60 and/or HCoV-HKU1) in humans and other mammals, for example. Respiratory virus RNA (e.g. mRNA) vaccines can be used as therapeutic or prophylactic agents. They may be used in medicine to prevent and/or treat infectious disease. In some embodiments, the respiratory RNA (e.g., mRNA) 65 vaccines of the present disclosure are used fin the priming of immune effector cells, for example, to activate peripheral

blood mononuclear cells (PBMCs) ex vivo, which are then infused (re-infused) into a subject.

In some embodiments, respiratory virus vaccine containing RNA (e.g., mRNA) polynucleotides as described herein can be administered to a subject (e.g., a mammalian subject, such as a human subject), and the RNA (e.g., mRNA) polynucleotides are translated in vivo to produce an antigenic polypeptide.

The respiratory virus RNA (e.g., mRNA) vaccines may be induced for translation of a polypeptide (e.g., antigen or immunogen) in a cell, tissue or organism. In some embodiments, such translation occurs in vivo, although such translation may occur ex vivo, in culture or in vitro. In some embodiments, the cell, tissue or organism is contacted with an effective amount of a composition containing a respiratory virus RNA (e.g., mRNA) vaccine that contains a polynucleotide that has at least one a translatable region encoding an antigenic polypeptide.

An "effective amount" of an respiratory virus RNA (e.g. target tissue, target cell type, means of administration, physical characteristics of the polynucleotide (e.g., size, and extent of modified nucleosides) and other components of the vaccine, and other determinants. In general, an effective amount of the respiratory virus RNA (e.g., mRNA) vaccine composition provides an induced or boosted immune response as a function of antigen production in the cell, preferably more efficient than a composition containing a corresponding unmodified polynucleotide encoding the same antigen or a peptide antigen. Increased antigen production may be demonstrated by increased cell transfection (the percentage of cells transfected with the RNA, e.g., mRNA, vaccine), increased protein translation from the polynucleotide, decreased nucleic acid degradation (as dem-35 onstrated, for example, by increased duration of protein translation from a modified polynucleotide), or altered antigen specific immune response of the host cell.

In some embodiments, RNA (e.g. mRNA) vaccines (including polynucleotides their encoded polypeptides) in accordance with the present disclosure may be used for treatment of hMPV, PIV3, RSV, MeV and/or BetaCoV (including MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH and/or HCoV-HKU1).

Respiratory RNA (e.g. mRNA) vaccines may be administered prophylactically or therapeutically as part of an active immunization scheme to healthy individuals or early in infection during the incubation phase or during active infection after onset of symptoms. In some embodiments, the amount of RNA (e.g., mRNA) vaccine of the present disclosure provided to a cell, a tissue or a subject may be an amount effective for immune prophylaxis.

Respiratory virus RNA (e.g. mRNA) vaccines may be administrated with other prophylactic or therapeutic com-55 pounds. As a non-limiting example, a prophylactic or therapeutic compound may be an adjuvant or a booster. As used herein, when referring to a prophylactic composition, such as a vaccine, the term "booster" refers to an extra administration of the prophylactic (vaccine) composition. A booster (or booster vaccine) may be given after an earlier administration of the prophylactic composition. The time of administration between the initial administration of the prophylactic composition and the booster may be, but is not limited to, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 6 minutes, 7 minutes, 8 minutes, 9 minutes, 10 minutes, 15 minutes, 20 minutes 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5

hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 1 day, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 10 days, 2 weeks, 3 weeks, 1 month, 2 months, 3 5 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 18 months, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, 14 years, 15 years, 16 years, 17 years, 18 years, 19 years, 20 years, 25 years, 30 10 years, 35 years, 40 years, 45 years, 50 years, 55 years, 60 years, 65 years, 70 years, 75 years, 80 years, 85 years, 90 years, 95 years or more than 99 years. In some embodiments, the time of administration between the initial administration of the prophylactic composition and the booster 15 may be, but is not limited to, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months or 1 year.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines may be administered intramuscularly or intradermally, similarly to the administration of inactivated 20 vaccines known in the art.

Respiratory virus RNA (e.g. mRNA) vaccines may be utilized in various settings depending on the prevalence of the infection or the degree or level of unmet medical need. As a non-limiting example, the RNA (e.g., mRNA) vaccines 25 may be utilized to treat and/or prevent a variety of respiratory infections. RNA (e.g., mRNA) vaccines have superior properties in that they produce much larger antibody titers and produce responses early than commercially available anti-viral agents/compositions. 30

Provided herein are pharmaceutical compositions including respiratory virus RNA (e.g. mRNA) vaccines and RNA (e.g. mRNA) vaccine compositions and/or complexes optionally in combination with one or more pharmaceutically acceptable excipients.

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered alone or in conjunction with one or more other components. For instance, hMPV/PIV3/RSV RNA (e.g., mRNA) vaccines (vaccine compositions) may comprise other components including, but not limited to, 40 adjuvants.

In some embodiments, respiratory virus (e.g. mRNA) vaccines do not include an adjuvant (they are adjuvant free).

Respiratory virus RNA (e.g. mRNA) vaccines may be formulated or administered in combination with one or more 45 pharmaceutically-acceptable excipients. In some embodiments, vaccine compositions comprise at least one additional active substances, such as, for example, a therapeutically-active substance, a prophylactically-active substance, or a combination of both. Vaccine compositions may be 50 sterile, pyrogen-free or both sterile and pyrogen-free. General considerations in the formulation and/or manufacture of pharmaceutical agents, such as vaccine compositions, may be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & 55 Wilkins, 2005 (incorporated herein by reference in its entirety).

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are administered to humans, human patients or subjects. For the purposes of the present disclo- 60 sure, the phrase "active ingredient" generally refers to the RNA (e.g., mRNA) vaccines or the polynucleotides contained therein, for example, RNA polynucleotides (e.g., mRNA polynucleotides) encoding antigenic polypeptides.

Formulations of the respiratory virus vaccine composi-65 tions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In

general, such preparatory methods include the step of bringing the active ingredient (e.g., mRNA polynucleotide) into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Respiratory virus RNA (e.g. mRNA) vaccines can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (e.g., from a depot formulation); (4) alter the biodistribution (e.g., target to specific tissues or cell types); (5) increase the translation of encoded protein in vivo; and/or (6) alter the release profile of encoded protein (antigen) in vivo. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with respiratory virus RNA (e.g. mRNA)vaccines (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

35 Stabilizing Elements

Naturally-occurring eukaryotic mRNA molecules have been found to contain stabilizing elements, including, but not limited to untranslated regions (UTR) at their 5'-end (5'UTR) and/or at their 3'-end (3'UTR), in addition to other structural features, such as a 5'-cap structure or a 3'-poly(A) tail. Both the 5'UTR and the 3'UTR are typically transcribed from the genomic DNA and are elements of the premature mRNA. Characteristic structural features of mature mRNA, such as the 5'-cap and the 3'-poly(A) tail are usually added to the transcribed (premature) mRNA during mRNA processing. The 3'-poly(A) tail is typically a stretch of adenine nucleotides added to the 3'-end of the transcribed mRNA. It can comprise up to about 400 adenine nucleotides. In some embodiments the length of the 3'-poly(A) tail may be an essential element with respect to the stability of the individual mRNA.

In some embodiments the RNA (e.g., mRNA) vaccine may include one or more stabilizing elements. Stabilizing elements may include for instance a histone stem-loop. A stem-loop binding protein (SLBP), a 32 kDa protein has been identified. It is associated with the histone stem-loop at the 3'-end of the histone messages in both the nucleus and the cytoplasm. Its expression level is regulated by the cell cycle; it peaks during the S-phase, when histone mRNA levels are also elevated. The protein has been shown to be essential for efficient 3'-end processing of histone premRNA by the U7 snRNP. SLBP continues to be associated with the stem-loop after processing, and then stimulates the translation of mature histone mRNAs into histone proteins in the cytoplasm. The RNA binding domain of SLBP is conserved through metazoa and protozoa; its binding to the histone stem-loop depends on the structure of the loop. The minimum binding site includes at least three nucleotides 5' and two nucleotides 3' relative to the stem-loop.

In some embodiments, the RNA (e.g., mRNA) vaccines include a coding region, at least one histone stem-loop, and optionally, a poly(A) sequence or polyadenylation signal. 5 The poly(A) sequence or polyadenylation signal generally should enhance the expression level of the encoded protein. The encoded protein, in some embodiments, is not a histone protein, a reporter protein (e.g. Luciferase, GFP, EGFP, β -Galactosidase, EGFP), or a marker or selection protein 10 (e.g. alpha-Globin, Galactokinase and Xanthine:guanine phosphoribosyl transferase (GPT)).

In some embodiments, the combination of a poly(A) sequence or polyadenylation signal and at least one histone stem-loop, even though both represent alternative mecha- 15 nisms in nature, acts synergistically to increase the protein expression beyond the level observed with either of the individual elements. It has been found that the synergistic effect of the combination of poly(A) and at least one histone stem-loop does not depend on the order of the elements or 20 the length of the poly(A) sequence.

In some embodiments, the RNA (e.g., mRNA) vaccine does not comprise a histone downstream element (HDE). "Histone downstream element" (HDE) includes a purinerich polynucleotide stretch of approximately 15 to 20 25 nucleotides 3' of naturally occurring stem-loops, representing the binding site for the U7 snRNA, which is involved in processing of histone pre-mRNA into mature histone mRNA. Ideally, the inventive nucleic acid does not include an intron. 30

In some embodiments, the RNA (e.g., mRNA) vaccine may or may not contain a enhancer and/or promoter sequence, which may be modified or unmodified or which may be activated or inactivated. In some embodiments, the histone stem-loop is generally derived from histone genes, 35 and includes an intramolecular base pairing of two neighbored partially or entirely reverse complementary sequences separated by a spacer, including (e.g., consisting of) a short sequence, which forms the loop of the structure. The unpaired loop region is typically unable to base pair with 40 either of the stem loop elements. It occurs more often in RNA, as is a key component of many RNA secondary structures, but may be present in single-stranded DNA as well. Stability of the stem-loop structure generally depends on the length, number of mismatches or bulges, and base 45 composition of the paired region. In some embodiments, wobble base pairing (non-Watson-Crick base pairing) may result. In some embodiments, the at least one histone stemloop sequence comprises a length of 15 to 45 nucleotides.

In other embodiments the RNA (e.g., mRNA) vaccine 50 DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids. 51 sequences, sometimes referred to as AURES are destabilizing sequences found in the 3'UTR. The AURES may be removed from the RNA (e.g., mRNA) vaccines. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections. Alternatively the AURES may remain in the RNA (e.g., mRNA) sections are alsoluted. Alternatively the AURES may remain in th

Nanoparticle Formulations

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines 60 are formulated in a lipid nanoparticle. In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines are formulated in a lipid-polycation complex, referred to as a cationic lipid nanoparticle. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide 65 such as, but not limited to, polylysine, polyornithine and/or polyarginine. In some embodiments, respiratory virus RNA

(e.g., mRNA) vaccines are formulated in a lipid nanoparticle that includes a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

A lipid nanoparticle formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (*Nature Biotech.* 2010 28:172-176), the lipid nanoparticle formulation is composed of 57.1% cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3% cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid can more effectively deliver siRNA to various antigen presenting cells (Basha et al. *Mol Ther.* 2011 19:2186-2200).

In some embodiments, lipid nanoparticle formulations may comprise 35 to 45% cationic lipid, 40% to 50% cationic lipid, 50% to 60% cationic lipid and/or 55% to 65% cationic lipid. In some embodiments, the ratio of lipid to RNA (e.g., mRNA) in lipid nanoparticles may be 5:1 to 20:1, 10:1 to 25:1, 15:1 to 30:1 and/or at least 30:1.

In some embodiments, the ratio of PEG in the lipid nanoparticle formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the lipid nanoparticle formulations. As a non-limiting example, lipid nanoparticle formulations may contain 0.5% to 3.0%, 1.0% to 3.5%, 1.5% to 4.0%, 2.0% to 4.5%, 2.5% to 5.0% and/or 3.0% to 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω -methoxy-poly(ethvleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-snglycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, an respiratory virus RNA (e.g. mRNA) vaccine formulation is a nanoparticle that comprises at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In some embodiments, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DCIn-DMA, DLin-DMA, DLin-MC3-DMA, DLin-KC2-DMA, DODMA and amino alcohol lipids.

The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorpothe cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9, 12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12-dien-1-yloxy] methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methyl}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12dien-1-yloxy]-2-[(octyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)octadeca-9,12-dien-1-yloxy]-2-{[(9Z, 12Z)-octadeca-9,12dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-

tyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-5 (dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, a lipid nanoparticle formulation 10 consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1, 3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2en-1-vl) 9-((4-(dimethylamino)butanoyl)oxy) 15 heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEGcDMA, in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, a lipid nanoparticle formulation includes 25% to 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1- 25 yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., 35 to 65%, 45 to 65%, 60%, 57.5%, 50% or 40% on a molar basis.

In some embodiments, a lipid nanoparticle formulation includes 0.5% to 15% on a molar basis of the neutral lipid, 30 e.g., 3 to 12%, 5 to 10% or 15%, 10%, or 7.5% on a molar basis. Examples of neutral lipids include, without limitation, DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes 5% to 50% on a molar basis of the sterol (e.g., 15 to 45%, 20 to 40%, 40%, 38.5%, 35%, 35 include 40% of a cationic lipid selected from 2,2-dilinoleylor 31% on a molar basis. A non-limiting example of a sterol is cholesterol. In some embodiments, a lipid nanoparticle formulation includes 0.5% to 20% on a molar basis of the PEG or PEG-modified lipid (e.g., 0.5 to 10%, 0.5 to 5%, 1.5%, 0.5%, 1.5%, 3.5%, or 5% on a molar basis. In some 40 embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In some embodiments, a PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 45 Da, or around 500 Da. Non-limiting examples of PEGmodified lipids include PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEG-cDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are 50 herein incorporated by reference in their entirety).

In some embodiments, lipid nanoparticle formulations include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin- 55 MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations 60 include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), 9-((4and di((Z)-non-2-en-1-yl) (L319), 65 (dimethylamino)butanoyl)oxy)heptadecanedioate 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

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In some embodiments, lipid nanoparticle formulations include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl)9-((4-(L319), (dimethylamino)butanoyl)oxy)heptadecanedioate 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 7.5% of the neutral lipid, 31% of the sterol, and 1.5% of the PEG or PEGmodified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), 20 dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 38.5% of the sterol, and 1.5% of the PEG or PEGmodified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 10% of the neutral lipid, 35% of the sterol, 4.5% or 5% of the PEG or PEG-modified lipid, and 0.5% of the targeting lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations 4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 15% of the neutral lipid, 40% of the sterol, and 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLindi((Z)-non-2-en-1-yl) 9-((4-MC3-DMA), and (dimethylamino)butanoyl)oxy)heptadecanedioate (L319). 7.1% of the neutral lipid, 34.3% of the sterol, and 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reves et al. (J. Controlled Release, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), 7.5% of the neutral lipid, 31.5% of the sterol, and 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in molar ratios of 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid. In some embodiments, lipid nanoparticle formulations consists essentially of a lipid mixture in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is 50/10/38.5/ 1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/ PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-

DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/ Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/ 0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/ 5 PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral 10 lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Non-limiting examples of lipid nanoparticle compositions 15 and methods of making them are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), *Angew. Chem. Int. Ed.*, 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by refer- 20 ence in their entirety).

In some embodiments, lipid nanoparticle formulations may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, a lipid nanoparticle may comprise 25 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% PEG lipid and 38.5% structural lipid. As yet another nonimiting example, a lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and 35 L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a 40 non-limiting example, the lipid nanoparticle may comprise 40-60% of cationic lipid, 5-15% of a non-cationic lipid, 1-2% of a PEG lipid and 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise 50% cationic lipid, 10% non-cationic lipid, 1.5% 45 PEG lipid and 38.5% structural lipid. As yet another nonlimiting example, the lipid nanoparticle may comprise 55% cationic lipid, 10% non-cationic lipid, 2.5% PEG lipid and 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but 50 not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a noncationic lipid, a PEG lipid and a structural lipid. As a 55 non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-KC2-DMA, 10% of the noncationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a nonlimiting example, the lipid nanoparticle comprise 50% of the 60 cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DSPC, 1.5% of the PEG lipid PEG-DOMG and 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-MC3-DMA, 10% of the non-cationic lipid 65 DSPC, 1.5% of the PEG lipid PEG-DMG and 38.5% of the structural lipid cholesterol. As yet another non-limiting

example, the lipid nanoparticle comprise 55% of the cationic lipid L319, 10% of the non-cationic lipid DSPC, 2.5% of the PEG lipid PEG-DMG and 32.5% of the structural lipid cholesterol.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a vaccine composition may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

In some embodiments, the respiratory virus RNA (e.g. mRNA) vaccine composition may comprise the polynucleotide described herein, formulated in a lipid nanoparticle comprising MC3, Cholesterol, DSPC and PEG2000-DMG, the buffer trisodium citrate, sucrose and water for injection. As a non-limiting example, the composition comprises: 2.0 mg/mL of drug substance (e.g., polynucleotides encoding H10N8 hMPV), 21.8 mg/mL of MC3, 10.1 mg/mL of cholesterol, 5.4 mg/mL of DSPC, 2.7 mg/mL of PEG2000-DMG, 5.16 mg/mL of trisodium citrate, 71 mg/mL of sucrose and 1.0 mL of water for injection.

In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 10-500 nm, 20-400 nm, 30-300 nm, 40-200 nm. In some embodiments, a nanoparticle (e.g., a lipid nanoparticle) has a mean diameter of 50-150 nm, 50-200 nm, 80-100 nm or 80-200 nm.

Liposomes, Lipoplexes, and Lipid Nanoparticles

The RNA (e.g., mRNA) vaccines of the disclosure can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In some embodiments, pharmaceutical compositions of RNA (e.g., mRNA) vaccines include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a small unicellular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients, the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-N,N-dimethylam-inopropane (DODMA) liposomes, DiLa2 liposomes from

Marina Biotech (Bothell, Wash.), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, Pa.).

In some embodiments, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge 20 et al. J Clin Invest. 2009 119:661-673; deFougerolles Hum Gene Ther. 2008 19:125-132; U.S. Patent Publication No US20130122104; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler et al. was a detergent dialysis method, which was 25 later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% 30 disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, 15% 1,2-dioleyloxy-N,N-dimethylaminopropane and (DODMA), as described by Jeffs et al. As another example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, 35 and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-N,N-dimethylaminopropane (DSDMA). DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

In some embodiments, liposome formulations may com- 40 prise from about 25.0% cholesterol to about 40.0% cholesterol, from about 30.0% cholesterol to about 45.0% cholesterol, from about 35.0% cholesterol to about 50.0% cholesterol and/or from about 48.5% cholesterol to about 60% cholesterol. In some embodiments, formulations may 45 comprise a percentage of cholesterol selected from the group consisting of 28.5%, 31.5%, 33.5%, 36.5%, 37.0%, 38.5%, 39.0% and 43.5%. In some embodiments, formulations may comprise from about 5.0% to about 10.0% DSPC and/or from about 7.0% to about 15.0% DSPC. 50

In some embodiments, the RNA (e.g., mRNA) vaccine pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, Wash.), SMARTICLES® (Marina Biotech, Bothell, Wash.), neutral DOPC (1,2-dioleoyl-sn-55 glycero-3-phosphocholine) based liposomes (e.g., siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel). 60

In some embodiments, the cationic lipid may be a low molecular weight cationic lipid such as those described in U.S. Patent Application No. 20130090372, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines 65 may be formulated in a lipid vesicle, which may have crosslinks between functionalized lipid bilayers.

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In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyomithine and/or polyarginine. In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid-polycation complex, which may further include a non-cationic lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(ω -methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristyloxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. In some embodiments, the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a lipid nanoparticle.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation comprising the polynucleotide is a nanoparticle which may comprise at least one lipid. The lipid may be selected from, but is not limited to, DLin-DMA, DLin-K-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DLin-KC2-DMA, DODMA, PLGA, PEG, PEG-DMG, PEGylated lipids and amino alcohol lipids. In another aspect, the lipid may be a cationic lipid such as, but not limited to, DLin-DMA, DLin-D-DMA, DLin-MC3-DMA, DLin-KC2-DMA. DODMA and amino alcohol lipids. The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, herein incorporated by reference in its entirety. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-2-{ [(9Z,2Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]

methyl}propan-1-ol (Compound 2 in US20130150625);
2-amino-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-2-[(oc-tyloxy)methyl]propan-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

Lipid nanoparticle formulations typically comprise a lipid, in particular, an ionizable cationic lipid, for example, 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-

tyrate (DLin-MC3-DMA), or di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), and further comprise a neutral lipid, a sterol and a molecule capable of reducing particle aggregation, for example a PEG or PEG-modified lipid.

In some embodiments, the lipid nanoparticle formulation consists essentially of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1, 3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2- 10 en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy) heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEGcDMA, in a molar ratio of about 20-60% cationic lipid: 15 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

In some embodiments, the formulation includes from about 25% to about 75% on a molar basis of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethyl- 20 aminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), e.g., from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 50% or about 40% on a molar basis. 25

In some embodiments, the formulation includes from about 0.5% to about 15% on a molar basis of the neutral lipid e.g., from about 3 to about 12%, from about 5 to about 10% or about 15%, about 10%, or about 7.5% on a molar basis. Examples of neutral lipids include, but are not limited to, 30 DSPC, POPC, DPPC, DOPE and SM. In some embodiments, the formulation includes from about 5% to about 50% on a molar basis of the sterol (e.g., about 15 to about 45%, about 20 to about 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. An exemplary sterol is 35 cholesterol. In some embodiments, the formulation includes from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (e.g., about 0.5 to about 10%, about 0.5 to about 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. In some embodiments, 40 the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In other embodiments, the PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of less than 2,000, for example around 1,500 Da, around 1,000 Da, or 45 around 500 Da. Examples of PEG-modified lipids include, but are not limited to, PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), PEGcDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are 50 herein incorporated by reference in their entirety)

In some embodiments, the formulations of the present disclosure include 25-75% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu- 55 tyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present 60 disclosure include 35-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-tyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 65 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

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In some embodiments, the formulations of the present disclosure include 45-65% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane

(DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-10% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 60% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-tyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.5% of the neutral lipid, about 31% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar

basis. In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 50% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 10% of the neutral lipid, about 35% of the sterol, about 4.5% or about 5% of the PEG or PEG-modified lipid, and about 0.5% of the targeting lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 40% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-tyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 15% of the neutral lipid, about 40% of the sterol, and about 5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.2% of a cationic lipid selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobu-tyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), about 7.1% of the neutral lipid, about 34.3% of the sterol, and about 1.4% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, the formulations of the present disclosure include about 57.5% of a cationic lipid selected from the PEG lipid is PEG-cDMA (PEG-cDMA is further discussed in Reyes et al. (*J. Controlled Release*, 107, 276-287 (2005), the contents of which are herein incorporated by reference in their entirety), about 7.5% of the neutral lipid, about 31.5% of the sterol, and about 3.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulation consists essentially of a lipid mixture in molar ratios of about 20-70% cationic lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid; more preferably in a molar ratio of about 20-60% cationic lipid: 5-25% neutral lipid: 25-55% cholesterol: 0.5-15% PEG-modified lipid.

In some embodiments, the molar lipid ratio is approximately 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, 5 e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/ 10 PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % 15 cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

Examples of lipid nanoparticle compositions and methods of making same are described, for example, in Semple et al. (2010) *Nat. Biotechnol.* 28:172-176; Jayarama et al. (2012), 20 *Angew. Chem. Int. Ed.*, 51: 8529-8533; and Maier et al. (2013) *Molecular Therapy* 21, 1570-1578 (the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the lipid nanoparticle formulations 25 described herein may comprise a cationic lipid, a PEG lipid and a structural lipid and optionally comprise a non-cationic lipid. As a non-limiting example, the lipid nanoparticle may comprise about 40-60% of cationic lipid, about 5-15% of a non-cationic lipid, about 1-2% of a PEG lipid and about 30 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise 35 about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may be 4 component lipid nanoparticles. The lipid nanoparticle may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle may comprise 45 about 40-60% of cationic lipid, about 5-15% of a noncationic lipid, about 1-2% of a PEG lipid and about 30-50% of a structural lipid. As another non-limiting example, the lipid nanoparticle may comprise about 50% cationic lipid, about 10% non-cationic lipid, about 1.5% PEG lipid and 50 about 38.5% structural lipid. As yet another non-limiting example, the lipid nanoparticle may comprise about 55% cationic lipid, about 10% non-cationic lipid, about 2.5% PEG lipid and about 32.5% structural lipid. In some embodiments, the cationic lipid may be any cationic lipid described 55 herein such as, but not limited to, DLin-KC2-DMA, DLin-MC3-DMA and L319.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a noncationic lipid, a PEG lipid and a structural lipid. As a 60 non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-KC2-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle 65 comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of

the PEG lipid PEG-DOMG and about 38.5% of the structural lipid cholesterol. As a non-limiting example, the lipid nanoparticle comprise about 50% of the cationic lipid DLin-MC3-DMA, about 10% of the non-cationic lipid DSPC, about 1.5% of the PEG lipid PEG-DMG and about 38.5% of the structural lipid cholesterol. As yet another non-limiting example, the lipid nanoparticle comprise about 55% of the cationic lipid L319, about 10% of the non-cationic lipid DSPC, about 2.5% of the PEG lipid PEG-DMG and about 32.5% of the structural lipid cholesterol.

As a non-limiting example, the cationic lipid may be selected from (20Z,23Z)-N,N-dimethylnonacosa-20,23dien-10-amine, (17Z,20Z)-N,N-dimemylhexacosa-17,20dien-9-amine. (1Z,19Z)-N5N-dimethylpentacosa-16, 19-dien-8-amine. (13Z,16Z)-N,N-dimethyldocosa-13,16dien-5-amine, (12Z, 15Z)-N,N-dimethylhenicosa-12,15dien-4-amine, (14Z, 17Z)-N,N-dimethyltricosa-14,17-dien-6-amine, (15Z, 18Z)-N,N-dimethyltetracosa-15,18-dien-7amine, (18Z,21Z)-N,N-dimethylheptacosa-18,21-dien-10-(15Z, 18Z)-N.N-dimethyltetracosa-15,18-dien-5amine. amine, (14Z, 17Z)-N,N-dimethyltricosa-14,17-dien-4amine, (19Z,22Z)-N,N-dimeihyloctacosa-19,22-dien-9-(18Z,21 Z)-N,N-dimethylheptacosa-18,21-dien-8amine, amine, (17Z,20Z)-N,N-dimethylhexacosa-17,20-dien-7amine, (16Z, 19Z)-N,N-dimethylpentacosa-16,19-dien-6-(22Z,25Z)-N,N-dimethylhentriaconta-22,25-dienamine, 10-amine, (21 Z,24Z)-N,N-dimethyltriaconta-21,24-dien-9amine, (18Z)-N,N-dimetylheptacos-18-en-10-amine, (17Z)-N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)-N,Ndimethyloctacosa-19,22-dien-7-amine, N.N-(20Z,23Z)-N-ethyl-Ndimethylheptacosan-10-amine, methylnonacosa-20,23-dien-10-amine, 1-[(11Z,14Z)-1pyrrolidine, nonylicosa-11,14-dien-1-yl] (20Z)-N,Ndimethylheptacos-20-en-10-amine, (15Z)-N,N-dimethyl eptacos-15-en-10-amine, (14Z)-N,N-dimethylnonacos-14en-10-amine, (17Z)-N,N-dimethylnonacos-17-en-10-amine, (24Z)-N,N-dimethyltritriacont-24-en-10-amine, (20Z)-N,Ndimethylnonacos-20-en-10-amine, (22Z)-N,N-dimethylhentriacont-22-en-10-amine, (16Z)-N,N-dimethylpentacos-16-40 en-8-amine, (12Z, 15Z)-N,N-dimethyl-2-nonylhenicosa-12, 15-dien-1-amine, (13Z, 16Z)-N,N-dimethyl-3-nonyldocosa-N,N-dimethyl-1-[(1S,2R)-2-13,16-dien-1-amine, eptadecan-8-amine, octylcyclopropyl] 1-[(1S,2R)-2hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(1S,2R)-2-octylcyclopropyl] henicosan-10-amine,N,N-dimethyl-1-[(1S,2S)-2-{[(1R, 2R)-2-pentylcyclopropyl]methyl}cyclopropyl]nonadecan-10-amine,N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl] hexadecan-8-amine, N,N-dimethyl-[(1R,2S)-2undecylcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl} dodecan-1-amine, 1-[(1R,2S)-2-heptylcyclopropyl]-N,N-dimethyloctadecan-1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethyl-9-amine. pentadecan-6-amine, N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]pentadecan-8-amine, R-N,N-dimethyl-1-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2amine, S-N,N-dimethyl-1-[(9Z, 12Z)-octadeca-9,12-dien-1yloxy]-3-(octyloxy)propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl] ethyl}pyrrolidine. (2S)-N,N-dimethyl-1-[(9Z, 12Z)octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy] propan-2-amine, 1-{2-[(9Z, 12Z)-octadeca-9,12-dien-1-(2S)-1yloxy]-1-[(octyloxy)methyl]ethyl}azetidine,

(hexyloxy)-N,N-dimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2S)-1-(heptyloxy)-N,Ndimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-

N,N-dimethyl-1-(nonyloxy)-3-[(9Z, 12Z)-2-amine. octadeca-9,12-dien-1-yloxy]propan-2-amine, N,Ndimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy) propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z, 12Z)-5 octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2amine, (2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,Ndimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,Ndimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-10 yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(13Z, 16Z)-docosa-13,16-dien-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13, 16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine. (2R)-N,N-dimethyl-H(1-metoylo ctyl)oxy]-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, 20 (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-N,N-dimethyl-1-{[8-(2-oc1ylcyclopropyl)octyl] 25 amine, oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)-N,Ndimethylnonacosa-11,20,2-trien-10-amine or pharmaceutically acceptable salt or stereoisomer thereof.

In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 3% 30 lipid molar ratio. In some embodiments, the LNP formulations of the RNA (e.g., mRNA) vaccines may contain PEG-c-DOMG at 1.5% lipid molar ratio.

In some embodiments, the pharmaceutical compositions of the RNA (e.g., mRNA) vaccines may include at least one 35 of the PEGylated lipids described in International Publication No. WO2012099755, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the LNP formulation may contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phophoe- 40 thanolamine-N-[methoxy(polyethylene glycol)-2000). In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In some embodiments, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in 45 the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 50 2:40:10:48 (see e.g., Geall et al., Nonviral delivery of self-amplifying RNA (e.g., mRNA) vaccines, PNAS 2012; PMID: 22908294, the contents of each of which are herein incorporated by reference in their entirety).

The lipid nanoparticles described herein may be made in 55 a sterile environment.

In some embodiments, the LNP formulation may be formulated in a nanoparticle such as a nucleic acid-lipid particle. As a non-limiting example, the lipid particle may comprise one or more active agents or therapeutic agents; 60 one or more cationic lipids comprising from about 50 mol % to about 85 mol % of the total lipid present in the particle; one or more non-cationic lipids comprising from about 13 mol % to about 49.5 mol % of the total lipid present in the particle; and one or more conjugated lipids that inhibit 65 aggregation of particles comprising from about 0.5 mol % to about 2 mol % of the total lipid present in the particle.

The nanoparticle formulations may comprise a phosphate conjugate. The phosphate conjugate may increase in vivo circulation times and/or increase the targeted delivery of the nanoparticle. As a non-limiting example, the phosphate conjugates may include a compound of any one of the formulas described in International Application No. WO2013033438, the contents of which are herein incorporated by reference in its entirety.

The nanoparticle formulation may comprise a polymer conjugate. The polymer conjugate may be a water soluble conjugate. The polymer conjugate may have a structure as described in U.S. Patent Application No. 20130059360, the contents of which are herein incorporated by reference in its entirety. In some embodiments, polymer conjugates with the polynucleotides of the present disclosure may be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, the contents of which are herein incorporated by reference in its entirety. In some embodiments, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Patent Publication No. US20130196948, the contents which are herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present disclosure in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In one aspect, the conjugate may be a "self" peptide designed from the human membrane protein CD47 (e.g., the "self" particles described by Rodriguez et al. (Science 2013 339, 971-975), herein incorporated by reference in its entirety). As shown by Rodriguez et al., the self peptides delayed macrophagemediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In another aspect, the conjugate may be the membrane protein CD47 (e.g., see Rodriguez et al. Science 2013 339, 971-975, herein incorporated by reference in its entirety). Rodriguez et al. showed that, similarly to "self" peptides, CD47 can increase the circulating particle ratio in a subject as compared to scrambled peptides and PEG coated nanoparticles.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure are formulated in nanoparticles which comprise a conjugate to enhance the delivery of the nanoparticles of the present disclosure in a subject. The conjugate may be the CD47 membrane or the conjugate may be derived from the CD47 membrane protein, such as the "self" peptide described previously. In some embodiments, the nanoparticle may comprise PEG and a conjugate of CD47 or a derivative thereof. In some embodiments, the nanoparticle may comprise both the "self" peptide described above and the membrane protein CD47.

In some embodiments, a "self" peptide and/or CD47 protein may be conjugated to a virus-like particle or pseudovirion, as described herein for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure.

In some embodiments, RNA (e.g., mRNA) vaccine pharmaceutical compositions comprising the polynucleotides of the present disclosure and a conjugate that may have a degradable linkage. Non-limiting examples of conjugates include an aromatic moiety comprising an ionizable hydrogen atom, a spacer moiety, and a water-soluble polymer. As a non-limiting example, pharmaceutical compositions comprising a conjugate with a degradable linkage and methods for delivering such pharmaceutical compositions are described in U.S. Patent Publication No. US20130184443, the contents of which are herein incorporated by reference in their entirety. The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a RNA (e.g., mRNA) vaccine. As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phtoglycogen octenyl succinate, phytoglycogen betadextrin, anhydride-modified phytoglycogen beta-dextrin. (See e.g., International Publication No. WO2012109121; the contents of which are herein incorporated by reference in their entirety).

Nanoparticle formulations of the present disclosure may be coated with a surfactant or polymer in order to improve the delivery of the particle. In some embodiments, the nanoparticle may be coated with a hydrophilic coating such as, but not limited to, PEG coatings and/or coatings that have 15 a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA (e.g., mRNA) vaccines within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making 20 such nanoparticles are described in U.S. Patent Publication No. US20130183244, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophilic polymer particles. 25 Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in U.S. Patent Publication No. US20130210991, the contents of which are herein incorporated by reference in their entirety. 30

In some embodiments, the lipid nanoparticles of the present disclosure may be hydrophobic polymer particles.

Lipid nanoparticle formulations may be improved by replacing the cationic lipid with a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanopar- 35 ticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can 40 improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still 45 maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

In some embodiments, the internal ester linkage may be located on either side of the saturated carbon.

In some embodiments, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publi-55 cation No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified 60 RNA and/or a polynucleotide described herein. In some embodiments, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

Lipid nanoparticles may be engineered to alter the surface 65 properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal 86

tissue such as, but not limited to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosa tissue within seconds or within a few hours. Large polymeric nanoparticles (200 nm-500 nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. Adv Drug Deliv Rev. 2009 61(2): 158-171; each of which is herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions which can penetrate a mucosal barrier may be made as described in U.S. Pat. No. 8,241,670 or International Patent Publication No. WO2013110028, the contents of each of which are herein incorporated by reference in its entirety.

The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of biocompatible polymers are described in International Patent Publication No. WO2013116804, the contents of which are herein incorporated by reference in their entirety. The polymeric material may additionally be irradiated. As a non-limiting example, the polymeric material may be gamma irradiated (see e.g., International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly (lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acidco-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly (L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,Llactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPOco-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly (ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), poly-

vinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth) 5 acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl (meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl (meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl (meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), 10 poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), PEG-PLGA-PEG 15 and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein 20 incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see e.g., U.S. Publication 20120121718 and U.S. Publication 20100003337 and U.S. Pat. No. 8,263, 665, the contents of each of which is herein incorporated by 25 reference in their entirety). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nano- 30 particles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; the contents of which are herein incorporated by reference in their entirety). A non-limiting scalable method to produce nanoparticles 35 which can penetrate human mucus is described by Xu et al. (see, e.g., J Control Release 2013, 170(2):279-86; the contents of which are herein incorporated by reference in their entirety).

The vitamin of the polymer-vitamin conjugate may be 40 vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon 45 chains and alkylene oxide chains).

The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, polynucleotides, anionic proteins (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for 50 example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, car- 55 bocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin 34 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed 60 (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see e.g., U.S. Publication 20100215580 and U.S. Publication 20080166414 and US20130164343; the contents of each of which are herein incorporated by reference in their entirety). 65

In some embodiments, the mucus penetrating lipid nanoparticles may comprise at least one polynucleotide described herein. The polynucleotide may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the particle. The polynucleotide may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion, which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

In some embodiments, the mucus penetrating lipid nanoparticles may be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation may be hypotonice for the epithelium to which it is being delivered. Non-limiting examples of hypotonic formulations may be found in International Patent Publication No. WO2013110028, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, in order to enhance the delivery through the mucosal barrier the RNA (e.g., mRNA) vaccine formulation may comprise or be a hypotonic solution.

Hypotonic solutions were found to increase the rate at which mucoinert particles such as, but not limited to, mucus-penetrating particles, were able to reach the vaginal epithelial surface (see e.g., Ensign et al. Biomaterials 2013 34(28):6922-9, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a lipoplex, such as, without limitation, the ATUPLEX[™] system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT[™] from STEMGENT® (Cambridge, Mass.), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids acids (Aleku et al. Cancer Res. 2008 68:9788-9798; Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293 Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci USA. 2007 6; 104:4095-4100; deFougerolles Hum Gene Ther. 2008 19:125-132, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types in vivo, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations, which have been shown to bind to apolipoprotein E and promote binding

and uptake of these formulations into hepatocytes in vivo (Akinc et al. Mol Ther. 2010 18:1357-1364, the contents of which are incorporated herein by reference in their entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exempli-5 fied by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et 10 al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 15 may include, but is not limited to, tri-block co-polymers. As 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci USA. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 20 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine is formulated as a solid lipid nanoparticle. A solid lipid nano- 25 particle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In some embodiments, the lipid nanoparticle may be a self-assembly 30 lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696-1702; the contents of which are herein incorporated by reference in their entirety). As a nonlimiting example, the SLN may be the SLN described in International Patent Publication No. WO2013105101, the 35 contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the SLN may be made by the methods or processes described in International Patent Publication No. WO2013105101, the contents of which are herein incorporated by reference in 40 their entirety.

Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of polynucleotides directed protein production as these formulations may be able to increase cell transfection by the RNA (e.g., mRNA) vaccine; and/or 45 increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15:713-720; the contents of which are incorporated herein by reference in their entirety). 50 The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the polynucleotide.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure can be formulated for controlled release and/or targeted delivery. As used herein, "controlled 55 release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a delivery agent described herein and/or known in 60 the art for controlled release and/or targeted delivery. As used herein, the term "encapsulate" means to enclose, surround or encase. As it relates to the formulation of the compounds of the disclosure, encapsulation may be substantial, complete or partial. The term "substantially encapsu- 65 lated" means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the

pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. "Partially encapsulation" means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the disclosure may be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation may be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the disclosure using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the disclosure are encapsulated in the delivery agent.

In some embodiments, the controlled release formulation a non-limiting example, the formulation may include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and WO2012131106, the contents of each of which are incorporated herein by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, Fla.), HYL-ENEX® (Halozyme Therapeutics, San Diego Calif.), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, Ga.), TISSELL® (Baxter International, Inc Deerfield, Ill.), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, Ill.).

In some embodiments, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another nonlimiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In some embodiments, the RNA (e.g., mRNA) vaccine formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxyethyl hydroxypropyl cellulose, cellulose. EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUA-COAT® and SURELEASE®).

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(Llactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release and/or targeted delivery formulation comprising at least one polynucleotide may comprise at least one PEG and/or PEG related polymer derivatives as described in U.S. Pat. No. 8,404,222, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine controlled release delivery formulation comprising at least one polynucleotide may be the controlled release polymer system described in US20130130348, the contents of which are incorporated herein by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be encapsulated in a therapeutic nanoparticle, referred to herein as "therapeutic nanoparticle⁵ RNA (e.g., mRNA) vaccines." Therapeutic nanoparticles may be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, U.S. Publication Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and U.S. Pat. Nos. 8,206,747, 8,293,276, 8,318,208 and 15 8,318,211; the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, therapeutic polymer nanoparticles may be identified by the methods described in US Pub No. US20120140790, the contents of which are herein incorporated by reference in 20 their entirety.

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccine may be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or compound that conforms to 25 a release rate over a specific period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides 30 of the present disclosure (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, the contents of each of which are incorporated herein by reference in their entirety). In another non-limiting example, the sustained 35 release formulation may comprise agents which permit persistent bioavailability such as, but not limited to, crystals, macromolecular gels and/or particulate suspensions (see U.S. Patent Publication No US20130150295, the contents of each of which are incorporated herein by reference in their 40 entirety).

In some embodiments, the therapeutic nanoparticle RNA (e.g., mRNA) vaccines may be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles may include a corticosteroid (see International Pub. 45 No. WO2011084518, the contents of which are incorporated herein by reference in their entirety). As a non-limiting example, the therapeutic nanoparticles may be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, so WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, the contents of each of which are incorporated herein by reference in their entirety.

In some embodiments, the nanoparticles of the present 55 disclosure may comprise a polymeric matrix. As a nonlimiting example, the nanoparticle may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyac- 60 etals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L- 65 lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

In some embodiments, the therapeutic nanoparticle comprises a diblock copolymer. In some embodiments, the diblock copolymer may include PEG in combination with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof. In yet another embodiment, the diblock copolymer may be a high-X diblock copolymer such as those described in International Patent Publication No. WO2013120052, the contents of which are incorporated herein by reference in their entirety.

As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (see U.S. Publication No. US20120004293 and U.S. Pat. No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (see U.S. Pat. No. 8,246,968 and International Publication No. WO2012166923, the contents of each of which are herein incorporated by reference in their entirety). In yet another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle or a target-specific stealth nanoparticle as described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In yet another non-limiting example, the lipid nanoparticle comprises the block copolymer PEG-PLGA-PEG (see e.g., the thermosensitive hydrogel (PEG-PLGA-PEG) was used as a TGF-beta1 gene delivery vehicle in Lee et al. Thermosensitive Hydrogel as a Tgf-ß1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. Pharmaceutical Research, 2003 20(12): 1995-2000; as a controlled gene delivery system in Li et al. Controlled Gene Delivery System Based on Thermosensitive Biodegradable Hydrogel. Pharmaceutical Research 2003 20(6):884-888; and Chang et al., Non-ionic amphiphilic biodegradable PEG-PLGA-PEG copolymer enhances gene delivery efficiency in rat skeletal muscle. J Controlled Release. 2007 118:245-253, the contents of each of which are herein incorporated by reference in their entirety). The RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles comprising the PEG-PLGA-PEG block copolymer.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (see e.g., U.S. Pat. Nos. 8,263,665 and 8,287,910 and U.S. Patent Pub. No. US20130195987, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the block copolymers described herein may be included in a polyion complex comprising a non-polymeric micelle and the block copolymer. (see e.g., U.S. Publication No. 20120076836, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticle may comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid,

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acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly (acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

In some embodiments, the therapeutic nanoparticles may comprise at least one poly(vinyl ester) polymer. The poly (vinyl ester) polymer may be a copolymer such as a random copolymer. As a non-limiting example, the random copolymer may have a structure such as those described in Inter- 10 national Application No. WO2013032829 or U.S. Patent Publication No US20130121954, the contents of each of which are herein incorporated by reference in their entirety. In some embodiments, the poly(vinyl ester) polymers may be conjugated to the polynucleotides described herein.

In some embodiments, the therapeutic nanoparticle may comprise at least one diblock copolymer. The diblock copolymer may be, but it not limited to, a poly(lactic) acid-poly (ethylene)glycol copolymer (see, e.g., International Patent Publication No. WO2013044219, the contents of which are 20 herein incorporated by reference in their entirety).

As a non-limiting example, the therapeutic nanoparticle may be used to treat cancer (see International publication No. WO2013044219, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

In some embodiments, the therapeutic nanoparticles may comprise at least one amine-containing polymer such as, but 30 not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers, poly(beta-amino esters) (see, e.g., U.S. Pat. No. 8,287,849, the contents of which are herein incorporated by reference in their entirety) and combinations thereof.

In some embodiments, the nanoparticles described herein may comprise an amine cationic lipid such as those described in International Patent Application No. WO2013059496, the contents of which are herein incorporated by reference in their entirety. In some embodiments, 40 the cationic lipids may have an amino-amine or an aminoamide moiety.

In some embodiments, the therapeutic nanoparticles may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters 45 include, but are not limited to, poly(serine ester), poly(Llactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In some embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer. 50

In some embodiments, the synthetic nanocarriers may contain an immunostimulatory agent to enhance the immune response from delivery of the synthetic nanocarrier. As a non-limiting example, the synthetic nanocarrier may comprise a Th1 immunostimulatory agent, which may enhance 55 a Th1-based response of the immune system (see International Pub No. WO2010123569 and U.S. Publication No. US20110223201, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarriers may be 60 formulated for targeted release. In some embodiments, the synthetic nanocarrier is formulated to release the polynucleotides at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle may be formulated to release the RNA (e.g., mRNA) vaccines 65 after 24 hours and/or at a pH of 4.5 (see International Publication Nos. WO2010138193 and WO2010138194 and

US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entireties).

In some embodiments, the synthetic nanocarriers may be formulated for controlled and/or sustained release of the polynucleotides described herein. As a non-limiting example, the synthetic nanocarriers for sustained release may be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline side chain (CYSC) polymer. CYSC polymers are described in U.S. Pat. No. 8,399,007, herein incorporated by reference in its entirety.

In some embodiments, the synthetic nanocarrier may be formulated for use as a vaccine. In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide which encode at least one antigen. As a nonlimiting example, the synthetic nanocarrier may include at least one antigen and an excipient for a vaccine dosage form (see International Publication No. WO2011150264 and U.S. Publication No. US20110293723, the contents of each of which are herein incorporated by reference in their entirety). As another non-limiting example, a vaccine dosage form may include at least two synthetic nanocarriers with the same or different antigens and an excipient (see International Publication No. WO2011150249 and U.S. Publication No. US20110293701, the contents of each of which are herein incorporated by reference in their entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International Publica-35 tion No. WO2011150258 and U.S. Publication No. US20120027806, the contents of each of which are herein incorporated by reference in their entirety).

In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide which encodes at least one adjuvant. As non-limiting example, the adjuvant may comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a mycobacterium (see, e.g., U.S. Pat. No. 8,241,610, the content of which is herein incorporated by reference in its entirety). In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant may be formulated by the methods described in International Publication No. WO2011150240 and U.S. Publication No. US20110293700, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may encapsulate at least one polynucleotide that encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier may include, but is not limited to, any of the nanocarriers described in International WO2012024621, WO201202629. Publication No. WO2012024632 and U.S. Publication No. US20120064110, US20120058153 and US20120058154, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the synthetic nanocarrier may be coupled to a polynucleotide which may be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response

(see, e.g., International Publication No. WO2013019669, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccine may be encapsulated in, linked to and/or associated with 5 zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in U.S. Patent Publication No. US20130216607, the contents of which are herein incorporated by reference in their entirety.

In some aspects, the zwitterionic lipids may be used in the liposomes and lipid nanoparticles described herein.

In some embodiments, the RNA (e.g., mRNA) vaccine may be formulated in colloid nanocarriers as described in U.S. Patent Publication No. US20130197100, the contents 15 of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticle may be optimized for oral administration. The nanoparticle may comprise at least one cationic biopolymer such as, but not limited to, 20 chitosan or a derivative thereof. As a non-limiting example, the nanoparticle may be formulated by the methods described in U.S. Publication No. 20120282343, the contents of which are herein incorporated by reference in their entirety. 25

In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832, the contents of which are herein incorporated by reference in their entirety. Activity and/or safety (as measured by examining one or more of ALT/AST, white 30 blood cell count and cytokine induction, for example) of LNP administration may be improved by incorporation of such lipids. LNPs comprising KL52 may be administered intravenously and/or in one or more doses. In some embodiments, administration of LNPs comprising KL52 results in 35 equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

In some embodiments, RNA (e.g., mRNA) vaccine may be delivered using smaller LNPs. Such particles may comprise a diameter from below 0.1 um up to 100 nm such as, 40 but not limited to, less than 0.1 um, less than 1.0 um, less than 5 um, less than 10 um, less than 15 um, less than 20 um, less than 25 um, less than 30 um, less than 35 um, less than 40 um, less than 50 um, less than 55 um, less than 60 um, less than 65 um, less than 70 um, less than 75 um, less than 45 80 um, less than 85 um, less than 90 um, less than 95 um, less than 100 um, less than 125 um, less than 150 um, less than 175 um, less than 200 um, less than 225 um, less than 250 um, less than 275 um, less than 300 um, less than 325 um, less than 350 um, less than 375 um, less than 400 um, 50 less than 425 um, less than 450 um, less than 475 um, less than 500 um, less than 525 um, less than 550 um, less than 575 um, less than 600 um, less than 625 um, less than 650 um, less than 675 um, less than 700 um, less than 725 um, less than 750 um, less than 775 um, less than 800 um, less 55 than 825 um, less than 850 um, less than 875 um, less than 900 um, less than 925 um, less than 950 um, less than 975 um, or less than 1000 um.

In some embodiments, RNA (e.g., mRNA) vaccines may be delivered using smaller LNPs, which may comprise a 60 diameter from about 1 nm to about 100 nm, from about 1 nm to about 10 nm, about 1 nm to about 20 nm, from about 1 nm to about 30 nm, from about 1 nm to about 40 nm, from about 1 nm to about 50 nm, from about 1 nm to about 60 nm, from about 1 nm to about 70 nm, from about 1 nm to about 65 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about from 100 nm, from about 5 nm to about 10 nm,

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about 5 nm to about 20 nm, from about 5 nm to about 30 nm, from about 5 nm to about 40 nm, from about 5 nm to about 50 nm, from about 5 nm to about 60 nm, from about 5 nm to about 70 nm, from about 5 nm to about 80 nm, from about 5 nm to about 90 nm, about 10 to about 50 nm, from about 20 to about 50 nm, from about 30 to about 50 nm, from about 40 to about 50 nm, from about 20 to about 60 nm, from about 30 to about 60 nm, from about 40 to about 60 nm, from about 20 to about 70 nm, from about 30 to about 70 nm, from about 40 to about 70 nm, from about 50 to about 70 nm, from about 60 to about 70 nm, from about 20 to about 80 nm, from about 30 to about 80 nm, from about 40 to about 80 nm, from about 50 to about 80 nm, from about 60 to about 80 nm, from about 20 to about 90 nm, from about 30 to about 90 nm, from about 40 to about 90 nm, from about 50 to about 90 nm, from about 60 to about 90 nm and/or from about 70 to about 90 nm.

In some embodiments, such LNPs are synthesized using methods comprising microfluidic mixers. Examples of microfluidic mixers may include, but are not limited to, a slit interdigital micromixer including, but not limited to those manufactured by Microinnova (Allerheiligen bei Wildon, Austria) and/or a staggered herringbone micromixer (SHM) (Zhigaltsev, I. V. et al., Bottom-up design and synthesis of limit size lipid nanoparticle systems with aqueous and triglyceride cores using millisecond microfluidic mixing have been published (Langmuir. 2012. 28:3633-40; Belliveau, N. M. et al., Microfluidic synthesis of highly potent limit-size lipid nanoparticles for in vivo delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012. 1:e37; Chen, D. et al., Rapid discovery of potent siRNA-containing lipid nanoparticles enabled by controlled microfluidic formulation. J Am Chem Soc. 2012. 134(16):6948-51, the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructureinduced chaotic advection (MICA). According to this method, fluid streams flow through channels present in a herringbone pattern causing rotational flow and folding the fluids around each other. This method may also comprise a surface for fluid mixing wherein the surface changes orientations during fluid cycling. Methods of generating LNPs using SHM include those disclosed in U.S. Application Publication Nos. 2004/0262223 and 2012/0276209, the contents of each of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccine of the present disclosure may be formulated in lipid nanoparticles created using a micromixer such as, but not limited to, a Slit Interdigital Microstructured Mixer (SIMM-V2) or a Standard Slit Interdigital Micro Mixer (SSIMM) or Caterpillar (CPMM) or Impinging-jet (IJMM) from the Institut fiir Mikrotechnik Mainz GmbH, Mainz Germany).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using microfluidic technology (see, e.g., Whitesides, George M. The Origins and the Future of Microfluidics. Nature, 2006 442: 368-373; and Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651; each of which is herein incorporated by reference in its entirety). As a non-limiting example, controlled microfluidic formulation includes a passive method for mixing streams of steady pressure-driven flows in micro channels at a low Reynolds number (see, e.g., Abraham et al. Chaotic Mixer for Microchannels. Science, 2002 295: 647-651, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the RNA (e.g., mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, Mass.) or Dolomite Microfluidics (Royston, UK). A micromixer 5 chip can be used for rapid mixing of two or more fluid streams with a split and recombine mechanism.

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated for delivery using the drug encapsulating microspheres described in International Pat-10 ent Publication No. WO2013063468 or U.S. Pat. No. 8,440, 614, the contents of each of which are herein incorporated by reference in their entirety. The microspheres may comprise a compound of the formula (I), (II), (II), (IV), (V) or (VI) as described in International Patent Publication No. 15 WO2013063468, the contents of which are herein incorporated by reference in their entirety. In some embodiments, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the RNA (e.g., mRNA) vaccines of the disclosure to cells (see International Patent Publication No. 20 WO2013063468, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines of the disclosure may be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, 25 but not limited to, about 10 to about 20 nm, about 10 to about 30 nm, about 10 to about 40 nm, about 10 to about 50 nm, about 10 to about 60 nm, about 10 to about 70 nm, about 10 to about 80 nm, about 10 to about 90 nm, about 20 to about 30 nm, about 20 to about 40 nm, about 20 to about 50 nm, 30 about 20 to about 60 nm, about 20 to about 70 nm, about 20 to about 80 nm, about 20 to about 90 nm, about 20 to about 100 nm, about 30 to about 40 nm, about 30 to about 50 nm, about 30 to about 60 nm, about 30 to about 70 nm, about 30 to about 80 nm, about 30 to about 90 nm, about 30 to about 35 100 nm, about 40 to about 50 nm, about 40 to about 60 nm, about 40 to about 70 nm, about 40 to about 80 nm, about 40 to about 90 nm, about 40 to about 100 nm, about 50 to about 60 nm, about 50 to about 70 nm about 50 to about 80 nm, about 50 to about 90 nm, about 50 to about 100 nm, about 40 60 to about 70 nm, about 60 to about 80 nm, about 60 to about 90 nm, about 60 to about 100 nm, about 70 to about 80 nm, about 70 to about 90 nm, about 70 to about 100 nm, about 80 to about 90 nm, about 80 to about 100 nm and/or about 90 to about 100 nm.

In some embodiments, the lipid nanoparticles may have a diameter from about 10 to 500 nm.

In some embodiments, the lipid nanoparticle may have a diameter greater than 100 nm, greater than 150 nm, greater than 200 nm, greater than 250 nm, greater than 300 nm, 50 greater than 350 nm, greater than 400 nm, greater than 450 nm, greater than 500 nm, greater than 550 nm, greater than 600 nm, greater than 650 nm, greater than 750 nm, greater than 550 nm, greater 550 nm, greater 550 nm, greater 550 nm, greater 550 nm, grea

In some embodiments, the lipid nanoparticle may be a limit size lipid nanoparticle described in International Patent Publication No. WO2013059922, the contents of which are herein incorporated by reference in their entirety. The limit 60 size lipid nanoparticle may comprise a lipid bilayer surrounding an aqueous core or a hydrophobic core; where the lipid bilayer may comprise a phospholipid such as, but not limited to, diacylphosphatidylcholine, a diacylphosphatidylethanolamine, a ceramide, a sphingomyelin, a dihy- 65 drosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphophatidylcholine, and 1-palmitoyl-2-oleoyl

phosphatidylcholine (POPC). In some embodiments, the limit size lipid nanoparticle may comprise a polyethylene glycol-lipid such as, but not limited to, DLPE-PEG, DMPE-PEG, DPPC-PEG and DSPE-PEG.

In some embodiments, the RNA (e.g., mRNA) vaccines may be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Patent Publication No. WO2013063530, the contents of which are herein incorporated by reference in their entirety. As a non-limiting example, a subject may be administered an empty polymeric particle prior to, simultaneously with or after delivering the RNA (e.g., mRNA) vaccines to the subject. The empty polymeric particle undergoes a change in volume once in contact with the subject and becomes lodged, embedded, immobilized or entrapped at a specific location in the subject.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in an active substance release system (see, e.g., U.S. Patent Publication No. US20130102545, the contents of which are herein incorporated by reference in their entirety). The active substance release system may comprise 1) at least one nanoparticle bonded to an oligonucleotide inhibitor strand which is hybridized with a catalytically active nucleic acid and 2) a compound bonded to at least one substrate molecule bonded to a therapeutically active substance (e.g., polynucleotides described herein), where the therapeutically active substance is released by the cleavage of the substrate molecule by the catalytically active nucleic acid.

In some embodiments, the RNA (e.g., mRNA) vaccines may be formulated in a nanoparticle comprising an inner core comprising a non-cellular material and an outer surface comprising a cellular membrane. The cellular membrane may be derived from a cell or a membrane derived from a virus. As a non-limiting example, the nanoparticle may be made by the methods described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the nanoparticle described in International Patent Publication No. WO2013052167, the contents of which are herein incorporated by reference in their entirety, may be used to deliver the RNA (e.g., mRNA) vaccines described herein.

In some embodiments, the RNA (e.g., mRNA) vaccines 45 may be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Patent Publication No. WO2013056132, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in polymeric nanoparticles as described in or made by the methods described in U.S. Pat. Nos. 8,420,123 and 8,518,963 and European Patent No. EP2073848B1, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, the polymeric nanoparticle may have a high glass transition temperature such as the nanoparticles described in U.S. Pat. No. 8,518,963, the contents of which are herein incorporated by reference in their entirety. As another non-limiting example, the polymer nanoparticle for oral and parenteral formulations may be made by the methods described in European Patent No. EP2073848B1, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the RNA (e.g., mRNA) vaccines described herein may be formulated in nanoparticles used in imaging. The nanoparticles may be liposome nanoparticles

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such as those described in U.S. Patent Publication No US20130129636, herein incorporated by reference in its entirety. As a non-limiting example, the liposome may comprise gadolinium(III)2-{4,7-bis-carboxymethyl-10-[(N, N-distearylamidomethyl-N'-amido-methyl]-1,4,7,10-tetra-azacyclododec-1-yl}-acetic acid and a neutral, fully saturated phospholipid component (see, e.g., U.S. Patent Publication No US20130129636, the contents of which are herein incorporated by reference in their entirety).

In some embodiments, the nanoparticles which may be used in the present disclosure are formed by the methods described in U.S. Patent Application No. US20130130348, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles of the present disclosure may further include nutrients such as, but not limited to, those which deficiencies can lead to health hazards from anemia to neural tube defects (see, e.g., the nanoparticles described in International Patent Publication No WO2013072929, the con-20 tents of which are herein incorporated by reference in their entirety). As a non-limiting example, the nutrient may be iron in the form of ferrous, ferric salts or elemental iron, iodine, folic acid, vitamins or micronutrients.

In some embodiments, the RNA (e.g., mRNA) vaccines of 25 the present disclosure may be formulated in a swellable nanoparticle. The swellable nanoparticle may be, but is not limited to, those described in U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety. As a non-limiting embodiment, the swellable 30 nanoparticle may be used for delivery of the RNA (e.g., mRNA) vaccines of the present disclosure to the pulmonary system (see, e.g., U.S. Pat. No. 8,440,231, the contents of which are herein incorporated by reference in their entirety).

The RNA (e.g., mRNA) vaccines of the present disclosure 35 may be formulated in polyanhydride nanoparticles such as, but not limited to, those described in U.S. Pat. No. 8,449, 916, the contents of which are herein incorporated by reference in their entirety.

The nanoparticles and microparticles of the present dis- 40 closure may be geometrically engineered to modulate macrophage and/or the immune response. In some embodiments, the geometrically engineered particles may have varied shapes, sizes and/or surface charges in order to incorporated the polynucleotides of the present disclosure for targeted 45 delivery such as, but not limited to, pulmonary delivery (see, e.g., International Publication No WO2013082111, the contents of which are herein incorporated by reference in their entirety). Other physical features the geometrically engineering particles may have include, but are not limited to, 50 fenestrations, angled arms, asymmetry and surface roughness, charge which can alter the interactions with cells and tissues. As a non-limiting example, nanoparticles of the present disclosure may be made by the methods described in International Publication No WO2013082111, the contents 55 of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure may be water soluble nanoparticles such as, but not limited to, those described in International Publication 60 No. WO2013090601, the contents of which are herein incorporated by reference in their entirety. The nanoparticles may be inorganic nanoparticles which have a compact and zwitterionic ligand in order to exhibit good water solubility. The nanoparticles may also have small hydrodynamic diam-65 eters (HD), stability with respect to time, pH, and salinity and a low level of non-specific protein binding.

In some embodiments the nanoparticles of the present disclosure may be developed by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the nanoparticles of the present disclosure are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety. The nanoparticles of the present disclosure may be made by the methods described in U.S. Patent Publication No. US20130172406, the contents of which are herein incorporated by reference in their entirety.

In some embodiments, the stealth or target-specific stealth nanoparticles may comprise a polymeric matrix. The polymeric matrix may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, polyurethanes, polymethacrylates, polyacrylates, polycyanoacrylates, polycyanoacrylates, polycyanoacrylates or combinations thereof.

In some embodiments, the nanoparticle may be a nanoparticle-nucleic acid hybrid structure having a high density nucleic acid layer. As a non-limiting example, the nanoparticle-nucleic acid hybrid structure may made by the methods described in U.S. Patent Publication No. US20130171646, the contents of which are herein incorporated by reference in their entirety. The nanoparticle may comprise a nucleic acid such as, but not limited to, polynucleotides described herein and/or known in the art.

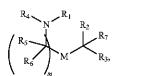
At least one of the nanoparticles of the present disclosure may be embedded in in the core a nanostructure or coated with a low density porous 3-D structure or coating which is capable of carrying or associating with at least one payload within or on the surface of the nanostructure. Non-limiting examples of the nanostructures comprising at least one nanoparticle are described in International Patent Publication No. WO2013123523, the contents of which are herein incorporated by reference in their entirety.

In some embodiments the RNA (e.g., mRNA) vaccine may be associated with a cationic or polycationic compounds, including protamine, nucleoline, spermine or spermidine, or other cationic peptides or proteins, such as poly-L-lysine (PLL), polyarginine, basic polypeptides, cell penetrating peptides (CPPs), including HIV-binding peptides, HIV-1 Tat (HIV), Tat-derived peptides, Penetratin, VP²² derived or analog peptides, Pestivirus Erns, HSV, VP²² (Herpes simplex), MAP, KALA or protein transduction domains (PTDs), PpT620, prolin-rich peptides, arginine-rich peptides, lysine-rich peptides, MPG-peptide(s), Pep-1, L-oligomers, Calcitonin peptide(s), Antennapedia-derived peptides (particularly from Drosophila antennapedia), pAntp, pIsl, FGF, Lactoferrin, Transportan, Buforin-2, Bac715-24, SynB, SynB(1), pVEC, hCT-derived peptides, SAP, histones, cationic polysaccharides, for example chitosan, polybrene, cationic polymers, e.g. polyethyleneimine (PEI), cationic lipids, e.g. DOTMA: [1-(2,3-sioleyloxy) propyl)]-N,N,N-trimethylammonium chloride, DMRIE, di-C14-amidine, DOTIM, SAINT, DC-Chol, BGTC, CTAP, DOPC, DODAP, DOPE: Dioleyl phosphatidylethanolamine, DOSPA, DODAB, DOIC, DMEPC, DOGS: Dioctadecylamidoglicylspermin, DIMRI: Dimyristooxypropyl

dimethyl hydroxyethyl ammonium bromide, DOTAP: dioleoyloxy-3-(trimethylammonio)propane, DC-6-14: O,Oditetradecanoyl-N-.alpha.-trimethylammonioacetyl)diethanolamine chloride, CLIP 1: rac-[(2,3-dioctadecyloxypropyl) (2-hydroxyethyl)]-dimethylammonium chloride, CLIP6: 5 rac-[2(2,3-dihexadecvloxvpropyloxymethyloxy)ethyl]trimethylammonium, CLIP9: rac-[2(2,3-dihexadecvloxypropyloxysuccinyloxy)ethyl]-trimethylammonium, oligofectamine, or cationic or polycationic polymers, e.g. modified polyaminoacids, such as beta-aminoacid-polymers or reversed polyamides, etc., modified polyethylenes, such as PVP (poly(N-ethyl-4-vinylpyridinium bromide)), etc., modified acrylates, such as pDMAEMA (poly(dimethylaminoethyl methylacrylate)), etc., modified amidoamines such as pAMAM (poly(amidoamine)), etc., modified polybetaminoester (PBAE), such as diamine end modified 1,4 butanediol diacrylate-co-5-amino-1-pentanol polymers, etc., dendrimers, such as polypropylamine dendrimers or pAMAM based dendrimers, etc., polyimine(s), such as PEI: 20 poly(ethyleneimine), poly(propyleneimine), etc., polyallylamine, sugar backbone based polymers, such as cyclodextrin based polymers, dextran based polymers, chitosan, etc., silan backbone based polymers, such as PMOXA-PDMS copolymers, etc., blockpolymers consisting of a combina- 25 tion of one or more cationic blocks (e.g. selected from a cationic polymer as mentioned above) and of one or more hydrophilic or hydrophobic blocks (e.g. polyethyleneglycole), etc.

In other embodiments the RNA (e.g., mRNA) vaccine is not associated with a cationic or polycationic compounds.

In some embodiments, a nanoparticle comprises compounds of Formula (I):



or a salt or isomer thereof, wherein:

 R_1 is selected from the group consisting of C_{5-30} alkyl, 45 C₅₋₂₀ alkenyl, -R*YR", -YR", and -R"M'R';

 \mathbf{R}_2 and \mathbf{R}_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3 , together with the atom to which they are attached, form a heterocycle or carbocycle; 50 R₄ is selected from the group consisting of a C₃₋₆ carbo-

cycle, $-(CH_2)_n Q$, $-(CH_2)_n CHQR$,

-CHQR, --CQ(R)₂, and unsubstituted C₁₋₆ alkyl, where Q is selected from a carbocycle, heterocycle, -OR, $-O(CH_2)_n N(R)_2$, -C(O)OR, -OC(O)R, —CX₃, 55 $-CX_2H, -CXH_2, -CN, -N(R)_2, -C(O)N(R)_2, -N(R)$ C(O)R, $-N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, -N(R)C(S)N $(R)_{2}, -N(R)R_{8}, -O(CH_{2})_{\mu}OR, -N(R)C(=NR_{9})N(R)_{2},$ $-N(R)C(=CHR_9)N(R)_2$, $-OC(O)N(R)_2$, -N(R)C(O)OR, -N(OR)C(O)R, $-N(OR)S(O)_2R$, -N(OR)C(O)OR, 60 ing of C_{1-3} alkyl, C_{2-3} alkenyl, and H; $-N(OR)C(O)N(R)_2$, $-N(OR)C(S)N(R)_2$, -N(OR)C $(=NR_9)N(R)_2, -N(OR)C(=CHR_9)N(R)_2, -C(=NR_9)N(R)_2$ $(R)_2$, $-C(=NR_9)R$, -C(O)N(R)OR, and $-C(R)N(R)_2C$ (O)OR, and each n is independently selected from 1, 2, 3, 4, and 5; 65

each R5 is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

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each R₆ is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

M and M' are independently selected from -C(O)O, -OC(O), -C(O)N(R'),

-N(R')C(O), -C(O), -C(S), -C(S)S, -SC(S)--, --CH(OH)--, --P(O)(OR')O--, --S(O)₂--, --S--

S—, an aryl group, and a heteroaryl group; R_7 is selected from the group consisting of $\rm C_{1-3}$ alkyl, $\rm C_{2-3}$

alkenyl, and H; R₈ is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

 R_9 is selected from the group consisting of H, CN, NO₂, C_{1-6} alkyl, -OR, $-S(O)_2R$, $-S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consist-15 ing of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R' is independently selected from the group consisting of C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, —R*YR", —YR", and H; each R" is independently selected from the group con-

sisting of C₃₋₁₄ alkyl and C₃₋₁₄ alkenyl; each R* is independently selected from the group consisting of C₁₋₁₂ alkyl and C₂₋₁₂ alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13.

In some embodiments, a subset of compounds of Formula (I) includes those in which when R_4 is $-(CH_2)_n Q$, $-(CH_2)_n$ CHQR, —CHQR, or $-CQ(R)_2$, then (i) Q is not $-N(R)_2$ when n is 1, 2, 3, 4 or 5, or (ii) Q is not 5, 6, or 7-membered heterocycloalkyl when n is 1 or 2.

In some embodiments, another subset of compounds of Formula (I) includes those in which

 $R_{\rm 1}$ is selected from the group consisting of $C_{\rm 5-30}$ alkyl, C₅₋₂₀ alkenyl, ---R*YR", ---YR", and ----R"M'R';

 R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3 , together with the atom to which they are attached, form a heterocycle or carbocycle; R_4 is selected from the group consisting of a C_{3-6} carbo-40 cycle, $-(CH_2)_n Q$, $-(CH_2)_n CHQR$,

-CHQR, -CQ(R)2, and unsubstituted C1-6 alkyl, where Q is selected from a C₃₋₆ carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR,

 $\begin{array}{l} - O(CH_2)N(R)_2, - C(O)OR, - OC(O)R, - CX_3, - CX_2H, \\ - CXH_2, - CN, - C(O)N(R)_2, - N(R)C(O)R, - N(R)S \end{array}$ $(O)_2 R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-CRN(R)_2$ $C(O)OR, -N(R)R_8, -O(CH_2)_nOR, -N(R)C(=NR_9)N$ $(R)_{2}, -N(R)C(=CHR_{9})N(R)_{2}, -OC(O)N(R)_{2}, -N(R)C(R)C(R)_{2}, -N(R)C(R)C(R)C(R)_{2}, -N(R)C(R)C(R)C(R)_{2}, -N(R)C(R)C(R)C(R)_{2}, -N(R)C(R)C(R)C(R)C(R)_{2}, -N(R)C(R)C(R)C(R)C(R)C(R))$ $(O)OR, -N(OR)C(O)R, -N(OR)S(O)_2R, -N(OR)C(O)$ $(=NR_9)N(R)_2, -N(OR)C(=CHR_9)N(R)_2, -C(=NR_9)N(R)_2$ $(R)_2$, $-C(=NR_9)R$, -C(O)N(R)O R, and a 5- to 14-membered heterocycloalkyl having one or more heteroatoms selected from N, O, and S which is substituted with one or more substituents selected from oxo (=O), OH, amino, mono- or di-alkylamino, and $\mathrm{C}_{1\text{-}3}$ alkyl, and each n is independently selected from 1, 2, 3, 4, and 5;

each R5 is independently selected from the group consist-

each R₆ is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O), -C(O)N(R'), -N(R')C(O), -C(O), -C(S), -C(S)S, -SC(S), -CH(OH), -P(O)(OR')O-, $-S(O)_2$, -S-S-, an aryl group, and a heteroaryl group;

(I)

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R7 is selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

 R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

 R_9 is selected from the group consisting of H, CN, NO₂, ⁵ C_{1-6} alkyl, -OR, $-S(O)_2R$, $-S(O)_2N(R)_2$, C_{2-6} alkenyl, C3-6 carbocycle and heterocycle;

each R is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R' is independently selected from the group consisting of C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, -R*YR", -YR", and H;

each R" is independently selected from the group consisting of C₃₋₁₄ alkyl and C₃₋₁₄ alkenyl;

each R* is independently selected from the group con- $_{15}$ sisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13, or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

 $R_{\rm 1}$ is selected from the group consisting of $C_{\text{5-30}}$ alkyl, C₅₋₂₀ alkenyl, —R*YR", —YR", and —R"M'R';

R₂ and R₃ are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3 , together with the atom

to which they are attached, form a heterocycle or carbocycle; R_{Δ} is selected from the group consisting of a C_{3-6} carbo- 30

cycle, $-(CH_2)_n Q$, $-(CH_2)_n CHQR$,

-CHQR, -CQ(R)₂, and unsubstituted C₁₋₆ alkyl, where Q is selected from a C_{3-6} carbocycle, a 5- to 14-membered heterocycle having one or more heteroatoms selected from N, O, and S, -OR,

 $-O(CH_2)_n N(R)_2$ -C(O)OR,-OC(O)R, ----CX,, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, -N(R)C(O)R,

 $-N(\overline{R})S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$,

 $-CRN(R)_2C(O)OR, -N(R)R_8,$

 $-N(R)C(=NR_9)N(R)_2,$ $-O(CH_2)_nOR$, -N(R)C 40 -N(R)C(O)OR, $(=CHR_9)N(R)_2$ $-OC(O)N(R)_2$ $-N(OR)S(O)_2R$, -N(OR)C(O)OR, -N(OR)C(O)R $-N(OR)C(O)N(R)_2$, $-N(OR)C(S)N(R)_2,$ -N(OR)C $(=NR_9)N(R)_2, -N(OR)C(=CHR_9)N(R)_2, -C(=NR_9)R,$ C(O)N(R)OR, and $-C(=NR_9)N(R)_2$, and each n is 45 independently selected from 1, 2, 3, 4, and 5; and when Q is a 5- to 14-membered heterocycle and (i) R_4 is $-(CH_2)_n Q$ in which n is 1 or 2, or (ii) R_4 is $-(CH_2)_n$ CHQR in which n is 1, or (iii) R_4 is —CHQR, and —CQ(R)₂, then Q is either

a 5- to 14-membered heteroaryl or 8- to 14-membered 50 heterocycloalkyl;

each R₅ is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R₆ is independently selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

M and M' are independently selected from ---C(O)O---, -OC(O), -C(O)N(R'), -N(R')C(O), -C(O)--C(S), -C(S)S, -SC(S), -CH(OH), -P(O)(OR)O, $-S(O)_2$, -S, an aryl group, and a heteroaryl group;

R7 is selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

 R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

R₉ is selected from the group consisting of H, CN, NO₂, 65 ing of F, Cl, Br, and I; and C_{1-6} alkyl, -OR, $-S(O)_2R$, $-S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

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each R is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R' is independently selected from the group consisting of C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, ---R*YR", ---YR", and H;

each R" is independently selected from the group consisting of C₃₋₁₄ alkyl and C₃₋₁₄ alkenyl;

each R* is independently selected from the group consisting of C₁₋₁₂ alkyl and C₂₋₁₂ alkenyl;

each Y is independently a C3-6 carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof. In some embodiments, another subset of compounds of

Formula (I) includes those in which

 R_1 is selected from the group consisting of C_{5-30} alkyl, C₅₋₂₀ alkenyl, —R*YR", —YR", and —R"M'R';

 R_2 and R_3 are independently selected from the group 20 consisting of H, C1-14 alkyl, C2-14 alkenyl, -R*YR",

-YR", and -R*OR", or R₂ and R₃, together with the atom to which they are attached, form a heterocycle or carbocycle;

 R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_n Q$, $-(CH_2)_n CHQR$,

-CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a C3-6 carbocycle, a 5- to 14-membered heteroaryl having one or more heteroatoms selected from N, O, and S, -OR,

 $-O(CH_2)_n N(R)_2,$ —C(O)OR, -OC(O)R, ----CX3, $-CX_2H$, $-CXH_2$, -CN, $-C(O)N(R)_2$, -N(R)C(O)R, $-N(R)C(O)N(R)_2$, $-N(R)C(S)N(R)_2$, $-N(R)S(O)_2R$ $-CRN(R)_2C(O)OR, -N(R)R_8, -O(CH_2)_nOR, -N(R)C$ $(=NR_9)N(R)_2, -N(R)C(=CHR_9)N(R)_2, -OC(O)N(R)_2,$ -N(R)C(O)OR, -N(OR)C(O)R, $-N(OR)S(O)_2R$ 35 -N(OR)C(O)OR, $-N(OR)C(O)N(R)_2$, -N(OR)C(S)N $(R)_2, -N(OR)C(=NR_9)N(R)_2, -N(OR)C(=CHR_9)N(R)$ $_{2}$, $-C(=NR_{9})R$, -C(O)N(R)OR, and $-C(=NR_{9})N(R)_{2}$, and each n is independently selected from 1, 2, 3, 4, and 5; each R5 is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R₆ is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

M and M' are independently selected from -C(O)O-, -OC(O), -C(O)N(R'), -N(R')C(O), -C(O)--C(S), -C(S)S, -SC(S), -CH(OH), -P(O)(OR')O, $-S(O)_2$, -S, an aryl group, and a heteroaryl group;

 R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

 R_8 is selected from the group consisting of C_{3-6} carbocycle and heterocycle;

 R_9 is selected from the group consisting of H, CN, NO₂, C_{1-6} alkyl, -OR, $-S(O)_2R$, $-S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

each R is independently selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

each R' is independently selected from the group consisting of C₁₋₁₈ alkyl, C₂₋₁₈ alkenyl, ---R*YR", ---YR", and H; each R" is independently selected from the group con-

60 sisting of C_{3-14} alkyl and C_{3-14} alkenyl; each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{2-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consist-

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13, or salts or isomers thereof.

In some embodiments, another subset of compounds of Formula (I) includes those in which

 R_1 is selected from the group consisting of C_{5-30} alkyl, C_{5-20} alkenyl, -R*YR'', -YR'', and -R''M'R';

R₂ and R₃ are independently selected from the group -5 consisting of H, C2-14 alkyl, C2-14 alkenyl, -R*YR",

-YR", and —R*OR", or R₂ and R₃, together with the atom to which they are attached, form a heterocycle or carbocycle;

 R_4 is $-(CH_2)_n Q$ or $-(CH_2)_n CHQR$, where Q is -N(R)2, and n is selected from 3, 4, and 5; 10

each R5 is independently selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

each R₆ is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

M and M are independently selected from -C(O)O-, 15

-OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -C(O)-, -C(S)-, -C(S)S-, -SC(S)-, -CH(OH)-, -P(O)(OR')O-, $-S(O)_2-$, -S-S-, an aryl group, and a heteroaryl group;

 R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} 20 alkenyl, and H;

each R is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R' is independently selected from the group consist-

ing of C_{1-18} alkyl, C_{2-18} alkenyl, -R*YR", -YR", and H; 25 each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C_{3-6} carbocycle;

each X is independently selected from the group consisting of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13, or salts or isomers thereof.

In some embodiments, another subset of compounds of 35 Formula (I) includes those in which

 $R_{\rm 1}$ is selected from the group consisting of $C_{\rm 5\text{-}30}$ alkyl, C_{5-20} alkenyl, -R*YR'', -YR'', and -R''M'R';

 $\overline{R_2}$ and $\overline{R_3}$ are independently selected from the group consisting of C1-14 alkyl, C2-14 alkenyl, -R*YR", -YR", 40 and -R*OR", or R_2 and R_3 , together with the atom to which

they are attached, form a heterocycle or carbocycle;

 R_4 is selected from the group consisting of $-(CH_2)_n Q$, $-(CH_2)_n CHQR$, --CHQR, and $--CQ(R)_2$, where Q is

 $-N(R)_2$, and n is selected from 1, 2, 3, 4, and 5;

each R5 is independently selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

each R₆ is independently selected from the group consisting of C1-3 alkyl, C2-3 alkenyl, and H;

M and M are independently selected from ---C(O)O---, 50 -OC(O), -C(O)N(R'), -N(R')C(O), -C(O)-C(S), -C(S)S, -SC(S), -CH(OH), -P(O)(OR')O, $-S(O)_2$, -S, an aryl group, and a heteroaryl group;

 R_7 is selected from the group consisting of C_{1-3} alkyl, C_{2-3} 55 alkenyl, and H;

each R is independently selected from the group consisting of C₁₋₃ alkyl, C₂₋₃ alkenyl, and H;

each R' is independently selected from the group consist-

ing of C_{1-18} alkyl, C_{2-18} alkenyl, --R*YR", --YR", and H; 60 each R" is independently selected from the group consisting of C3-14 alkyl and C3-14 alkenyl;

each R* is independently selected from the group consisting of C_{1-12} alkyl and C_{1-12} alkenyl;

each Y is independently a C₃₋₆ carbocycle;

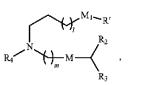
each X is independently selected from the group consist-

ing of F, Cl, Br, and I; and

m is selected from 5, 6, 7, 8, 9, 10, 11, 12, and 13,

or salts or isomers thereof.

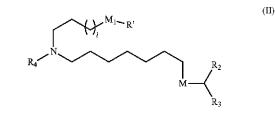
In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IA):



or a salt or isomer thereof, wherein 1 is selected from 1, 2, 3, 4, and 5; m is selected from 5, 6, 7, 8, and 9; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_n Q$, in which Q is OH, --NHC(S)N(R)2, --NHC(O)N(R)2, --N(R) $C(O)R, -N(R)S(O)_2R, -N(R)R_8, -NHC(=NR_9)N(R)_2,$ $-NHC(=CHR_9)N(R)_2$, $-OC(O)N(R)_2$, -N(R)C(O)OR, heteroaryl or heterocycloalkyl; M and M' are independently selected

from -C(O)O-, -OC(O)-, -C(O)N(R')-, -P(O)(OR')O-, -S-S-, an aryl group, and a heteroaryl group; and R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl.

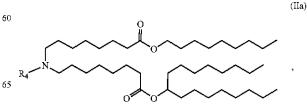
In some embodiments, a subset of compounds of Formula ₃₀ (I) includes those of Formula (II):

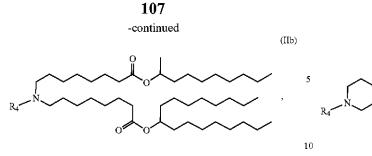


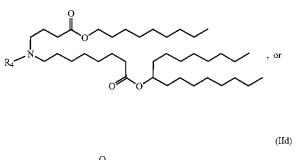
or a salt or isomer thereof, wherein 1 is selected from 1, 2, 3, 4, and 5; M_1 is a bond or M'; R_4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_n Q$, in which n is 2, 3, or 4, and Q is OH, -NHC(S)N(R)₂, -NHC(O)N(R)₂, -N(R)C(O)R, -N(R) $-N(R)R_8$, $-NHC(=NR_9)N(R)_2$, $S(O)_{2}R_{1}$ ----NHC $(=CHR_9)N(R)_2$, $-OC(O)N(R)_2$, -N(R)C(O)OR, heteroaryl or heterocycloalkyl; M and M' are independently selected

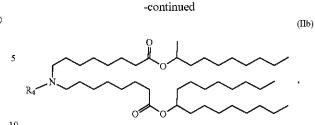
from -C(O)O, -OC(O), -C(O)N(R'), -P(O)(OR')O—, —S—S—, an aryl group, and a heteroaryl group; and R2 and R3 are independently selected from the group consisting of H, C1-14 alkyl, and C2-14 alkenyl.

In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):





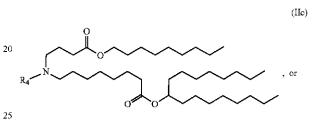




(IIc)

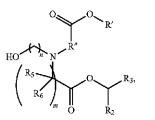
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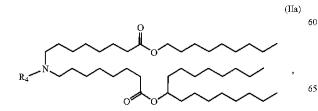
or a salt or isomer thereof, wherein R_4 is as described herein.

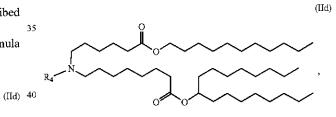
In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):



or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, R', R", and R₂ through R₆ are as described herein. For example, each of R₂ and R₃ may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

In some embodiments, a subset of compounds of Formula ⁵⁵ (I) includes those of Formula (IIa), (IIb), (IIc), or (IIe):

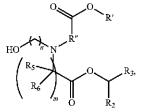




or a salt or isomer thereof, wherein R_4 is as described herein. $^{\rm 45}$

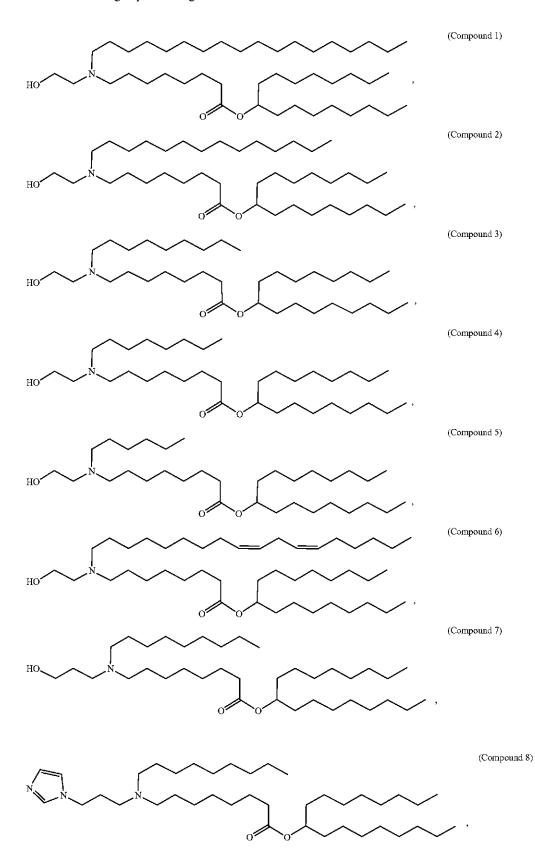
In some embodiments, a subset of compounds of Formula (I) includes those of Formula (IId):

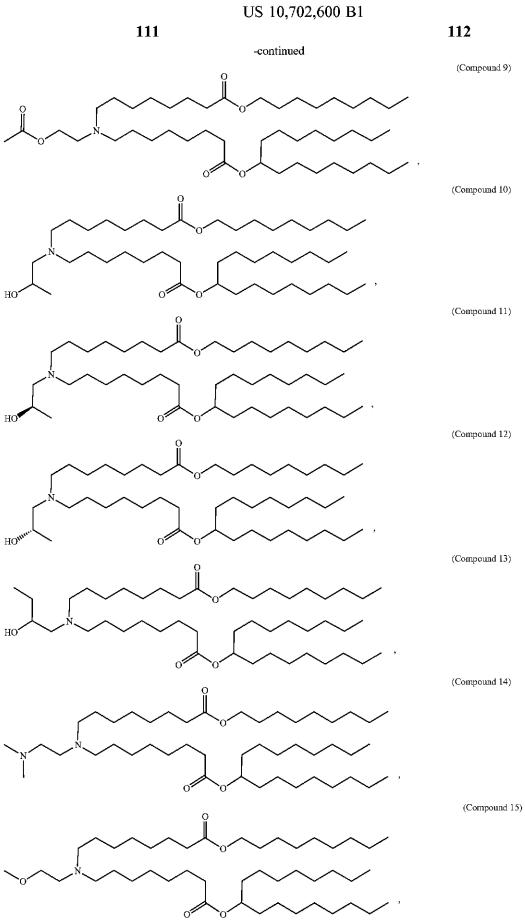
(IId)

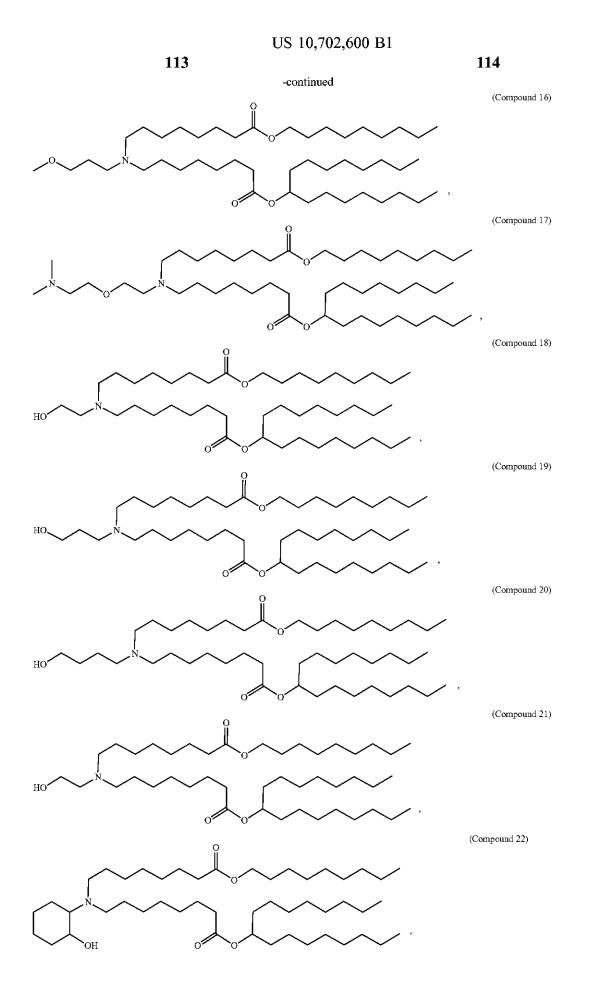


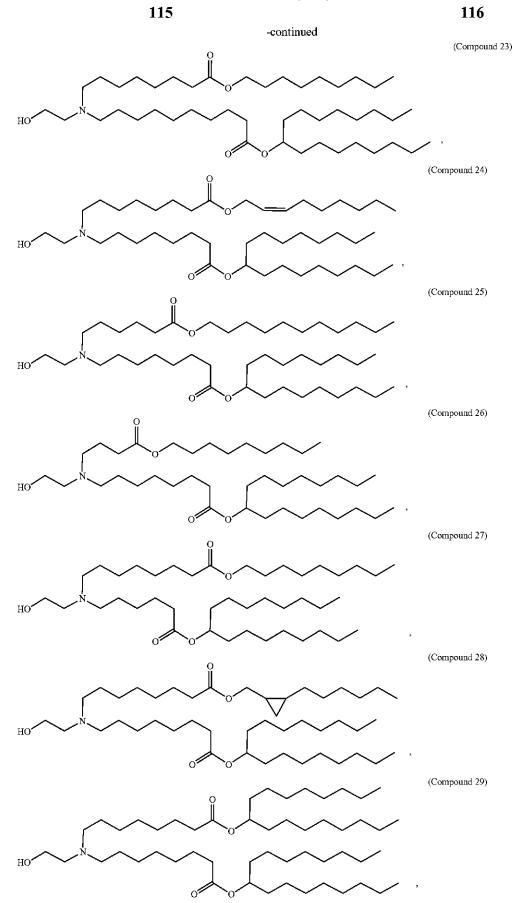
or a salt or isomer thereof, wherein n is 2, 3, or 4; and m, 65 R', R", and R₂ through R₆ are as described herein. For example, each of R₂ and R₃ may be independently selected from the group consisting of C_{5-14} alkyl and C_{5-14} alkenyl.

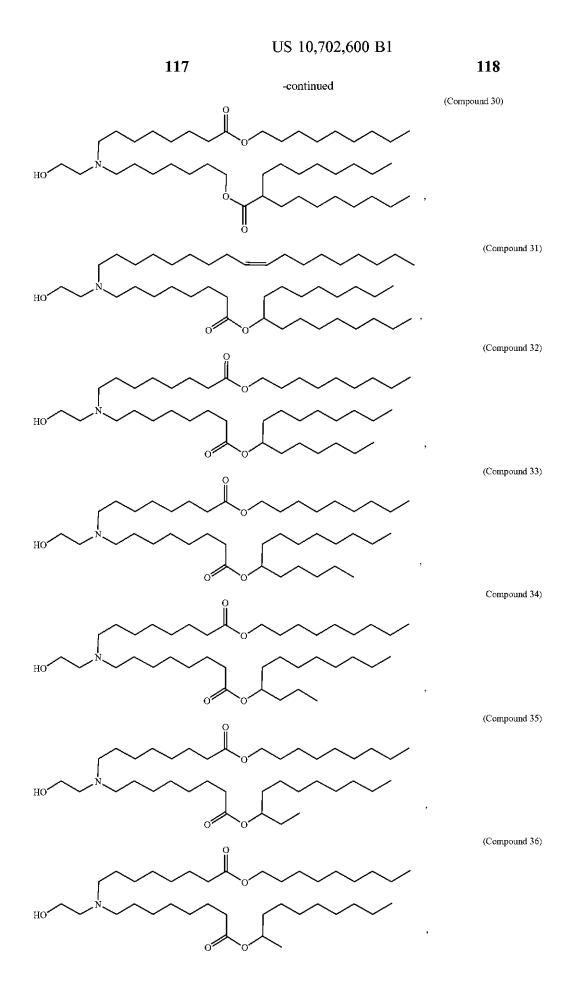
109 In some embodiments, the compound of Formula (I) is selected from the group consisting of:

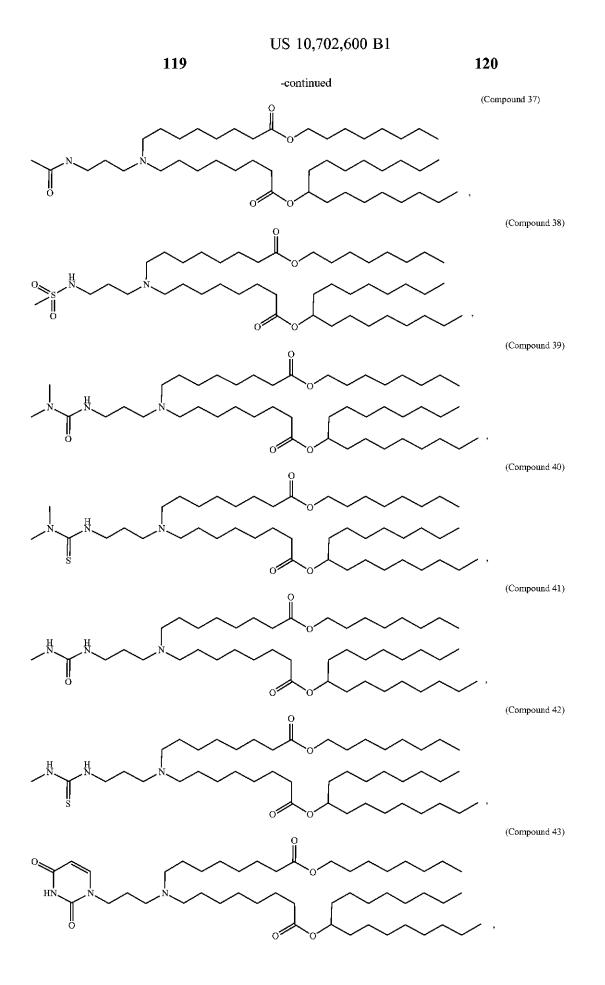


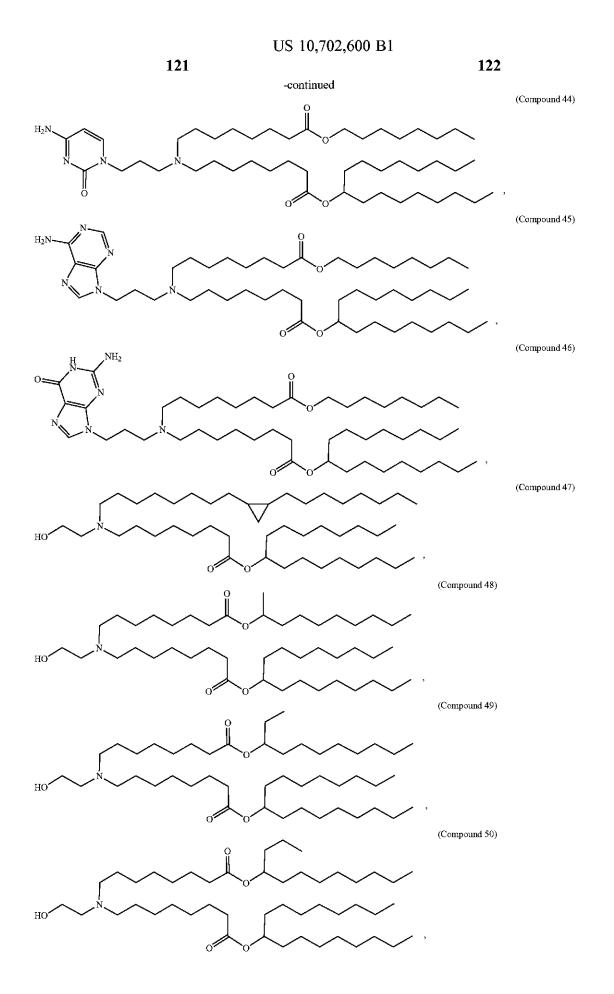


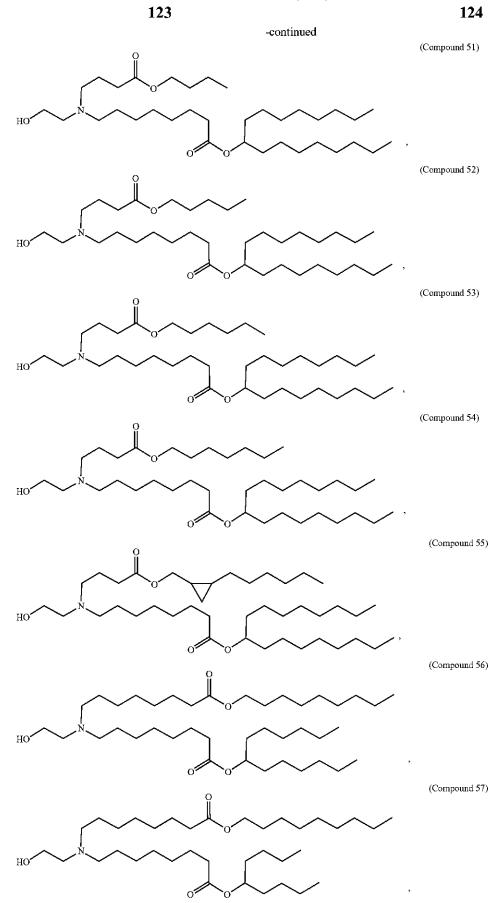


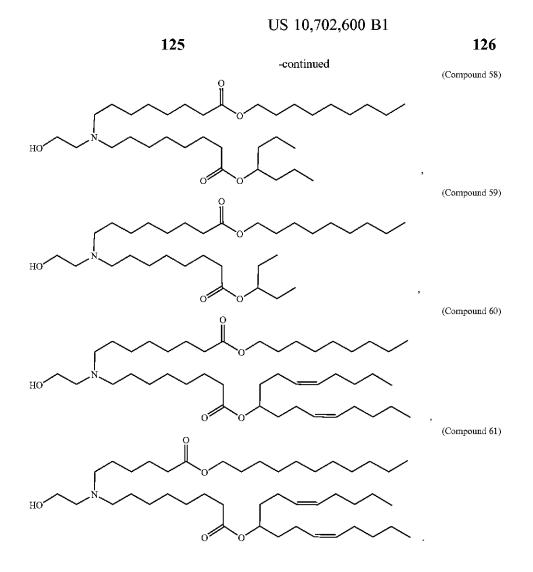




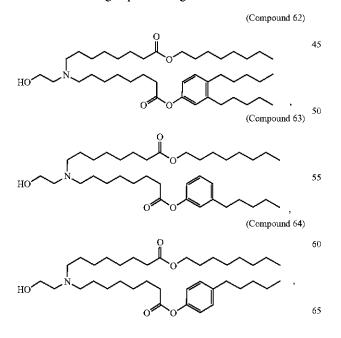


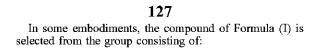


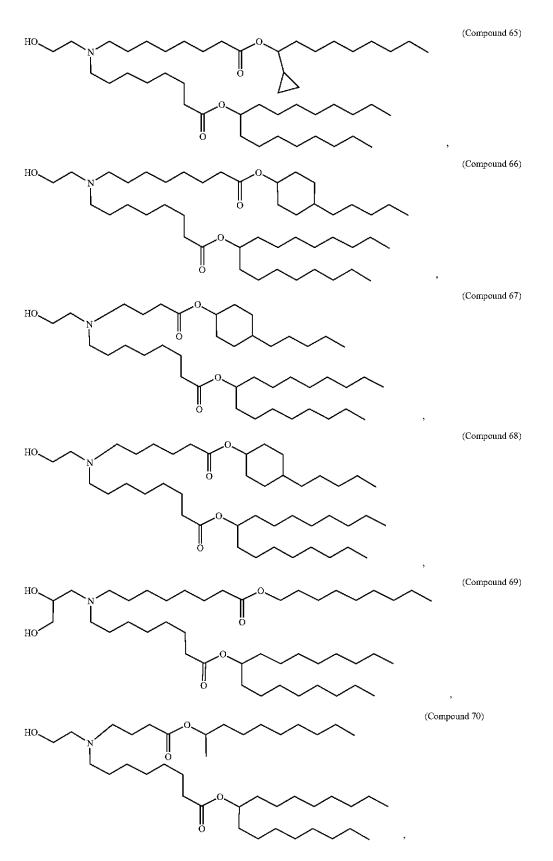


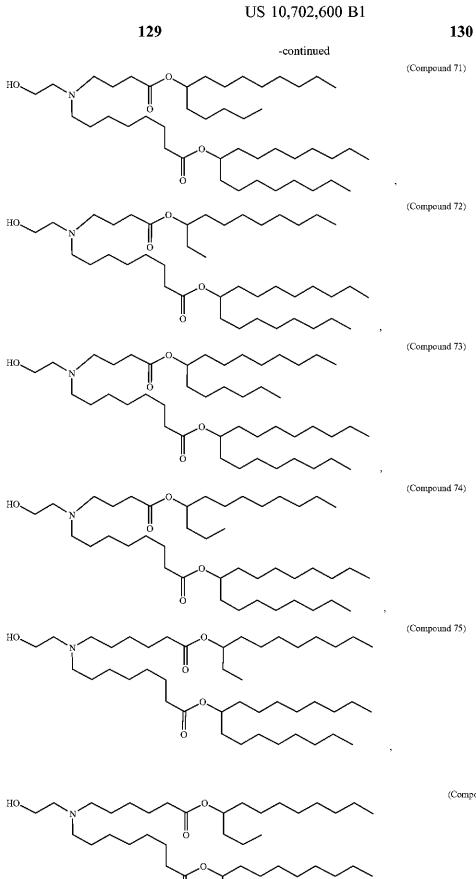


In further embodiments, the compound of Formula (I) is 40 selected from the group consisting of:



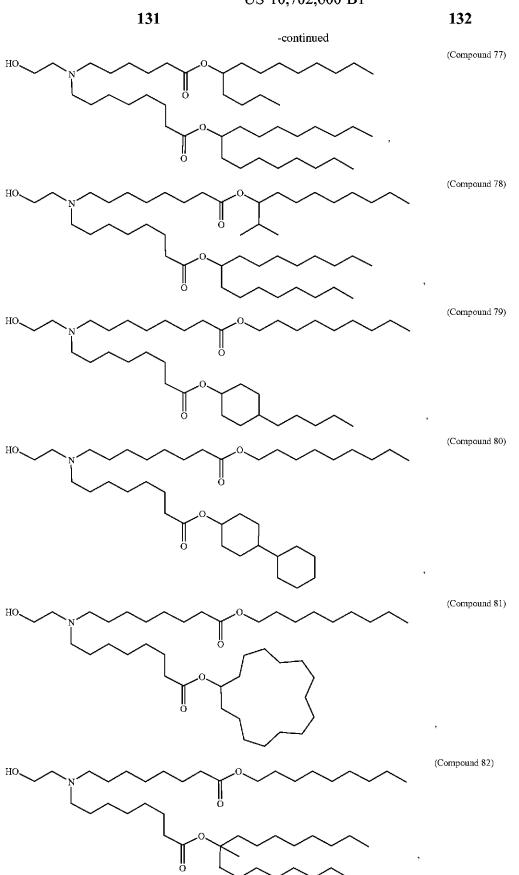




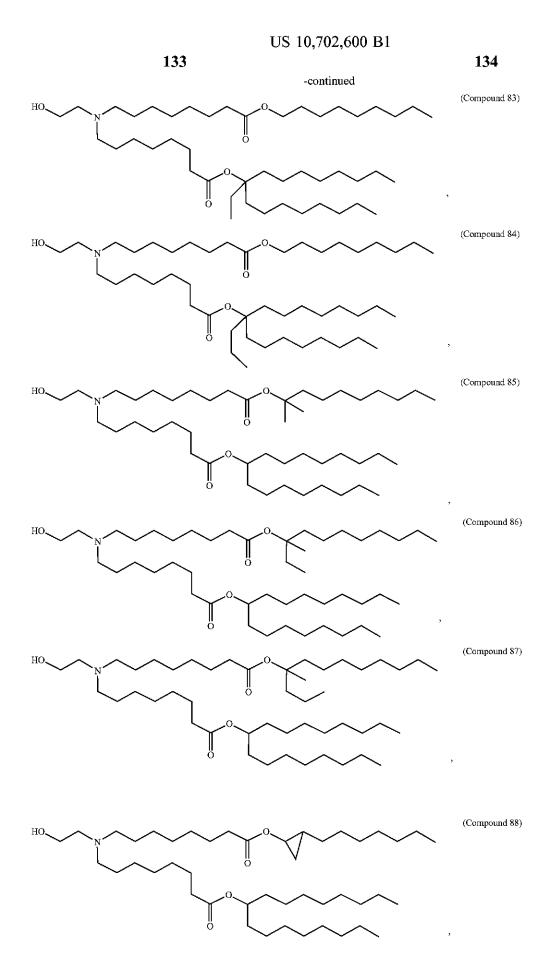


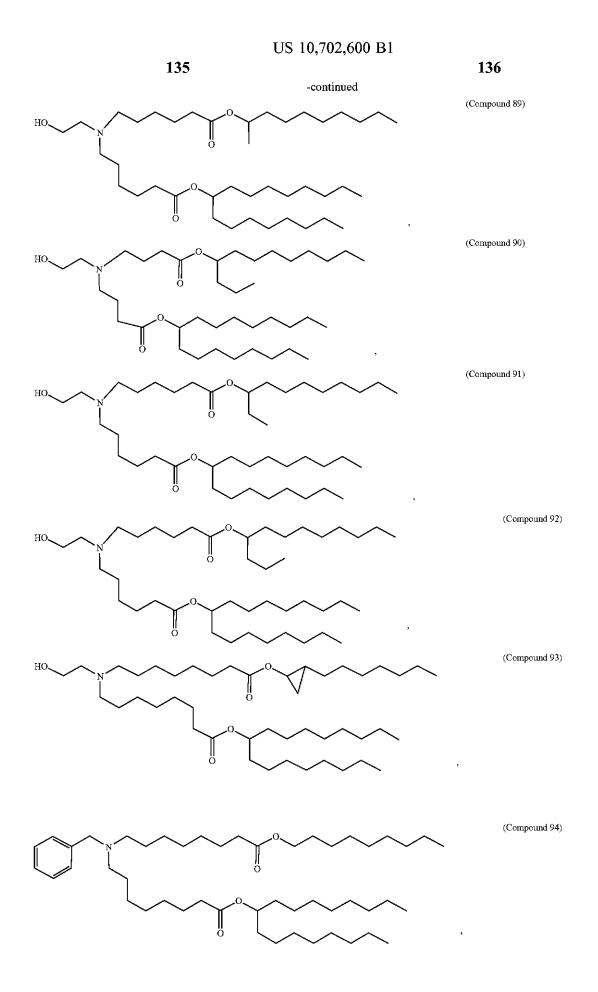
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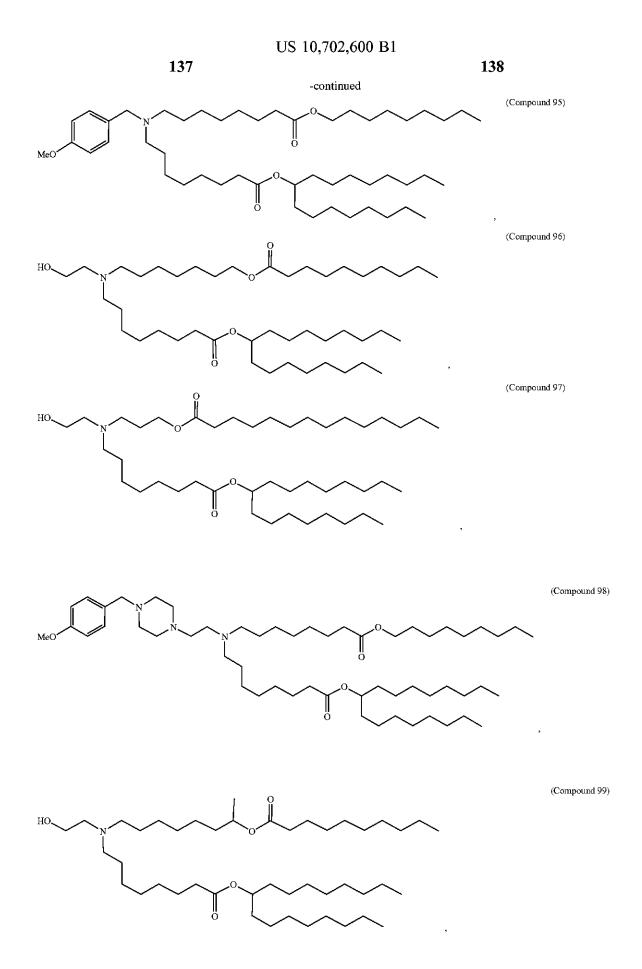
(Compound 76)

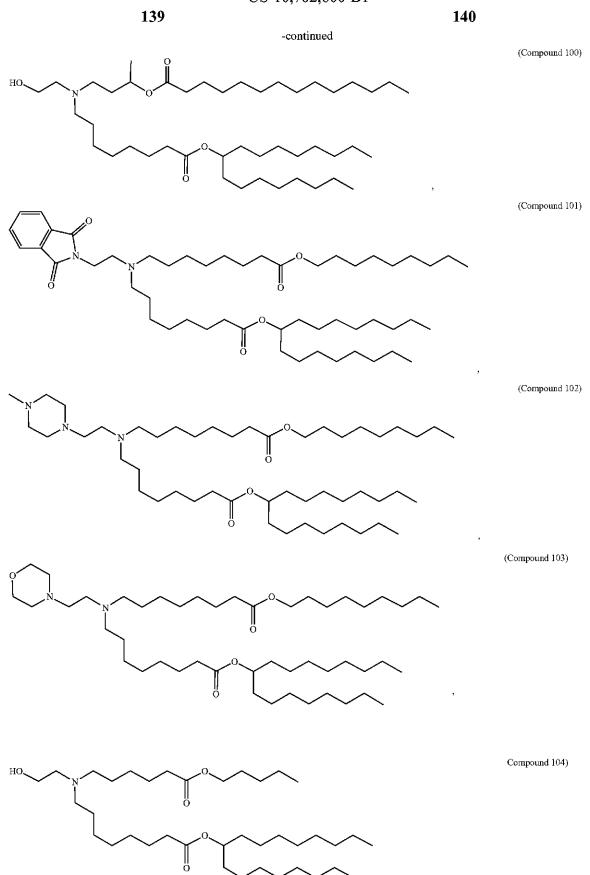


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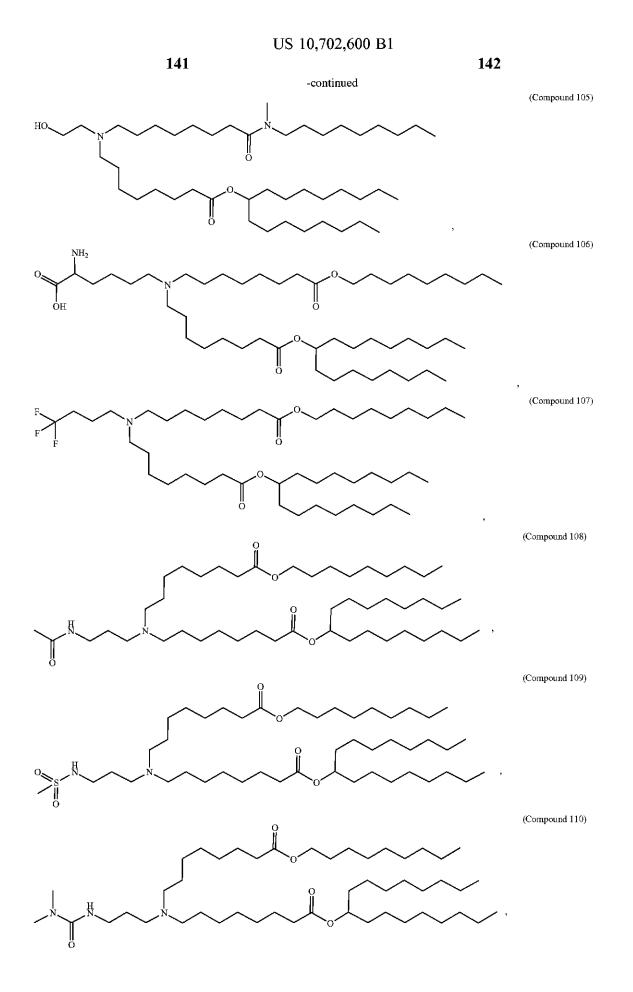


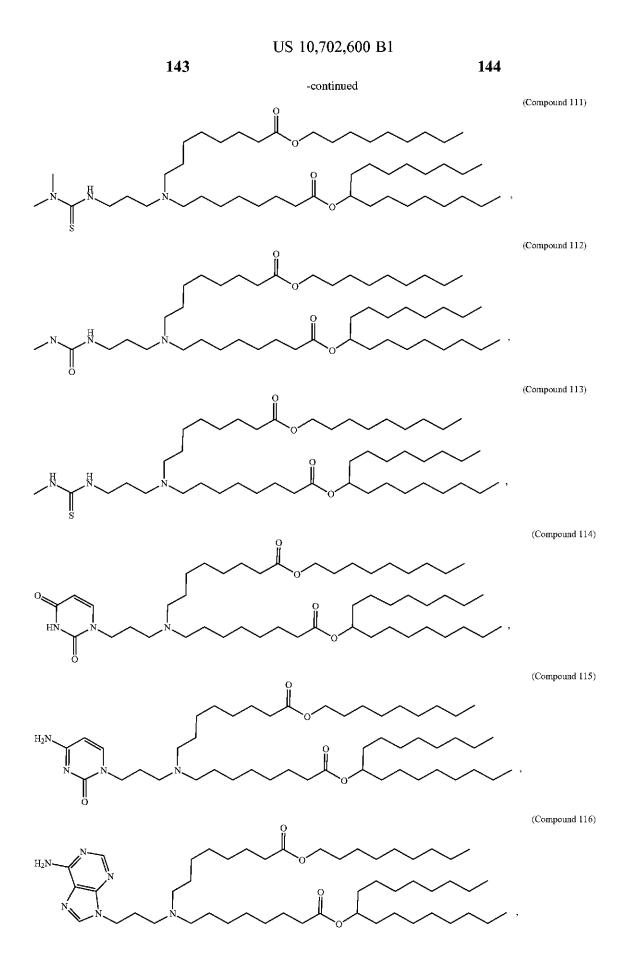


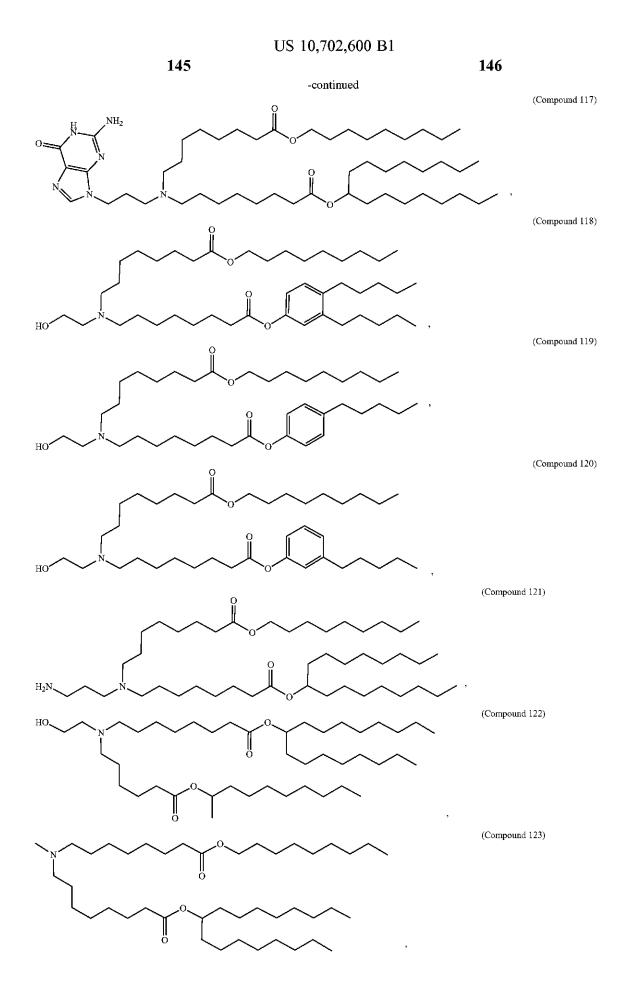


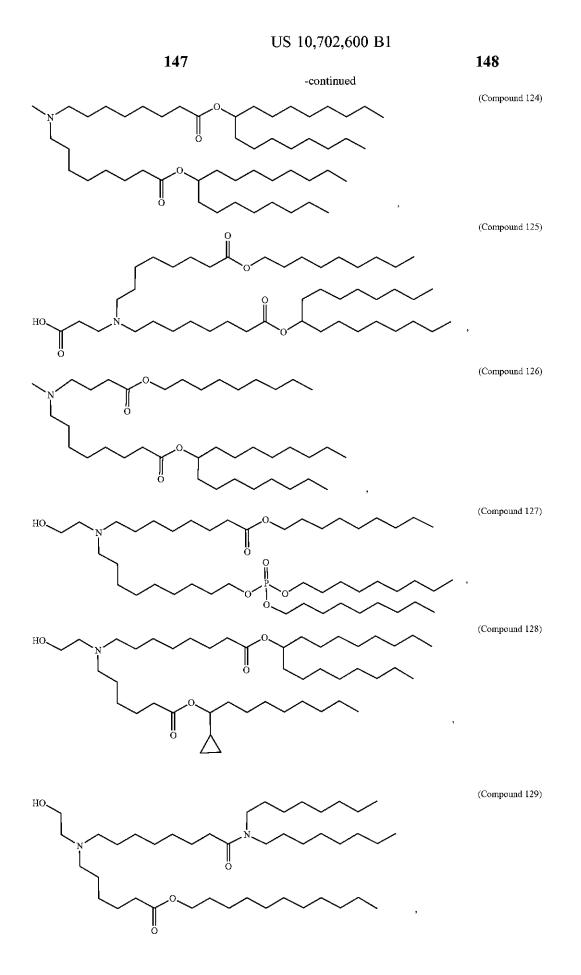


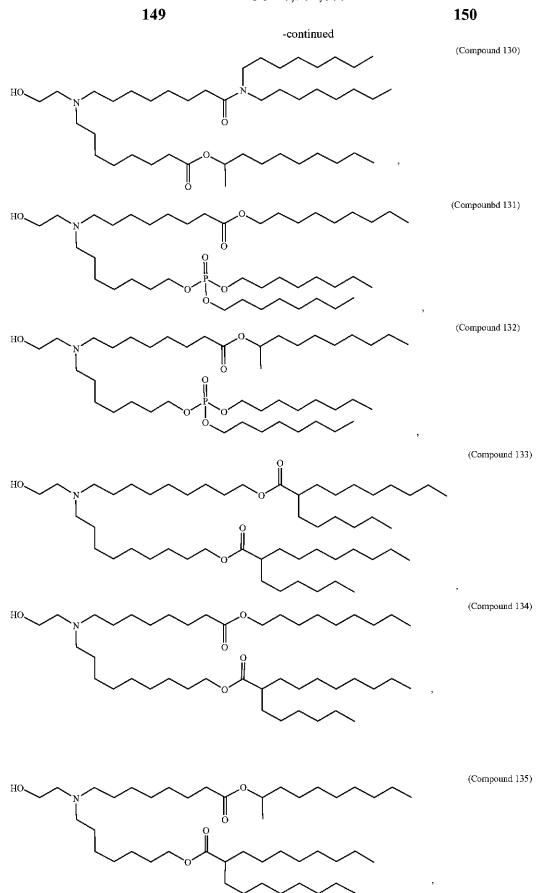
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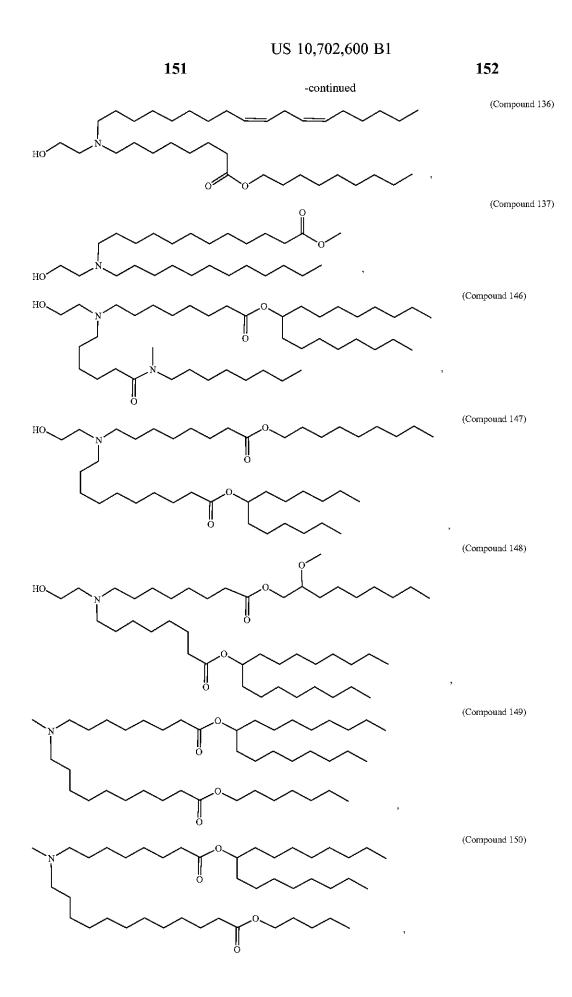


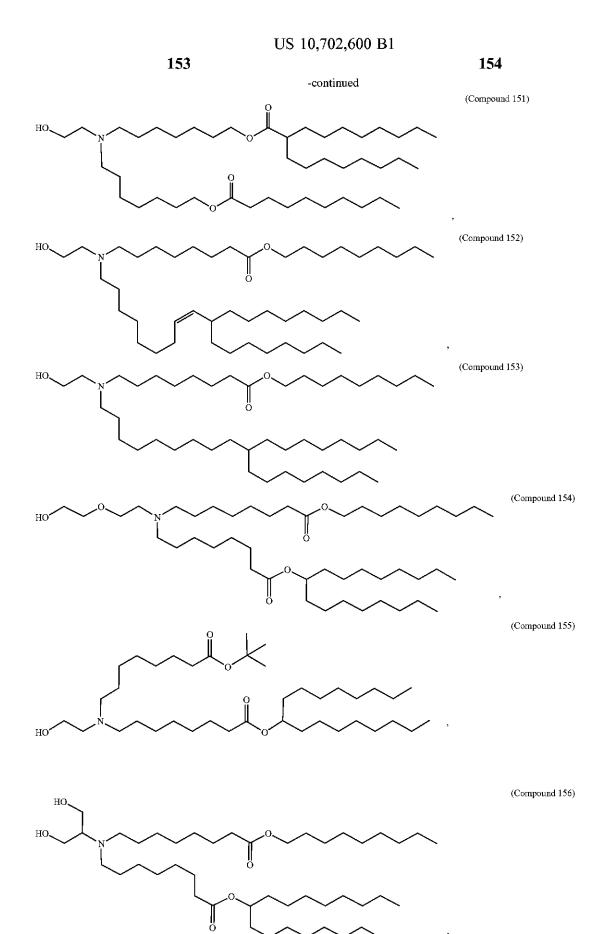


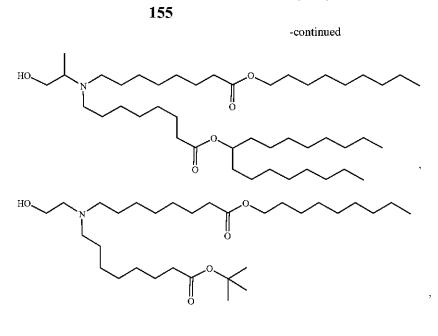










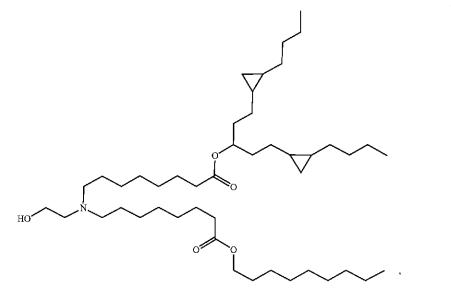


(Compound 158)

(Compound 157)

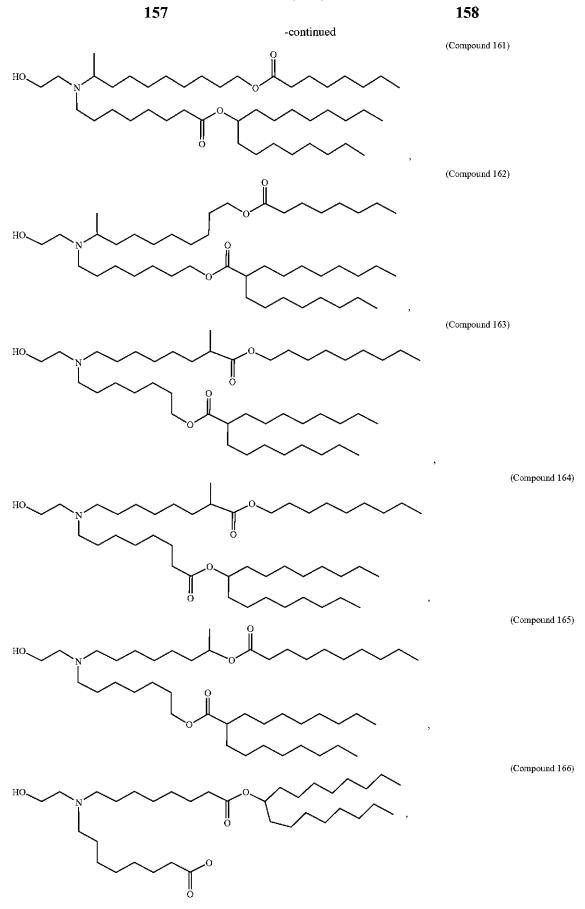
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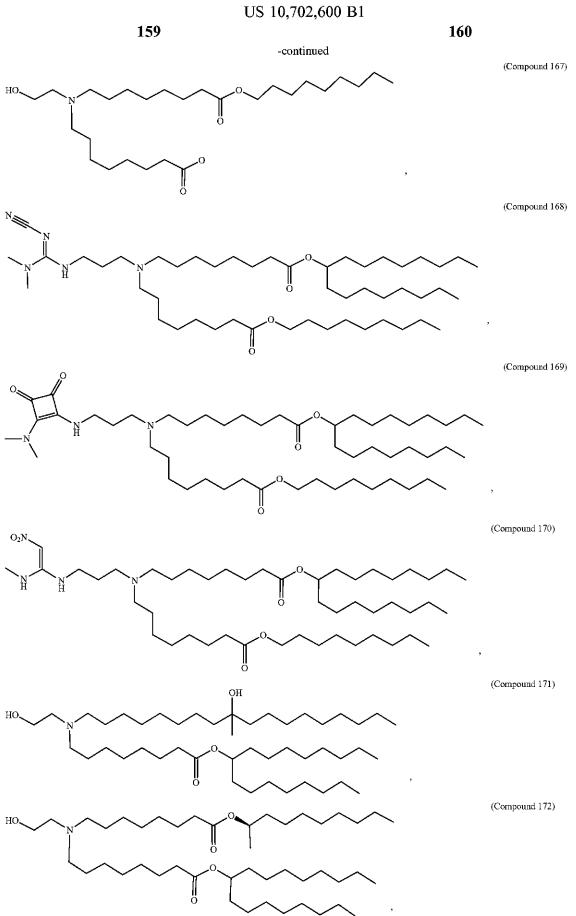
(Compound 159)

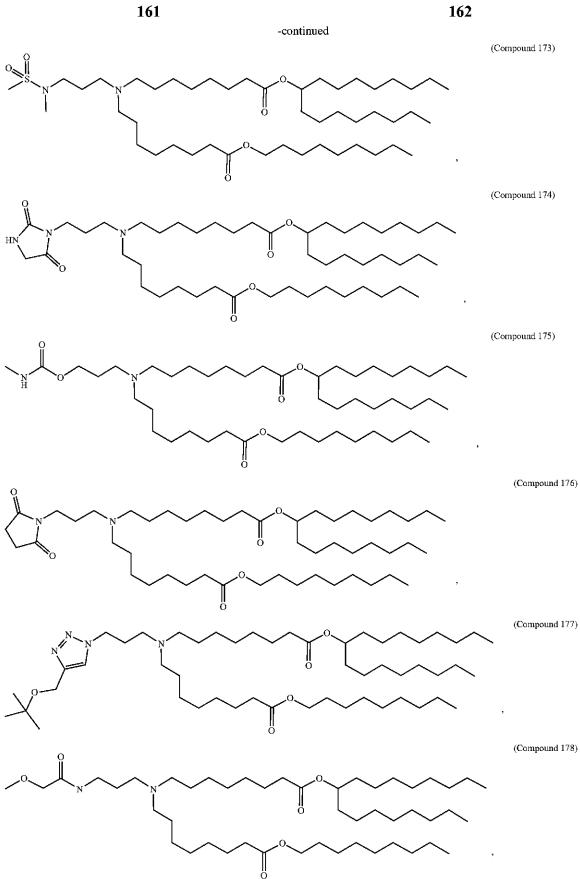


(Compound 160)

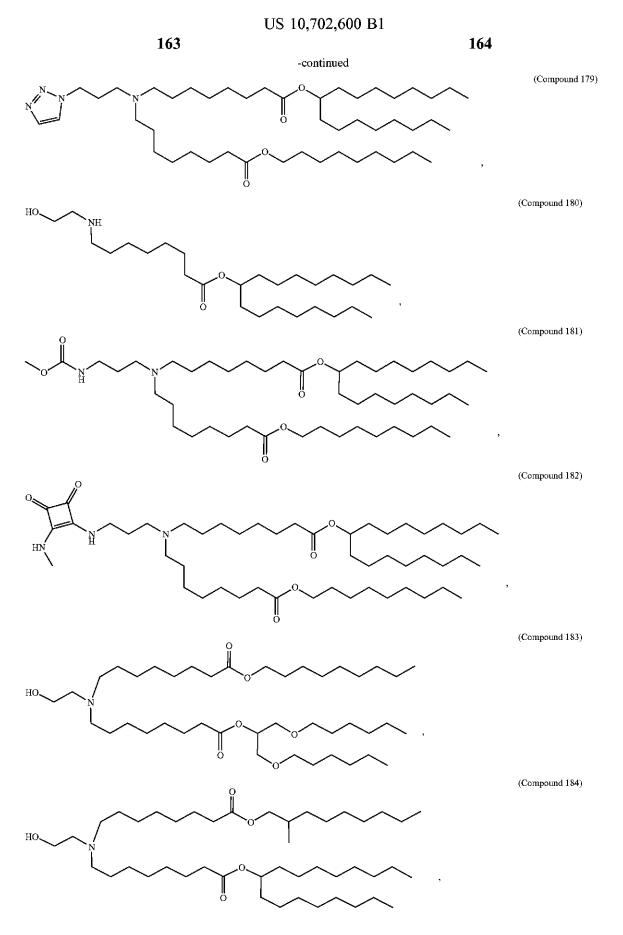
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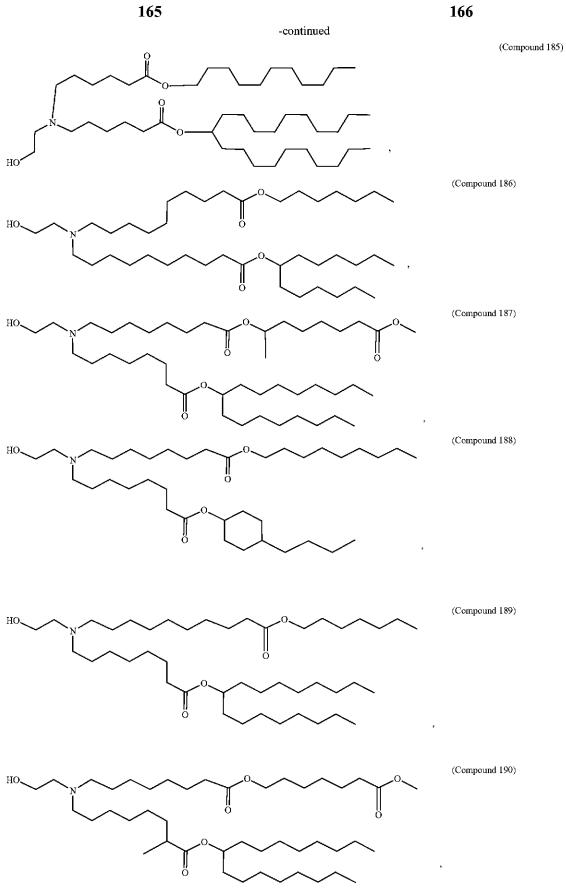


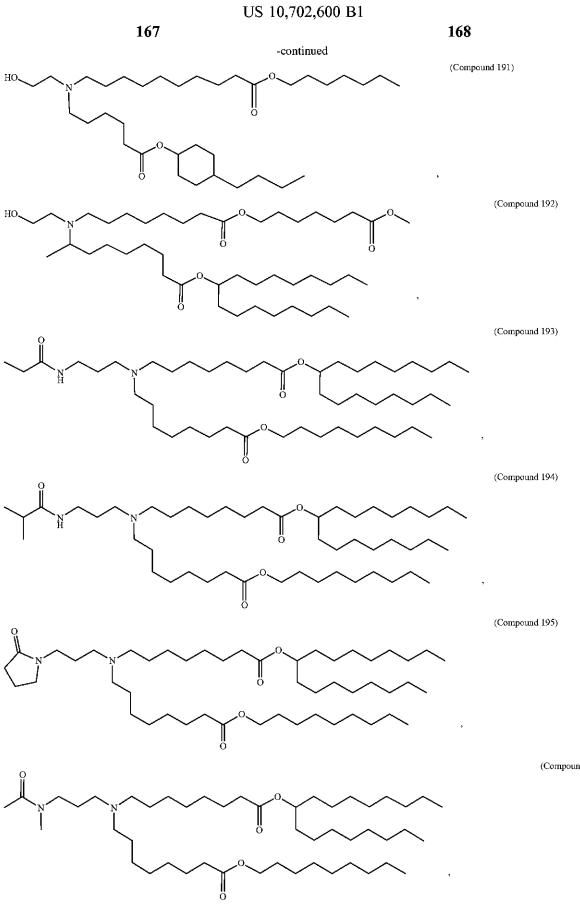




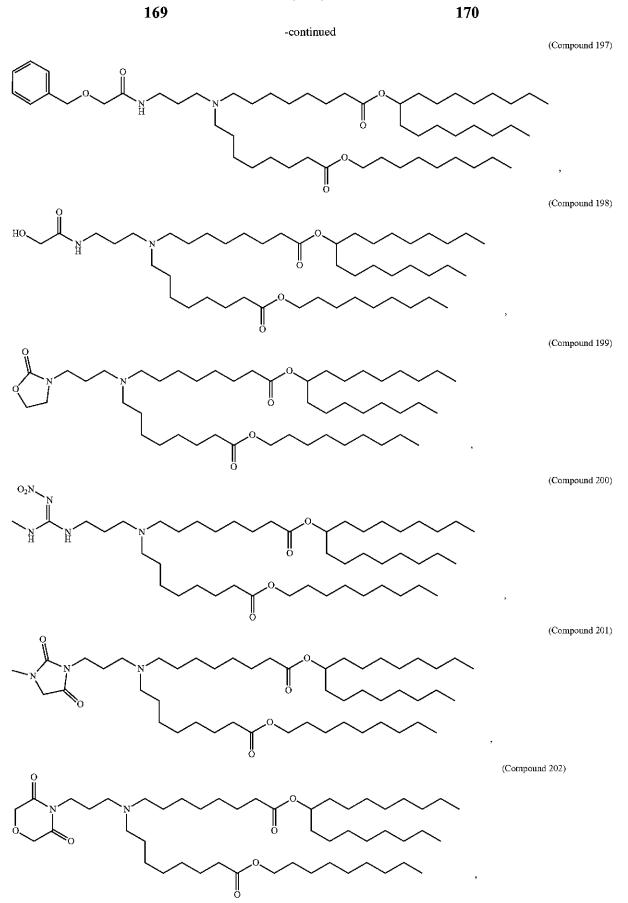


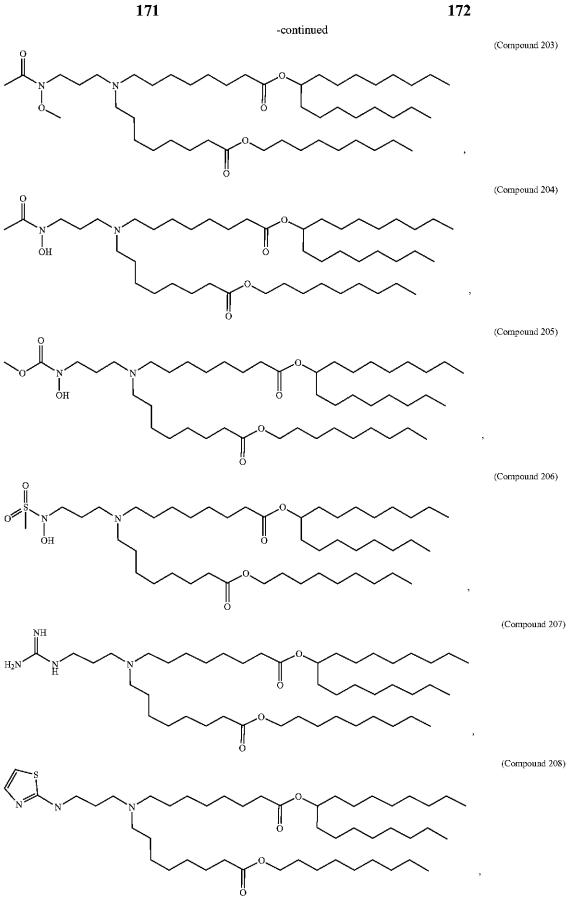


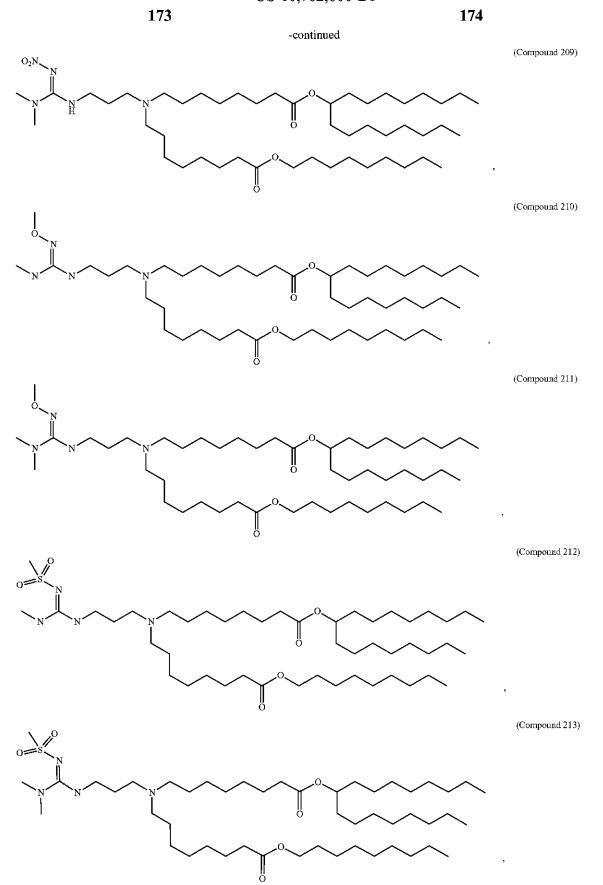




(Compound 196)

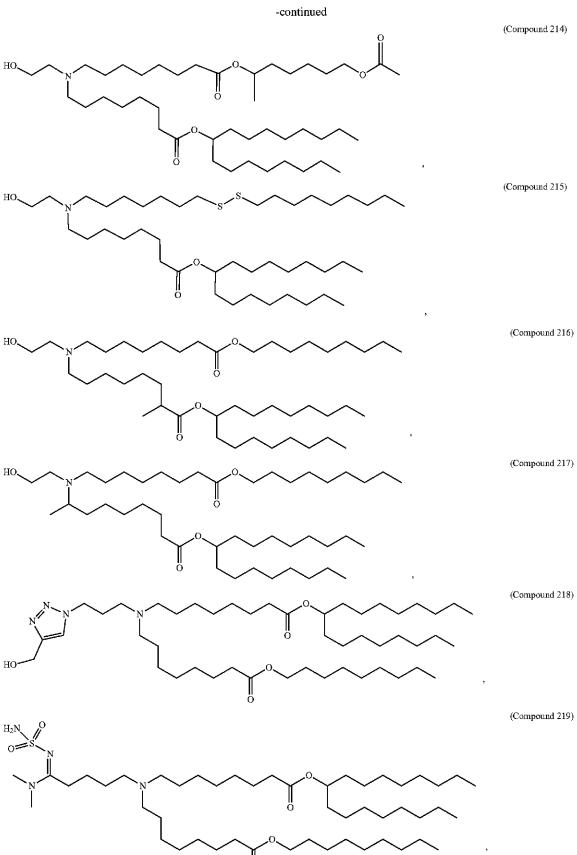


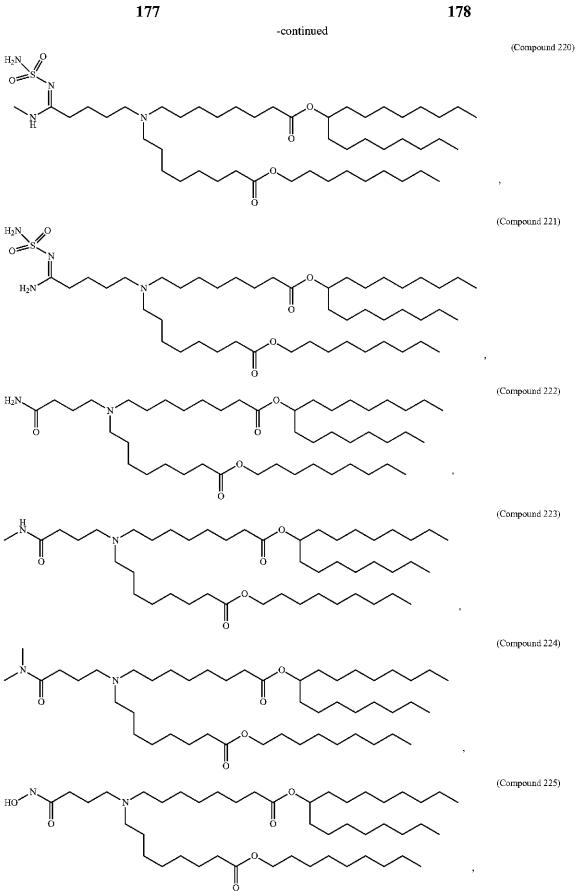


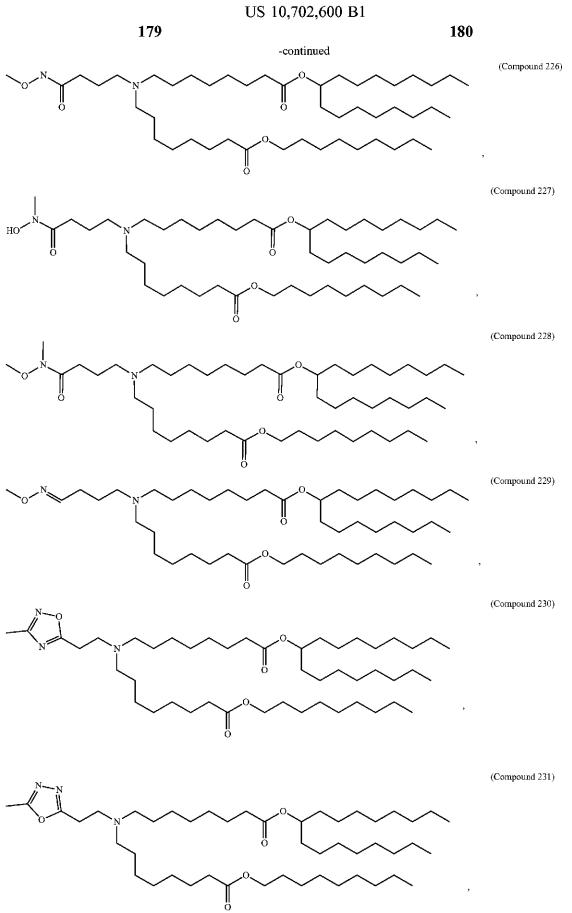


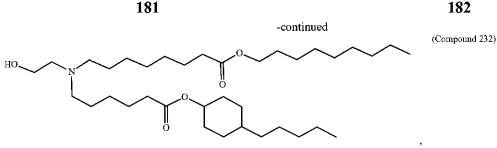
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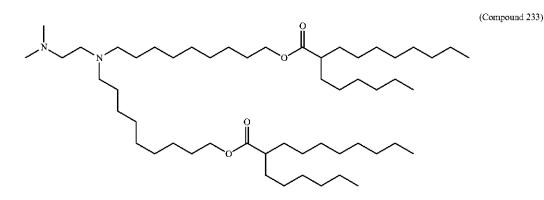




and salts and isomers thereof.

In some embodiments, a nanoparticle comprises the following compound:

ing the cell with a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a



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or salts and isomers thereof.

In some embodiments, the disclosure features a nanoparticle composition including a lipid component comprising a compound as described herein (e.g., a compound according to Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe)).

In some embodiments, the disclosure features a pharmaceutical composition comprising a nanoparticle composition $_{\Delta 0}$ according to the preceding embodiments and a pharmaceutically acceptable carrier. For example, the pharmaceutical composition is refrigerated or frozen for storage and/or shipment (e.g., being stored at a temperature of 4° C. or lower, such as a temperature between about -150° C. and 45 about 0° C. or between about -80° C. and about -20° C. (e.g., about -5° C., -10° C., -15° C., -20° C., -25° C., -30° C., -40° C., -50° C., -60° C., -70° C., -80° C., -90° C., -130° C. or -150° C.). For example, the pharmaceutical composition is a solution that is refrigerated for storage 50 and/or shipment at, for example, about -20° C., -30° C., -40° C., -50° C., -60° C., -70° C., or -80° C.

In some embodiments, the disclosure provides a method of delivering a therapeutic and/or prophylactic (e.g., RNA, such as mRNA) to a cell (e.g., a mammalian cell). This 55 method includes the step of administering to a subject (e.g., a mammal, such as a human) a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), 60 (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic, in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the cell.

In some embodiments, the disclosure provides a method 65 of producing a polypeptide of interest in a cell (e.g., a mammalian cell). The method includes the step of contact-

compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) an mRNA encoding the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide.

In some embodiments, the disclosure provides a method of treating a disease or disorder in a mammal (e.g., a human) in need thereof. The method includes the step of administering to the mammal a therapeutically effective amount of a nanoparticle composition including (i) a lipid component including a phospholipid (such as a polyunsaturated lipid), a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA).

In some embodiments, the disease or disorder is characterized by dysfunctional or aberrant protein or polypeptide activity. For example, the disease or disorder is selected from the group consisting of rare diseases, infectious diseases, cancer and proliferative diseases, genetic diseases (e.g., cystic fibrosis), autoimmune diseases, diabetes, neurodegenerative diseases, cardio- and reno-vascular diseases, and metabolic diseases.

In some embodiments, the disclosure provides a method of delivering (e.g., specifically delivering) a therapeutic and/or prophylactic to a mammalian organ (e.g., a liver, spleen, lung, or femur). This method includes the step of administering to a subject (e.g., a mammal) a nanoparticle composition including (i) a lipid component including a phospholipid, a PEG lipid, a structural lipid, and a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe) and (ii) a therapeutic and/or prophylactic (e.g., an mRNA), in which administering involves contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic is delivered to the target organ (e.g., a liver, spleen, lung, or femur).

In some embodiments, the disclosure features a method for the enhanced delivery of a therapeutic and/or prophylactic (e.g., an mRNA) to a target tissue (e.g., a liver, spleen, lung, or femur). This method includes administering to a subject (e.g., a mammal) a nanoparticle composition, the 5 composition including (i) a lipid component including a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe), a phospholipid, a structural lipid, and a PEG lipid; and (ii) a therapeutic and/or prophylactic, the administering including contacting the target tissue with the nanoparticle 10 composition, whereby the therapeutic and/or prophylactic is delivered to the target tissue.

In some embodiments, the disclosure features a method of lowering immunogenicity comprising introducing the nanoparticle composition of the disclosure into cells, wherein the 15 nanoparticle composition reduces the induction of the cellular immune response of the cells to the nanoparticle composition, as compared to the induction of the cellular immune response in cells induced by a reference composition which comprises a reference lipid instead of a com- 20 pound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe). For example, the cellular immune response is an innate immune response, an adaptive immune response, or both.

The disclosure also includes methods of synthesizing a compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) 25 or (IIe) and methods of making a nanoparticle composition including a lipid component comprising the compound of Formula (I), (IA), (II), (IIa), (IIb), (IIc), (IId) or (IIe). Modes of Vaccine Administration

Respiratory virus RNA (e.g. mRNA) vaccines may be 30 administered by any route which results in a therapeutically effective outcome. These include, but are not limited, to intradermal, intramuscular, and/or subcutaneous administration. The present disclosure provides methods comprising administering RNA (e.g., mRNA) vaccines to a subject in 35 need thereof. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Respiratory virus RNA (e.g., 40 mRNA) vaccines compositions are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of RNA (e.g., mRNA) vaccine compositions may be decided by the attending physician within the scope of sound 45 medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound 50 employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with 55 5 years later, or Day 0 and 10 years later) at a total dose of the specific compound employed; and like factors well known in the medical arts.

In some embodiments, respiratory virus RNA (e.g. mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0001 mg/kg to 100 60 mg/kg, 0.001 mg/kg to 0.05 mg/kg, 0.005 mg/kg to 0.05 mg/kg, 0.001 mg/kg to 0.005 mg/kg, 0.05 mg/kg to 0.5 mg/kg, 0.01 mg/kg to 50 mg/kg, 0.1 mg/kg to 40 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.01 mg/kg to 10 mg/kg, 0.1 mg/kg to 10 mg/kg, or 1 mg/kg to 25 mg/kg, of subject body weight 65 per day, one or more times a day, per week, per month, etc. to obtain the desired therapeutic, diagnostic, prophylactic, or

imaging effect (see, e.g., the range of unit doses described in International Publication No WO2013078199, the contents of which are herein incorporated by reference in their entirety). The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, every four weeks, every 2 months, every three months, every 6 months, etc. In some embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. In exemplary embodiments, respiratory virus RNA (e.g., mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0005 mg/kg to 0.01 mg/kg, e.g., about 0.0005 mg/kg to about 0.0075 mg/kg, e.g., about 0.0005 mg/kg, about 0.001 mg/kg, about 0.002 mg/kg, about 0.003 mg/kg, about 0.004 mg/kg or about 0.005 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered once or twice (or more) at dosage levels sufficient to deliver 0.025 mg/kg to 0.250 mg/kg, 0.025 mg/kg to 0.500 mg/kg, 0.025 mg/kg to 0.750 mg/kg, or 0.025 mg/kg to 1.0 mg/kg.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and 5 years later, or Day 0 and 10 years later) at a total dose of or at dosage levels sufficient to deliver a total dose of 0.0100 mg, 0.025 mg, 0.050 mg, 0.075 mg, 0.100 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg, 0.225 mg, 0.250 mg, 0.275 mg, 0.300 mg, 0.325 mg, 0.350 mg, 0.375 mg, 0.400 mg, 0.425 mg, 0.450 mg, 0.475 mg, 0.500 mg, 0.525 mg, 0.550 mg, 0.575 mg, 0.600 mg, 0.625 mg, 0.650 mg, 0.675 mg, 0.700 mg, 0.725 mg, 0.750 mg, 0.775 mg, 0.800 mg, 0.825 mg, 0.850 mg, 0.875 mg, 0.900 mg, 0.925 mg, 0.950 mg, 0.975 mg, or 1.0 mg. Higher and lower dosages and frequency of administration are encompassed by the present disclosure. For example, a respiratory virus RNA (e.g., mRNA) vaccine composition may be administered three or four times.

In some embodiments, respiratory virus RNA (e.g., mRNA) vaccine compositions may be administered twice (e.g., Day 0 and Day 7, Day 0 and Day 14, Day 0 and Day 21, Day 0 and Day 28, Day 0 and Day 60, Day 0 and Day 90, Day 0 and Day 120, Day 0 and Day 150, Day 0 and Day 180, Day 0 and 3 months later, Day 0 and 6 months later, Day 0 and 9 months later, Day 0 and 12 months later, Day 0 and 18 months later, Day 0 and 2 years later, Day 0 and or at dosage levels sufficient to deliver a total dose of 0.010 mg, 0.025 mg, 0.100 mg or 0.400 mg.

In some embodiments, the respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 µg/kg and 400 µg/kg of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments the RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of between 10 μ g and 400 μ g of the nucleic acid vaccine (in an effective amount to vaccinate the subject). In some embodiments, a respiratory virus RNA (e.g.,

mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as a single dosage of 25-1000 μg (e.g., a single dosage of mRNA encoding hMPV, PIV3, RSV, MeV and/or BetaCoV antigen). In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine is adminis- 5 tered to the subject as a single dosage of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 µg. For example, a respiratory virus RNA (e.g., mRNA) vaccine may be administered to a subject as a single dose of 25-100, 25-500, 50-100, 50-500, 10 50-1000, 100-500, 100-1000, 250-500, 250-1000, or 500-1000 µg. In some embodiments, a respiratory virus RNA (e.g., mRNA) vaccine for use in a method of vaccinating a subject is administered to the subject as two dosages, the combination of which equals 25-1000 µg of the respiratory 15 virus RNA (e.g., mRNA) vaccine.

A respiratory virus RNA (e.g. mRNA) vaccine pharmaceutical composition described herein can be formulated into a dosage form described herein, such as an intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, 20 intravitreal, intramuscular, intradermal, intracardiac, intraperitoneal, and subcutaneous).

Respiratory Virus RNA (e.g., mRNA) Vaccine Formulations and Methods of Use

Some aspects of the present disclosure provide formula- 25 tions of the respiratory virus RNA (e.g., mRNA) vaccine, wherein the RNA (e.g., mRNA) vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject (e.g., production of antibodies specific to an hMPV, PIV3, RSV, MeV and/or BetaCoV antigenic 30 polypeptide). "An effective amount" is a dose of an RNA (e.g., mRNA) vaccine effective to produce an antigenspecific immune response. Also provided herein are methods of inducing an antigen-specific immune response in a subject. 35

In some embodiments, the antigen-specific immune response is characterized by measuring an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide antibody titer produced in a subject administered a respiratory virus RNA (e.g., mRNA) vaccine as 40 provided herein. An antibody titer is a measurement of the amount of antibodies within a subject, for example, antibodies that are specific to a particular antigen (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) or epitope of an antigen. 45 Antibody titer is typically expressed as the inverse of the greatest dilution that provides a positive result. Enzymelinked immunosorbent assay (ELISA) is a common assay for determining antibody titers, for example.

In some embodiments, an antibody titer is used to assess 50 whether a subject has had an infection or to determine whether immunizations are required. In some embodiments, an antibody titer is used to determine the strength of an autoimmune response, to determine whether a booster immunization is needed, to determine whether a previous 55 vaccine was effective, and to identify any recent or prior infections. In accordance with the present disclosure, an antibody titer may be used to determine the strength of an immune response induced in a subject by the respiratory virus RNA (e.g., mRNA) vaccine. 60

In some embodiments, an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased by at least 1 log relative to a control. For example, anti-antigenic polypeptide antibody titer pro-65 duced in a subject may be increased by at least 1.5, at least 2, at least 2.5, or at least 3 log relative to a control. In some

embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1, 1.5, 2, 2.5 or 3 log relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased by 1-1.5, 1-2, 1-2.5, 1-3, 1.5-2, 1.5-2.5, 1.5-3, 2-2.5, 2-3, or 2.5-3 log relative to a control.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject is increased at least 2 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is increased 2, 3, 4, 5, 6, 7, 8, 9, or 10 times relative to a control. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject is increased 2-10 times relative to a control. For example, the anti-antigenic polypeptide antibody titer produced in a subject may be increased 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 5-10, 5-9, 5-8, 5-7, 5-6, 6-10, 6-9, 6-8, 6-7, 7-10, 7-9, 7-8, 8-10, 8-9, or 9-10 times relative to a control.

A control, in some embodiments, is the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has not been administered a respiratory virus RNA (e.g., mRNA) vaccine of the present disclosure. In some embodiments, a control is an antiantigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered a live attenuated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. An attenuated vaccine is a vaccine produced by reducing the virulence of a viable (live). An attenuated virus is altered in a manner that renders it harmless or less virulent relative to live, unmodified virus. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an antihMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. Recombinant protein vaccines typically include protein antigens that either have been produced in a heterologous expression system (e.g., bacteria or yeast) or purified from large amounts of the pathogenic organism. In some embodiments, a control is an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject who has been administered an hMPV, PIV3, RSV, MeV and/or BetaCoV virus-like particle (VLP) vaccine. For example, an hMPV VLP vaccine used as a control may be a hMPV VLPs, comprising (or consisting of) viral matrix (M) and fusion (F) proteins, generated by expressing viral proteins in suspension-adapted human embryonic kidney epithelial (293-F) cells (see, e.g., Cox R G et al., J Virol. 2014 June; 88(11): 6368-6379, the contents of which are herein incorporated by reference).

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose that is reduced compared to the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. A "standard of care," as provided herein, refers to 5 a medical or psychological treatment guideline and can be general or specific. "Standard of care" specifies appropriate treatment based on scientific evidence and collaboration between medical professionals involved in the treatment of a given condition. It is the diagnostic and treatment process 10 that a physician/clinician should follow for a certain type of patient, illness or clinical circumstance. A "standard of care dose," as provided herein, refers to the dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, or a live attenuated or inactivated hMPV, 15 PIV3, RSV, MeV and/or BetaCoV vaccine, that a physician/ clinician or other medical professional would administer to a subject to treat or prevent hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoVrelated condition, while following the standard of care 20 guideline for treating or preventing hMPV, PIV3, RSV, MeV and/or BetaCoV, or a hMPV-, PIV3-, RSV-, MeV- and/or BetaCoV-related condition.

In some embodiments, the anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or 25 anti-BetaCoV antigenic polypeptide) antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide (e.g., an anti-hMPV, anti-PIV3, anti-RSV, anti-MeV and/or anti-BetaCoV antigenic 30 polypeptide) antibody titer produced in a control subject administered a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least 2-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. For example, an effective amount 40 9 to 300-, 9 to 200-, 9 to 100-, 9 to 90-, 9 to 80-, 9 to 70-, of a respiratory virus RNA (e.g., mRNA) vaccine may be a dose equivalent to an at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or 45 BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to an at least at least 100-fold, at least 500-fold, or at least 1000-fold reduction in a standard of care dose of a recombinant or purified hMPV, PIV3, RSV, 50 MeV and/or BetaCoV protein vaccine. In some embodiments, an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 50-, 100-, 250-, 500-, or 1000-fold reduction in a standard of care dose of a recombinant or 55 purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, the anti-antigenic polypeptide antibody titer produced in a subject administered an effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is equivalent to an anti-antigenic polypeptide anti- 60 body titer produced in a control subject administered the standard of care dose of a recombinant or protein hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, an effective 65 amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2-fold to 1000-fold (e.g., 2-fold to

100-fold, 10-fold to 1000-fold) reduction in the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine, wherein the antiantigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a dose equivalent to a 2 to 1000-, 2 to 900-, 2 to 800-, 2 to 700-, 2 to 600-, 2 to 500-, 2 to 400-, 2 to 300-, 2 to 200-, 2 to 100-, 2 to 90-, 2 to 80-, 2 to 70-, 2 to 60-, 2 to 50-, 2 to 40-, 2 to 30-, 2 to 20-, 2 to 10-, 2 to 9-, 2 to 8-, 2 to 7-, 2 to 6-, 2 to 5-, 2 to 4-, 2 to 3-, 3 to 1000-, 3 to 900-, 3 to 800-, 3 to 700-, 3 to 600-, 3 to 500-, 3 to 400-, 3 to 3 to 00-, 3 to 200-, 3 to 100-, 3 to 90-, 3 to 80-, 3 to 70-, 3 to 60-, 3 to 50-, 3 to 40-, 3 to 30-, 3 to 20-, 3 to 10-, 3 to 9-, 3 to 8-, 3 to 7-, 3 to 6-, 3 to 5-, 3 to 4-, 4 to 1000-, 4 to 900-, 4 to 800-, 4 to 700-, 4 to 600-, 4 to 500-, 4 to 400-, 4 to 4 to 00-, 4 to 200-, 4 to 100-, 4 to 90-, 4 to 80-, 4 to 70-, 4 to 60-, 4 to 50-, 4 to 40-, 4 to 30-, 4 to 20-, 4 to 10-, 4 to 9-, 4 to 8-, 4 to 7-, 4 to 6-, 4 to 5-, 4 to 4-, 5 to 1000-, 5 to 900-, 5 to 800-, 5 to 700-, 5 to 600-, 5 to 500-, 5 to 400-, 5 to 300-, 5 to 200-, 5 to 100-, 5 to 90-, 5 to 80-, 5 to 70-, 5 to 60-, 5 to 50-, 5 to 40-, 5 to 30-, 5 to 20-, 5 to 10-, 5 to 9-, 5 to 8-, 5 to 7-, 5 to 6-, 6 to 1000-, 6 to 900-, 6 to 800-, 6 to 700-, 6 to 600-, 6 to 500-, 6 to 400-, 6 to 300-, 6 to 200-, 6 to 100-, 6 to 90-, 6 to 80-, 6 to 70-, 6 to 60-, 6 to 50-, 6 to 40-, 6 to 30-, 6 to 20-, 6 to 10-, 6 to 9-, 6 to 8-, 6 to 7-, 7 to 1000-, 7 to 900-, 7 to 800-, 7 to 700-, 7 to 600-, 7 to 500-, 7 to 400-, 7 to 300-, 7 to 200-, 7 to 100-, 7 to 90-, 7 to 80-, 7 to 70-, 7 to 60-, 7 to 50-, 7 to 40-, 7 to 30-, 7 to 20-, 7 to 10-, 7 to 9-, 7 to 8-, 8 to 1000-, 8 to 900-, 8 to 800-, 8 to 700-, 8 to 600-, 8 to 500-, 8 to 400-, 8 to 300-, 8 to 200-, 8 to 100-, 8 to 90-, 8 to 80-, 8 to 70-, 8 to 60-, 8 to 50-, 8 to 40-, 8 to 30-, 8 to 20-, 8 to 10-, 8 to 9-, 9 to 1000-, 9 to 900-, 9 to 800-, 9 to 700-, 9 to 600-, 9 to 500-, 9 to 400-, 9 to 60-, 9 to 50-, 9 to 40-, 9 to 30-, 9 to 20-, 9 to 10-, 10 to 1000-, 10 to 900-, 10 to 800-, 10 to 700-, 10 to 600-, 10 to 500-, 10 to 400-, 10 to 300-, 10 to 200-, 10 to 100-, 10 to 90-, 10 to 80-, 10 to 70-, 10 to 60-, 10 to 50-, 10 to 40-, 10 to 30-, 10 to 20-, 20 to 1000-, 20 to 900-, 20 to 800-, 20 to 700-, 20 to 600-, 20 to 500-, 20 to 400-, 20 to 300-, 20 to 200-, 20 to 100-, 20 to 90-, 20 to 80-, 20 to 70-, 20 to 60-, 20 to 50-, 20 to 40-, 20 to 30-, 30 to 1000-, 30 to 900-, 30 to 800-, 30 to 700-, 30 to 600-, 30 to 500-, 30 to 400-, 30 to 300-, 30 to 200-, 30 to 100-, 30 to 90-, 30 to 80-, 30 to 70-, 30 to 60-, 30 to 50-, 30 to 40-, 40 to 1000-, 40 to 900-, 40 to 800-, 40 to 700-, 40 to 600-, 40 to 500-, 40 to 400-, 40 to 300-, 40 to 200-, 40 to 100-, 40 to 90-, 40 to 80-, 40 to 70-, 40 to 60-, 40 to 50-, 50 to 1000-, 50 to 900-, 50 to 800-, 50 to 700-, 50 to 600-, 50 to 500-, 50 to 400-, 50 to 300-, 50 to 200-, 50 to 100-, 50 to 90-, 50 to 80-, 50 to 70-, 50 to 60-, 60 to 1000-, 60 to 900-, 60 to 800-, 60 to 700-, 60 to 600-, 60 to 500-, 60 to 400-, 60 to 300-, 60 to 200-, 60 to 100-, 60 to 90-, 60 to 80-, 60 to 70-, 70 to 1000-, 70 to 900-, 70 to 800-, 70 to 700-, 70 to 600-, 70 to 500-, 70 to 400-, 70 to 300-, 70 to 200-, 70 to 100-, 70 to 90-, 70 to 80-, 80 to 1000-, 80 to 900-, 80 to 800-, 80 to 700-, 80 to 600-, 80 to 500-, 80 to 400-, 80 to 300-, 80 to 200-, 80 to 100-, 80 to 90-, 90 to 1000-, 90 to 900-, 90 to 800-, 90 to 700-, 90 to 600-, 90 to 500-, 90 to 400-, 90 to 300-, 90 to 200-, 90 to 100-, 100 to 1000-, 100 to 900-, 100 to 800-, 100 to 700-, 100 to 600-, 100 to 500-, 100 to 400-, 100 to 300-, 100 to 200-, 200 to

1000-, 200 to 900-, 200 to 800-, 200 to 700-, 200 to 600-, 200 to 500-, 200 to 400-, 200 to 300-, 300 to 1000-, 300 to 900-, 300 to 800-, 300 to 700-, 300 to 600-, 300 to 500-, 300 to 400-, 400 to 1000-, 400 to 900-, 400 to 800-, 400 to 700-, 400 to 600-, 400 to 500-, 500 to 1000-, 500 to 900-, 500 to 5 800-, 500 to 700-, 500 to 600-, 600 to 1000-, 600 to 900-, 600 to 800-, 600 to 700-, 700 to 1000-, 700 to 900-, 700 to 800-, 800 to 1000-, 800 to 900-, or 900 to 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine. 10 In some embodiments, the anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified hMPV, PIV3, RSV, MeV and/or 15 encompassed by the following numbered paragraphs: BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine. In some embodiments, the effective amount is a dose equivalent to (or equivalent to an at least) 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 110-, 120-, 130-, 20 140-, 150-, 160-, 170-, 1280-, 190-, 200-, 210-, 220-, 230-, 240-, 250-, 260-, 270-, 280-, 290-, 300-, 310-, 320-, 330-, 340-, 350-, 360-, 370-, 380-, 390-, 400-, 410-, 420-, 430-, 440-, 450-, 4360-, 470-, 480-, 490-, 500-, 510-, 520-, 530-, 540-, 550-, 560-, 5760-, 580-, 590-, 600-, 610-, 620-, 630-, 25 640-, 650-, 660-, 670-, 680-, 690-, 700-, 710-, 720-, 730-, 740-, 750-, 760-, 770-, 780-, 790-, 800-, 810-, 820-, 830-, 840-, 850-, 860-, 870-, 880-, 890-, 900-, 910-, 920-, 930-, 940-, 950-, 960-, 970-, 980-, 990-, or 1000-fold reduction in the standard of care dose of a recombinant hMPV, PIV3, 30 RSV, MeV and/or BetaCoV protein vaccine. In some embodiments, an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or 35 purified hMPV, PIV3, RSV, MeV and/or BetaCoV protein vaccine or a live attenuated or inactivated hMPV, PIV3, RSV, MeV and/or BetaCoV vaccine.

In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 40 hMPV antigenic polypeptide comprises an amino acid 50-1000 µg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 50-1000, 50-900, 50-800, 50-700, 50-600, 50-500, 50-400, 50-300, 50-200, 50-100, 50-90, 50-80, 50-70, 50-60, 60-1000, 60-900, 60-800, 60-700, 60-600, 60-500, 45 60-400, 60-300, 60-200, 60-100, 60-90, 60-80, 60-70, 70-1000, 70-900, 70-800, 70-700, 70-600, 70-500, 70-400, 70-300, 70-200, 70-100, 70-90, 70-80, 80-1000, 80-900, 80-800, 80-700, 80-600, 80-500, 80-400, 80-300, 80-200, 80-100, 80-90, 90-1000, 90-900, 90-800, 90-700, 90-600, 50 90-500, 90-400, 90-300, 90-200, 90-100, 100-1000, 100-900, 100-800, 100-700, 100-600, 100-500, 100-400, 100-300, 100-200, 200-1000, 200-900, 200-800, 200-700, 200-600, 200-500, 200-400, 200-300, 300-1000, 300-900, 300-800, 300-700, 300-600, 300-500, 300-400, 400-1000, 400- 55 reading frame encoding a hMPV antigenic polypeptide or an 900, 400-800, 400-700, 400-600, 400-500, 500-1000, 500-900, 500-800, 500-700, 500-600, 600-1000, 600-900, 600-900, 600-700, 700-1000, 700-900, 700-800, 800-1000, 800-900, or 900-1000 µg. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is 60 a total dose of 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 µg. In some embodiments, the effective amount is a dose of 25-500 µg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory 65 virus RNA (e.g., mRNA) vaccine is a dose of 25-500, 25-400, 25-300, 25-200, 25-100, 25-50, 50-500, 50-400,

50-300, 50-200, 50-100, 100-500, 100-400, 100-300, 100-200, 150-500, 150-400, 150-300, 150-200, 200-500, 200-400, 200-300, 250-500, 250-400, 250-300, 300-500, 300-400, 350-500, 350-400, 400-500 or 450-500 µg administered to the subject a total of two times. In some embodiments, the effective amount of a respiratory virus RNA (e.g., mRNA) vaccine is a total dose of 25, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 µg administered to the subject a total of two times.

EXAMPLES OF ADDITIONAL EMBODIMENTS OF THE DISCLOSURE

Additional embodiments of the present disclosure are

1. A respiratory virus vaccine, comprising: at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one, at least two, at least three, at least four or at least five antigenic polypeptides selected from human metapneumovirus (hMPV) antigenic polypeptides or immunogenic fragments thereof, human parainfluenza virus type 3 (PIV3) antigenic polypeptides or immunogenic fragments thereof, respiratory syncytial virus (RSV) antigenic polypeptides or immunogenic fragments thereof, measles virus (MeV) antigenic polypeptides or immunogenic fragments thereof, and betacoronavirus (Beta-CoV) antigenic polypeptides or immunogenic fragments thereof.

2. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a PIV3 antigenic polypeptide or an immunogenic fragment thereof; or at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof.

3. The respiratory virus vaccine of paragraph 2, wherein the sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

4. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

5. The respiratory virus vaccine of paragraph 4, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8.

6. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open 5 reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

7. The respiratory virus vaccine of paragraph 6, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an 10 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at 15 least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

8. The respiratory virus vaccine of paragraph 1, comprising: at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immu- 20 nogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof and one having an open 25 reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

9. The respiratory virus vaccine of paragraph 8, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an 30 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at 35 least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

10. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading 40 frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an 45 immunogenic fragment thereof and one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof.

11. The respiratory virus vaccine of paragraph 10, wherein the PIV3 antigenic polypeptide comprises an amino acid 50 sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13.

12. The respiratory virus vaccine of paragraph 1, compris- 55 ing:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or 60

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

13. The respiratory virus vaccine of paragraph 12, wherein the PIV3 antigenic polypeptide comprises an amino acid

sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

14. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

- 15. The respiratory virus vaccine of paragraph 14, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID
- NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

16. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

17. The respiratory virus vaccine of paragraph 16, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50.

18. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

19. The respiratory virus vaccine of paragraph 18, wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

20. The respiratory virus vaccine of paragraph 1, comprising:

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at least one RNA polynucleotide having an open reading frame encoding a MeV antigenic polypeptide or an immu-

nogenic fragment thereof and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two RNA polynucleotides, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof and one having an open 5 reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

21. The respiratory virus vaccine of paragraph 20, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an 10 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at 15 least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

22. The respiratory virus vaccine of paragraph 1, comprising

at least one RNA polynucleotide having an open reading 20 frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a RSV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an 25 open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a RSV antigenic polypeptide or an 30 immunogenic fragment thereof.

23. The respiratory virus vaccine of paragraph 22, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to 35 an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence 40 open reading frame encoding a hMPV antigenic polypeptide identified by any one of SEQ ID NO: 12-13.

24. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immu- 45 nogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide 50 or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

25. The respiratory virus vaccine of paragraph 24, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID 60 NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV anti- 65 genic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid

sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50. 26. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

27. The respiratory virus vaccine of paragraph 26, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13 and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34. 28. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

29. The respiratory virus vaccine of paragraph 28, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence 55 identified by any one of SEQ ID NO: 47-50.

30. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open

reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

31. The respiratory virus vaccine of paragraph 30, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an 5 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEO ID NO: 5-8, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

32. The respiratory virus vaccine of paragraph 1, comprising

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open 25 reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

33. The respiratory virus vaccine of paragraph 32, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an 30 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% 35 or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino 40 acid sequence identified by any one of SEQ ID NO: 23-34. 34. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immu- 45 nogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide 50 or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

35. The respiratory virus vaccine of paragraph 34, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID 60 NO: 12-13, and/or wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50. 65

36. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

37. The respiratory virus vaccine of paragraph 36, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one 20 of SEO ID NO: 23-34 or an amino acid sequence having at

least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

38. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

39. The respiratory virus vaccine of paragraph 38, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34.

40. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two or three RNA polynucleotides, one having an 55 open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

41. The respiratory virus vaccine of paragraph 40, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ

ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 23-34 or an amino acid 5 sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 23-34. 42. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading 10 frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, and a MeV antigenic polypeptide or an immunogenic fragment thereof; 15 having an open reading frame encoding a hMPV antigenic or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic 20 polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof.

43. The respiratory virus vaccine of paragraph 42, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID 30 NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the MeV anti- 35 genic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50. 44. The respiratory virus vaccine of paragraph 1, compris- 40 ing:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic poly- 45 peptide or an immunogenic fragment thereof, and a Beta-CoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic 50 polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, and one hav- 55 ing an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

45. The respiratory virus vaccine of paragraph 44, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an 60 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% 65 or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, and/or wherein the BetaCoV

antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34. 46. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a Beta-CoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

47. The respiratory virus vaccine of paragraph 46, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEO ID NO: 5-8 or an 25 amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

48. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

49. The respiratory virus vaccine of paragraph 48, wherein the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90%

or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino 5 acid sequence identified by any one of SEQ ID NO: 24-34. 50. The respiratory virus vaccine of paragraph 1, comprising:

at least one RNA polynucleotide having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or 15

at least two, three or four RNA polynucleotides, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an 20 open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

51. The respiratory virus vaccine of paragraph 50, wherein 25 the PIV3 antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide com- 30 prises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence 35 identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34. 52. The respiratory virus vaccine of paragraph 1, compris-40 ing:

at least one RNA polynucleotide having an open reading frame encoding a hMPV antigenic polypeptide or an immunogenic fragment thereof, a PIV3 antigenic polypeptide or an immunogenic fragment thereof, a RSV antigenic polypeptide or an immunogenic fragment thereof, a MeV antigenic polypeptide or an immunogenic fragment thereof, and a BetaCoV antigenic polypeptide or an immunogenic fragment thereof; or

at least two, three, four or five RNA polynucleotides, one having an open reading frame encoding a hMPV antigenic 50 polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a PIV3 antigenic polypeptide or an immunogenic fragment thereof, one having an open reading frame encoding a RSV antigenic polypeptide or an immunogenic fragment thereof, one having an 55 open reading frame encoding a MeV antigenic polypeptide or an immunogenic fragment thereof, and one having an open reading frame encoding a BetaCoV antigenic polypeptide or an immunogenic fragment thereof.

53. The respiratory virus vaccine of paragraph 52, wherein 60 the hMPV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 5-8 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 5-8, wherein the PIV3 antigenic polypeptide comprises 65 an amino acid sequence identified by any one of SEQ ID NO: 12-13 or an amino acid sequence having at least 90%

or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 12-13, wherein the MeV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 47-50 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 47-50, and/or wherein the BetaCoV antigenic polypeptide comprises an amino acid sequence identified by any one of SEQ ID NO: 24-34 or an amino acid sequence having at least 90% or 95% identity to an amino acid sequence identified by any one of SEQ ID NO: 24-34.

54. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has less than 80% identity to wild-type mRNA sequence.

- 55. The vaccine of any one of paragraphs 1-53, wherein at least one RNA polynucleotide has at least 80% identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.
- 56. The vaccine of any one of paragraphs 1-55, wherein at least one antigenic polypeptide has membrane fusion activity, attaches to cell receptors, causes fusion of viral and cellular membranes, and/or is responsible for binding of the virus to a cell being infected.
- 57. The vaccine of any one of paragraphs 1-56, wherein at least one RNA polynucleotide comprises at least one chemical modification.
- 58. The vaccine of paragraph 57, wherein the chemical modification is selected from pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcyto sine, 5-methyluridine, 2-thio-1methyl-1-deaza-pseudouridine, 2-thio-1-methylpseudouridine, 2-thio-5-aza-uridine, 2-thiodihydropseudouridine, 2-thio-dihydrouridine, 2-thio-
- pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine.
- 59. The vaccine of paragraph 57 or 58, wherein the chemical modification is in the 5-position of the uracil.

60. The vaccine of any one of paragraphs 57-59, wherein the chemical modification is a N1-methylpseudouridine or N1-ethylpseudouridine.

61. The vaccine of any one of paragraphs 57-60, wherein at least 80%, at least 90% or 100% of the uracil in the open reading frame have a chemical modification.

62. The vaccine of any one of paragraphs 1-61, wherein at least one RNA polynucleotide further encodes at least one 5' terminal cap, optionally wherein the 5' terminal cap is 7mG(5')ppp(5')NImpNp.

63. The vaccine of any one of paragraphs 1-62, wherein at least one antigenic polypeptide or immunogenic fragment thereof is fused to a signal peptide selected from: a HuIgGk signal peptide (METPAQLLFLLLWLPDTTG; SEQ ID NO: 15); IgE heavy chain epsilon-1 signal peptide (MD-WTWILFLVAAATRVHS; SEQ ID NO: 16); Japanese encephalitis PRM signal sequence (MLGSNSGQRV-VFTILLLLVAPAYS; SEQ ID NO: 17), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 18) and Japanese encephalitis JEV signal sequence (MWLVS-LAIVTACAGA; SEQ ID NO: 19).

64. The vaccine of paragraph 63, wherein the signal peptide is fused to the N-terminus or the C-terminus of at least one antigenic polypeptide.

65. The vaccine of any one of paragraphs 1-64, wherein the antigenic polypeptide or immunogenic fragment thereof comprises a mutated N-linked glycosylation site.

66. The vaccine of any one of paragraphs 1-65 formulated in a nanoparticle, optionally a a lipid nanoparticle.

67. The vaccine of paragraph 66, wherein the lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid; optionally wherein the lipid 5 nanoparticle carrier comprises a molar ratio of about 20-60% cationic lipid, 0.5-15% PEG-modified lipid, 25-55% sterol, and 25% non-cationic lipid; optionally wherein the cationic lipid is an ionizable cationic lipid and the non-cationic lipid is a neutral lipid, and the sterol is a 10 cholesterol; and optionally wherein the cationic lipid is selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate 15 (L319). Formula (II) 68. The vaccine of paragraph 66 or 67, wherein the nanoparticle (e.g., lipid nanoparticle) comprises a compound of Formula (I) and/or Formula (II), optionally Compound 3, 18, 20, 25, 26, 29, 30, 60, 108-112, or 122. 69. The vaccine of any one of paragraphs 1-68 further 20 comprising an adjuvant, optionally a flagellin protein or peptide that optionally comprises an amino acid sequence identified by any one of SEQ ID NO: 54-56.

70. The vaccine of any one of paragraphs 1-69, wherein the open reading frame is codon-optimized.

71. The vaccine of any one of paragraphs 1-70 formulated in an effective amount to produce an antigen-specific immune response.

72. A method of inducing an immune response in a subject, the method comprising administering to the subject the 30 vaccine of any one of paragraphs 1-71 in an amount effective to produce an antigen-specific immune response in the subject.

73. The method of paragraph 72, wherein the subject is administered a single dose of the vaccine, or wherein the 35 subject is administered a first dose and then a booster dose of the vaccine.

74. The method of paragraph 72 or 73, wherein the vaccine is administered to the subject by intradermal injection or intramuscular injection.

75. The method of any one of paragraphs 72-74, wherein an anti-antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control, and/or wherein the anti-antigenic polypeptide antibody titer produced in the subject is increased at least 2 times relative 45 to a control.

76. The method of any one of paragraphs 72-75, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has not been administered a vaccine against the virus, and/or wherein the control is an anti- 50 antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated vaccine or an inactivated vaccine against the virus, and/or, wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant 55 protein vaccine or purified protein vaccine against the virus, and/or wherein the control is an anti-antigenic polypeptide antibody titer produced in a subject who has been administered a VLP vaccine against the virus.

77. The method of any one of paragraphs 72-76, wherein the 60 effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a recombinant protein vaccine or a purified protein vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-anti- 65 genic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant

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protein vaccine or a purified protein vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a live attenuated vaccine or an inactivated vaccine against the virus, respectively; and/or wherein the effective amount is a dose equivalent to an at least 2-fold reduction in the standard of care dose of a VLP vaccine against the virus, and wherein an anti-antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a VLP vaccine against the virus.

78. The method of any one of paragraphs 72-77, wherein the effective amount is a total dose of 50 µg-1000 µg, optionally wherein the effective amount is a dose of 25 μ g, 100 μ g, 400 μ g, or 500 μ g administered to the subject a total of two times. 79. The method of any one of paragraphs 72-78, wherein the efficacy of the vaccine against the virus is greater than 65%; and/or wherein the vaccine immunizes the subject against the virus for up to 2 years or wherein the vaccine immunizes the subject against the virus for more than 2 years.

80. The method of any one of paragraphs 72-79, wherein the subject has an age of about 5 years old or younger or wherein the subject has an age of about 60 years old or older; and/or wherein the subject has a chronic pulmonary disease; and/or the subject has been exposed to the virus, wherein the subject is infected with the virus, or wherein the subject is at risk of infection by the virus; and/or wherein the subject is immunocompromised.

81. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an 40 open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and about 0.5-15% PEG-modified lipid, and/or

(b) comprising a compound of Formula (I) and/or Formula (II),

wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification.

82. The respiratory virus vaccine of any one of paragraphs 1-71, comprising at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide having an open reading frame encoding at least one (e.g., at least two, at least three, at least four, or at least five) antigenic polypeptide selected from hMPV antigenic polypeptides (SEQ ID NO: 5-8), PIV3 antigenic polypeptides (SEQ ID NO: 12-13), RSV antigenic polypeptides, MeV antigenic polypeptides (SEQ ID NO: 47-50) and BetaCoV antigenic polypeptides (e.g., MERS-CoV, SARS-CoV, HCoV-OC43,

HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1; (SEQ ID NO: 24-34)), formulated in a cationic lipid nanoparticle

(a) having a molar ratio of about 20-60% cationic lipid, about 5-25% non-cationic lipid, about 25-55% sterol, and 5 about 0.5-15% PEG-modified lipid, and/or

(b) comprising at least one (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14) Compound selected from Compounds 3, 18, 20, 25, 26, 29, 30, 60, 108-112 and 122. 83. The respiratory virus vaccine of paragraphs 81 or 82, wherein the at least one antigenic polypeptide is selected from hMPV antigentic polypeptides (e.g., SEQ ID NO: 5-8). 84. The respiratory virus vaccine of any one of paragraphs 81-83, wherein the at least one antigenic polypeptide is 15 selected from PIV3 antigentic polypeptides (e.g., SEQ ID NO: 12-13).

85. The respiratory virus vaccine of any one of paragraphs 81-84, wherein the at least one antigenic polypeptide is selected from RSV antigentic polypeptides.

86. The respiratory virus vaccine of any one of paragraphs 81-85, wherein the at least one antigenic polypeptide is selected from MeV antigentic polypeptides (e.g., SEQ ID NO: 47-50).

87. The respiratory virus vaccine of any one of paragraphs 25 81-86, wherein the at least one antigenic polypeptide is selected from BetaCoV antigentic polypeptides (e.g., SEQ ID NO: 24-34).

88. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are MERS antigentic polypeptides.

89. The respiratory virus vaccine of paragraph 87, wherein the BetaCoV antigentic polypeptides are SARS antigentic polypeptides.

35 90. The respiratory virus vaccine of any one of paragraphs 81-89, wherein the at least one (e.g., at least two, at least three, at least four, or at least five) RNA polynucleotide comprises at least one chemical modification (e.g., selected from pseudouridine, N1-methylpseudouridine, N1-ethylp- 40 seudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcvtosine, 5-methyluridine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-4-methoxy-2-thio-pseudouridine, 45 pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine).

91. A respiratory virus vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) poly- 50 nucleotide having a 5' terminal cap, an open reading frame encoding at least one respiratory virus antigenic polypeptide, and a 3' polyA tail.

92. The vaccine of paragraph 91, wherein the at least one mRNA polynucleotide comprises a sequence identified by 55 any one of SEQ ID NO: 57-80.

93. The vaccine of paragraph 91 or 92, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp. 94. The vaccine of any one of paragraphs 91-93, wherein 100% of the uracil in the open reading frame is modified to 60 include N1-methyl pseudouridine at the 5-position of the uracil.

95. The vaccine of any one of paragraphs 91-94, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3- 65 phosphocholine (DSPC); and polyethylene glycol (PEG) 2000-DMG.

96. The vaccine of paragraph 95, wherein the lipid nanoparticle further comprises trisodium citrate buffer, sucrose and water.

97. A respiratory syncytial virus (RSV) vaccine, comprising: at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by any one of SEO ID NO: 57-80 and a 3' polyA tail, formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3phosphocholine (DSPC), and polyethylene glycol (PEG) 2000-DMG, wherein the uracil nucleotides of the sequence identified by any one of SEQ ID NO: 57-80 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide.

This disclosure is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The disclosure is capable of other embodiments 20 and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing," "involving," and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

EXAMPLES

Example 1: Manufacture of Polynucleotides

According to the present disclosure, the manufacture of polynucleotides and/or parts or regions thereof may be accomplished utilizing the methods taught in International Publication WO2014/152027, entitled "Manufacturing Methods for Production of RNA Transcripts," the contents of which is incorporated herein by reference in its entirety.

Purification methods may include those taught in International Publication WO2014/152030 and International Publication WO2014/152031, each of which is incorporated herein by reference in its entirety.

Detection and characterization methods of the polynucleotides may be performed as taught in International Publication WO2014/144039, which is incorporated herein by reference in its entirety.

Characterization of the polynucleotides of the disclosure may be accomplished using polynucleotide mapping, reverse transcriptase sequencing, charge distribution analysis, detection of RNA impurities, or any combination of two or more of the foregoing. "Characterizing" comprises determining the RNA transcript sequence, determining the purity of the RNA transcript, or determining the charge heterogeneity of the RNA transcript, for example. Such methods are taught in, for example, International Publication WO2014/ 144711 and International Publication WO2014/144767, the content of each of which is incorporated herein by reference in its entirety.

Example 2: Chimeric Polynucleotide Synthesis

According to the present disclosure, two regions or parts of a chimeric polynucleotide may be joined or ligated using triphosphate chemistry. A first region or part of 100 nucleotides or less is chemically synthesized with a 5' monophosphate and terminal 3'desOH or blocked OH, for example. If the region is longer than 80 nucleotides, it may be synthesized as two strands for ligation.

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If the first region or part is synthesized as a non-positionally modified region or part using in vitro transcription (IVT), conversion the 5'monophosphate with subsequent capping of the 3' terminus may follow.

Monophosphate protecting groups may be selected from 5 any of those known in the art.

The second region or part of the chimeric polynucleotide may be synthesized using either chemical synthesis or IVT methods. IVT methods may include an RNA polymerase that can utilize a primer with a modified cap. Alternatively, a cap of up to 130 nucleotides may be chemically synthesized and coupled to the IVT region or part.

For ligation methods, ligation with DNA T4 ligase, followed by treatment with DNase should readily avoid con-15 catenation.

The entire chimeric polynucleotide need not be manufactured with a phosphate-sugar backbone. If one of the regions or parts encodes a polypeptide, then such region or part may comprise a phosphate-sugar backbone.

Ligation is then performed using any known click chemistry, orthoclick chemistry, solulink, or other bioconjugate chemistries known to those in the art.

Synthetic Route

The chimeric polynucleotide may be made using a series ²⁵ of starting segments. Such segments include:

(a) a capped and protected 5' segment comprising a normal 3'OH (SEG. 1)

(b) a 5' triphosphate segment, which may include the coding region of a polypeptide and a normal 3'OH (SEG. 2) ³⁰

(c) a 5' monophosphate segment for the 3' end of the chimeric polynucleotide (e.g., the tail) comprising cordycepin or no 3'OH (SEG. 3)

After synthesis (chemical or IVT), segment 3 (SEG. 3) may be treated with cordycepin and then with pyrophos- ³⁵ phatase to create the 5' monophosphate.

Segment 2 (SEG. 2) may then be ligated to SEG. 3 using RNA ligase. The ligated polynucleotide is then purified and treated with pyrophosphatase to cleave the diphosphate.

The treated SEG.2-SEG. 3 construct may then be purified 40 and SEG. 1 is ligated to the 5' terminus. A further purification step of the chimeric polynucleotide may be performed.

Where the chimeric polynucleotide encodes a polypeptide, the ligated or joined segments may be represented as: 5'UTR (SEG. 1), open reading frame or ORF (SEG. 2) and 45 3'UTR+PolyA (SEG. 3).

The yields of each step may be as much as 90-95%.

Example 3: PCR for cDNA Production

PCR procedures for the preparation of cDNA may be performed using $2\times$ KAPA HIFITM HotStart ReadyMix by Kapa Biosystems (Woburn, Mass.). This system includes $2\times$ KAPA ReadyMix 12.5 µl; Forward Primer (10 µM) 0.75 µl; Reverse Primer (10 PM) 0.75 µl; Template cDNA 100 ng; 55 and dH₂O diluted to 25.0 µl. The reaction conditions may be at 95° C. for 5 min. The reaction may be performed for 25 cycles of 98° C. for 20 sec, then 58° C. for 15 sec, then 72° C. for 45 sec, then 72° C. for 5 min, then 4° C. to termination. 60

The reaction may be cleaned up using Invitrogen's PURELINKTM PCR Micro Kit (Carlsbad, Calif.) per manufacturer's instructions (up to 5 μ g). Larger reactions may require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA may be quantified using 65 the NANODROPTM and analyzed by agarose gel electrophoresis to confirm that the cDNA is the expected size. The

cDNA may then be submitted for sequencing analysis before proceeding to the in vitro transcription reaction.

Example 4: In Vitro Transcription (IVT)

The in vitro transcription reaction generates RNA polynucleotides. Such polynucleotides may comprise a region or part of the polynucleotides of the disclosure, including chemically modified RNA (e.g., mRNA) polynucleotides. The chemically modified RNA polynucleotides can be uniformly modified polynucleotides. The in vitro transcription reaction utilizes a custom mix of nucleotide triphosphates (NTPs). The NTPs may comprise chemically modified NTPs, or a mix of natural and chemically modified NTPs, or natural NTPs.

A typical in vitro transcription reaction includes the following:

1)	Template cDNA	1.0 µg
2)	10x transcription buffer	2.0 μl
	(400 mM Tris-HCl pH 8.0, 190 mM	
	MgCl ₂ , 50 mM DTT, 10 mM Spermidine)	
3)	Custom NTPs (25 mM each)	0.2 μl
4)	RNase Inhibitor	20 U
5)	T7 RNA polymerase	3000 U
6)	dH ₂ 0	up to $20.0 \ \mu$ l. and
7)	Incubation at 37° C. for 3 hr-5 hrs.	

The crude IVT mix may be stored at 4° C. overnight for cleanup the next day. 1 U of RNase-free DNase may then be used to digest the original template. After 15 minutes of incubation at 37° C., the mRNA may be purified using Ambion's MEGACLEARTM Kit (Austin, Tex.) following the manufacturer's instructions. This kit can purify up to 500 μ g of RNA. Following the cleanup, the RNA polynucleotide may be quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA polynucle-otide is the proper size and that no degradation of the RNA has occurred.

Example 5: Enzymatic Capping

Capping of a RNA polynucleotide is performed as follows where the mixture includes: IVT RNA 60 μ g-180 μ g and dH₂O up to 72 μ l. The mixture is incubated at 65° C. for 5 minutes to denature RNA, and then is transferred immediately to ice.

The protocol then involves the mixing of $10\times$ Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM MgCl₂) (10.0 µl); 20 mM GTP (5.0 µl); 20 mM S-Adenosyl Methionine (2.5 µl); RNase Inhibitor (100 U); 2'-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH₂O (Up to 28 µl); and incubation at 37° C. for 30 minutes for 60 µg RNA or up to 2 hours for 180 µg of RNA.

The RNA polynucleotide may then be purified using Ambion's MEGACLEAR[™] Kit (Austin, Tex.) following
⁵⁵ the manufacturer's instructions. Following the cleanup, the RNA may be quantified using the NANODROP[™] (ThermoFisher, Waltham, Mass.) and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has
⁶⁰ occurred. The RNA polynucleotide product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 6: PolyA Tailing Reaction

Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is

done by mixing capped IVT RNA (100 µl); RNase Inhibitor (20 U); 10x Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM MgCl₂) (12.0 µl); 20 mM ATP (6.0 µl); Poly-A Polymerase (20 U); dH₂O up to 123.5 µl and incubation at 37° C. for 30 min. If the poly-A tail is already 5 in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGA-CLEAR™ kit (Austin, Tex.) (up to 500 µg). Poly-A Polymerase may be a recombinant enzyme expressed in yeast.

It should be understood that the processivity or integrity of the polyA tailing reaction may not always result in an exact size polyA tail. Hence, polyA tails of approximately between 40-200 nucleotides, e.g., about 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 15 104, 105, 106, 107, 108, 109, 110, 150-165, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the present disclosure.

Example 7: Natural 5' Caps and 5' Cap Analogues

5'-capping of polynucleotides may be completed concomitantly during the in vitro-transcription reaction using the following chemical RNA cap analogs to generate the 5'-guanosine cap structure according to manufacturer pro- 25 tocols: 3'-O-Me-m7G(5')ppp(5') G [the ARCA cap];G(5') ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp (5')G (New England BioLabs, Ipswich, Mass.). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the 30 "Cap 0" structure: m7G(5')ppp(5')G (New England Bio-Labs, Ipswich, Mass.). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2'-O methyl-transferase to generate: m7G(5')ppp(5')G-2'-O-35 methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2'-O-methylation of the 5'-antepenultimate nucleotide using a 2'-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2'-O-methylation of the 5'-preantepenulti- $_{40}$ mate nucleotide using a 2'-0 methyl-transferase. Enzymes are preferably derived from a recombinant source.

When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, e.g., 24, 36, 48, 60, 72 or greater than 72 45 hours

Example 8: Capping Assays

Protein Expression Assay

Polynucleotides (e.g., mRNA) encoding a polypeptide, containing any of the caps taught herein, can be transfected into cells at equal concentrations. The amount of protein secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. Synthetic 55 polynucleotides that secrete higher levels of protein into the medium correspond to a synthetic polynucleotide with a higher translationally-competent cap structure. Purity Analysis Synthesis

RNA (e.g., mRNA) polynucleotides encoding a polypep- 60 tide, containing any of the caps taught herein can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. RNA polynucleotides with a single, consolidated band by electrophoresis correspond to the higher purity product compared to polynucleotides with 65 multiple bands or streaking bands. Chemically modified RNA polynucleotides with a single HPLC peak also corre-

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spond to a higher purity product. The capping reaction with a higher efficiency provides a more pure polynucleotide population.

Cytokine Analysis

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be transfected into cells at multiple concentrations. The amount of pro-inflammatory cytokines, such as TNF-alpha and IFNbeta, secreted into the culture medium can be assayed by ELISA at 6, 12, 24 and/or 36 hours post-transfection. RNA polynucleotides resulting in the secretion of higher levels of pro-inflammatory cytokines into the medium correspond to a polynucleotides containing an immune-activating cap structure.

Capping Reaction Efficiency

RNA (e.g., mRNA) polynucleotides encoding a polypeptide, containing any of the caps taught herein can be analyzed for capping reaction efficiency by LC-MS after nucle-20 ase treatment. Nuclease treatment of capped polynucleotides yield a mixture of free nucleotides and the capped 5'-5triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total polynucleotide from the reaction and correspond to capping reaction efficiency. The cap structure with a higher capping reaction efficiency has a higher amount of capped product by LC-MS.

> Example 9: Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

Individual RNA polynucleotides (200-400 ng in a 20 µl volume) or reverse transcribed PCR products (200-400 ng) may be loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, Calif.) and run for 12-15 minutes, according to the manufacturer protocol.

> Example 10: Nanodrop Modified RNA Quantification and UV Spectral Data

Chemically modified RNA polynucleotides in TE buffer (1 µl) are used for Nanodrop UV absorbance readings to quantitate the yield of each polynucleotide from an chemical synthesis or in vitro transcription reaction.

Example 11: Formulation of Modified mRNA Using Lipidoids

RNA (e.g., mRNA) polynucleotides may be formulated 50 for in vitro experiments by mixing the polynucleotides with the lipidoid at a set ratio prior to addition to cells. In vivo formulation may require the addition of extra ingredients to facilitate circulation throughout the body. To test the ability of these lipidoids to form particles suitable for in vivo work, a standard formulation process used for siRNA-lipidoid formulations may be used as a starting point. After formation of the particle, polynucleotide is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

Example 12: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate hMPV vaccines comprising a mRNA polynucleotide encoding Fusion (F) glycoprotein, major surface glycoprotein G, or a combination thereof, obtained from hMPV.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each ⁵ immunization until weeks 33-51. Serum antibody titers against Fusion (F) glycoprotein or major surface glycoprotein (G) protein are determined by ELISA. Sera collected from each mouse during weeks 10-16 are pooled, and total IgG purified. Purified antibodies are used for immunoelectron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 13: hMPV Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate hMPV vaccines against a lethal challenge using an hMPV vaccine comprising mRNA encoding Fusion (F) glycoprotein, major surface glycoprotein G, or a combination of both antigens obtained from hMPV. Cotton rats are challenged with a lethal dose of the hMPV.

Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate hMPV vaccines with and without adjuvant. Can-25 didate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of hMPV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or ³⁰ paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios ³⁵ 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example. 40

Example 14: Immunogenicity of hMPV mRNA Vaccine in BALB/c Mice

The instant study was designed to test the immunogenic- 45 ity in BALB/c mice of hMPV vaccines comprising an mRNA polynucleotide encoding the hMPV Fusion (F) glycoprotein. The mRNA polynucleotide encodes the fulllength fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain. Mice were 50 divided into 3 groups (n=8 for each group) and immunized intramuscularly (IM) with PBS, a 10 µg dose of mRNA vaccines encoding hMPV fusion protein, or a 2 µg dose of mRNA vaccines encoding hMPV fusion protein. A total of two immunizations were given at 3-week intervals (i.e., at 55 weeks 0, and 3 weeks), and sera were collected after each immunization according to the schedule described in Table 1. Serum antibody titers against hMPV fusion glycoprotein were determined by ELISA and antibodies were detected in the sera collected on day 14 onward. Both vaccine doses 60 tested induced comparable levels of immune response in mice (FIGS. 2A-2C).

Additionally, mice sera were used for IgG isotyping (FIGS. **3A-3**C). Both hMPV fusion protein-specific IgG1 and IgG2a were detected in mice sera. hMPV fusion protein 65 mRNA vaccine also induced Th1 and Th2 cytokine responses, with a Th1 bias.

Sera from mice immunized with either $10 \mu g$ or $2 \mu g$ doses of the hMPV fusion protein mRNA vaccine contain neutralizing antibodies. The ability of these antibodies to neutralize hMPV B2 strain was also tested. The antibody-containing sera successfully neutralized the hMPV B2 virus (FIG. 4).

Example 15: T-Cell Stimulation

The instant study was designed to test T-cell stimulation in the splenocytes of mice immunized with mRNA vaccines encoding hMPV fusion protein, as described herein. Immunization of BALB/c mice was performed as described in Example 14. The splenocytes for each group were pooled and split into two parts. One part of splenocytes from each group of mice was stimulated with hMPV-free media, Con-¹⁵ canavalin A or a hMPV fusion protein peptide pool comprising 15-mers (15 amino acids long); while the other part of splenocytes from each group of mice was stimulated with hMPV-free media, Concanavalin A or inactivated hMPV virus. Secreted mouse cytokines were measured using the 20 Meso Scale Discovery (MSD) assay.

Cytokines specific to Th1 or Th2 responses were measured. For Th1 response, IFN- γ , IL2 and IL12 were detected from splenocytes stimulated with the hMPV fusion protein peptide pool at a level comparable to that of Concanavalin A (FIGS. **5A-5**C). For a Th2 response, the hMPV fusion protein peptide pool induced the secretion of detectable IL10, TNF- α , IL4 and IL, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. **6A-6**E) at a much higher level.

In contrast, inactivated hMPV virus only induced the secretion of IL2 in the Th1 response comparable to that of Concanavalin A (FIGS. 7A-7C). For the Th2 response, the inactivated hMPV virus induced the secretion of detectable IL10, TNF- α , IL4 and IL6, but not IL5, while Concanavalin A stimulated the secretion of all the above-mentioned Th2 cytokines (FIGS. 8A-8E) at a much higher level.

Example 16: hMPV Rodent Challenge in Cotton Rats Immunized with mRNA Vaccine Encoding hMPV Fusion Protein

The instant study was designed to test the efficacy in cotton rats of hMPV vaccines against a lethal challenge. mRNA vaccines encoding hMPV fusion protein were used. The mRNA polynucleotide encodes a full-length fusion protein and comprises the wild-type nucleotide sequence obtained from the hMPV A2a strain.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with the mRNA vaccines encoding hMPV fusion protein with either 2 μ g or 10 μ g doses for each immunization. The animals were then challenged with a lethal dose of hMPV in week 7 post initial immunization via IV, IM or ID. The endpoint was day 13 post infection, death or euthanasia. Viral titers in the noses and lungs of the cotton rats were measured. The results (FIGS. 9A and 9B) show that a 10 μ g dose of mRNA vaccine protected the cotton mice 100% in the lung and drastically reduced the viral titer in the nose after challenge (~2 log reduction). Moreover, a 2 μ g dose of mRNA vaccine showed a 1 log reduction in lung viral titer in the cotton mice challenged.

Further, the histopathology of the lungs of the cotton mice immunized and challenged showed no pathology associated with vaccine-enhanced disease (FIG. **10**).

Example 17: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate PIV3 vaccines comprising a mRNA

polynucleotide encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Candidate vaccines are chemically modified or unmodified. A ⁵ total of four immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each immunization until weeks 33-51. Serum antibody titers against hemagglutinin-neuraminidase or fusion protein (F or F0) are determined by ELISA. Sera collected from each ¹⁰ mouse during weeks 10-16 are, optionally, pooled, and total IgGs are purified. Purified antibodies are used for immunoelectron microscopy, antibody-affinity testing, and in vitro protection assays.

Example 18: PIV3 Rodent Challenge

The instant study is designed to test the efficacy in cotton rats of candidate PIV3 vaccines against a lethal challenge 20 using a PIV3 vaccine comprising mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. Cotton rats are challenged with a lethal dose of the PIV3.

Animals are immunized intravenously (IV), intramuscu- 25 larly (IM), or intradermally (ID) at week 0 and week 3 with candidate PIV3 vaccines with and without adjuvant. Candidate vaccines are chemically modified or unmodified. The animals are then challenged with a lethal dose of PIV3 on week 7 via IV, IM or ID. Endpoint is day 13 post infection, ³⁰ death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formu-³⁵ lation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 40 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 19: hMPV/PIV Cotton Rat Challenge

The instant study was designed to test the efficacy in cotton rats of candidate hMPV mRNA vaccines, PIV3 mRNA vaccines, or hMPV/PIV combination mRNA vaccines against a lethal challenge using PIV3 strain or hMPV/A2 strain. The study design is shown in Table 9.

Cotton rats of 10-12 weeks old were divided into 12 groups (n=5), and each group was vaccinated with mRNA vaccines indicated in Table 9. The PIV3 vaccine comprises mRNA encoding hemagglutinin-neuraminidase or fusion protein (F or F0) obtained from PIV3. The hMPV mRNA 55 vaccine encodes the full-length hMPV fusion protein. The hMPV/PIV combination mRNA vaccine is a mixture of the PIV3 vaccine and hMPV vaccine at a 1:1 ratio.

Cotton rats were immunized intramuscularly (IM) at week 0 and week 3 with candidate vaccines with the doses 60 indicated in Table 9. Cotton rats immunized with hMPV mRNA vaccines or hMPV/PIV combination mRNA vaccines were challenged with a lethal dose of hMPV/A2 strain on week 7 via IM. Cotton rats immunized with PIV mRNA vaccines or hMPV/PIV combination mRNA vaccines were 65 challenged with a lethal dose of PIV3 strain on week 7 via IM.

The endpoint was day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis were euthanized. Body temperature and weight were assessed and recorded daily.

Lung and nose hMPV/A2 (FIG. 12) or PIV3 (FIG. 13) viral titers were assessed. Lung histopathology of the immunized and challenged cotton rat immunized and challenged were assessed to determine pathology associated with vaccine enhance disease. Neutralization antibody titers in the serum of immunized cotton rats on day 0 and 42 post immunization were assessed (FIG. 11).

hMPV/A2 (FIG. 14) or PIV3 (FIG. 15) neutralizing antibody titers in the serum samples of the immunized ¹⁵ cotton rat 42 days post immunization were measured. All mRNA vaccines tested induced strong neutralizing antibodies cotton rats. Lung histopathology of the immunized cotton rats were also evaluated (FIG. 16). Low occurrence of alevolitis and interstitial pneumonia was observed, indicat-²⁰ ing no antibody-dependent enhancement (ADE) of hMPV or PIV associated diseases.

Example 20: Betacoronavirus Immunogenicity Study

The instant study is designed to test the immunogenicity in rabbits of candidate betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1 or a combination thereof) vaccines comprising a mRNA polynucleotide encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from a betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

Rabbits are vaccinated on week 0 and 3 via intravenous (IV), intramuscular (IM), or intradermal (ID) routes. One group remains unvaccinated and one is administered inactivated betacoronavirus. Serum is collected from each rabbit on weeks 1, 3 (pre-dose) and 5. Individual bleeds are tested for anti-S1 or anti-S2 activity via a virus neutralization assay from all three time points, and pooled samples from week 5 only are tested by Western blot using inactivated betacoronavirus (e.g., inactivated MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %) or DLin-MC3-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

Example 21: Betacoronavirus Challenge

The instant study is designed to test the efficacy in rabbits of candidate betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccines against a lethal challenge using a betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-HKU1 or a combination thereof) vaccine comprising mRNA encoding the spike (S) protein, the S1 subunit (S1) of the spike protein, or the S2 subunit (S2) of the spike protein obtained from betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1). Rabbits are challenged with a lethal dose (10xLD90; ~100 plaque-forming units; PFU) of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1).

The animals used are 6-8 week old female rabbits in groups of 10. Rabbits are vaccinated on weeks 0 and 3 via an IM, ID or IV route of administration. Candidate vaccines are chemically modified or unmodified. Rabbit serum is tested for microneutralization (see Example 14). Rabbits are ¹⁰ then challenged with ~1 LD90 of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) on week 7 via an IN, IM, ID or IV route of administration. Endpoint is day 13 post infection, death or euthanasia. ¹⁵ Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

Example 22: Microneutralization Assay

Nine serial 2-fold dilutions (1:50-1:12,800) of rabbit serum are made in 50 µl virus growth medium (VGM) with trypsin in 96 well microtiter plates. Fifty microliters of virus 25 containing ~50 pfu of betacoronavirus (e.g., MERS-CoV, SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-NL, HCoV-NH or HCoV-HKU1) is added to the serum dilutions and allowed to incubate for 60 minutes at room temperature (RT). Positive control wells of virus 30 without sera and negative control wells without virus or sera are included in triplicate on each plate. While the serumvirus mixtures incubate, a single cell suspension of Madin-Darby Canine-Kidney cells are prepared by trypsinizing (Gibco 0.5% bovine pancrease trypsin in EDTA) a confluent 35 monolayer and suspended cells are transferred to a 50 ml centrifuge tube, topped with sterile PBS and gently mixed. The cells are then pelleted at 200 g for 5 minutes, supernatant aspirated and cells resuspended in PBS. This procedure is repeated once and the cells are resuspended at a concen- 40 tration of 3×10^5 /ml in VGM with porcine trypsin. Then, 100 µl of cells are added to the serum-virus mixtures and the plates incubated at 35° C. in C02 for 5 days. The plates are fixed with 80% acetone in phosphate buffered saline (PBS) for 15 minutes at RT, air dried and then blocked for 30 45 minutes containing PBS with 0.5% gelatin and 2% FCS. An antibody to the S proteins, S1 protein or S2 protein is diluted in PBS with 0.5% gelatin/2% FCS/0.5% Tween 20 and incubated at RT for 2 hours. Wells are washed and horseradish peroxidase-conjugated goat anti-mouse IgG added, 50 followed by another 2 hour incubation. After washing, O-phenylenediamine dihydrochloride is added and the neutralization titer is defined as the titer of serum that reduced color development by 50% compared to the positive control wells.

Example 23: MERS CoV Vaccine Immunogenicity Study in Mice

The instant study was designed to test the immunogenic- 60 ity in mice of candidate MERS-CoV vaccines comprising a mRNA polynucleotide encoding the full-length Spike (S) protein, or the S2 subunit (S2) of the Spike protein obtained from MERS-CoV.

Mice were vaccinated with a 10 µg dose of MERS-CoV 65 mRNA vaccine encoding either the full-length MERS-CoV Spike (S) protein, or the S2 subunit (S2) of the Spike protein

on days 0 and 21. Sera were collected from each mice on days 0, 21, 42, and 56. Individual bleeds were tested for anti-S, anti-S2 activity via a virus neutralization assay from all four time points.

As shown in FIG. 17, the MERS-CoV vaccine encoding the full-length S protein induced strong immune response after the boost dose on day 21. Further, full-length S protein vaccine generated much higher neutralizing antibody titers as compared to S2 alone (FIG. 18).

Example 24: MERS CoV Vaccine Immunogenicity Study in New Zealand White Rabbits

The instant study was designed to test the immunogenic-15 ity of candidate MERS-CoV mRNA vaccines encoding the full-length Spike (S) protein. The New Zealand white rabbits used in this study weighed about 4-5 kg. The rabbits were divided into three groups (Group 1a, Group 1b, and Group 2, n=8). Rabbits in Group 1a were immunized intramuscu-²⁰ larly (IM) with one 20 µg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0. Rabbits in Group 1b were immunized intramuscularly (IM) with one 20 µg dose of the MERS-CoV mRNA vaccine encoding the full-length Spike protein on day 0, and again on day 21 (booster dose). Group 2 received placebo (PBS). The immunized rabbits were then challenged and samples were collected 4 days after challenge. The viral loads in the lungs, bronchoalveolar lavage (Bal), nose, and throat of the rabbits were determined, e.g., via quantitative PCR. Replicating virus in the lung tissues of the rabbits were also detected. Lung histopathology were evaluated and the neutralizing antibody titers in serum samples of the rabbits were determined.

Two 20 μ g doses of MERS-CoV mRNA vaccine resulted in a 3 log reduction of viral load in the nose and led to complete protection in the throat of the New Zealand white rabbits (FIG. **19**A). Two 20 μ g doses of MERS-CoV mRNA vaccine also resulted in a 4 log reduction of viral load in the BAL of the New Zealand white rabbits (FIG. **19**B). One 20 μ g dose of MERS-CoV mRNA vaccine resulted in a 2 log reduction of viral load, while two 20 μ g doses of MERS-CoV mRNA vaccine resulted in an over 4 log reduction of viral load in the lungs of the New Zealand white rabbits (FIG. **19**C).

Quantitative PCR results show that two 20 µg doses of MERS-CoV mRNA vaccine reduced over 99% (2 log) of viruses in the lungs of New Zealand white rabbits (FIG. 20A). No replicating virus were detected in the lungs (FIG. 20B).

Further, as shown in FIG. 21, two 20 µg doses of MERS-CoV mRNA vaccine induced significant amount of neutralizing antibodies against MERS-CoV (ECso between 500-1000).

The MERS-CoV mRNA vaccine induced antibody titer is 55 3-5 fold better than any other vaccines tested in the same model.

Example 25: Immunogenicity Study

The instant study is designed to test the immunogenicity in mice of candidate MeV vaccines comprising a mRNA polynucleotide encoding MeV hemagglutinin (HA) protein, MeV Fusion (F) protein or a combination of both.

Mice are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) with candidate vaccines. Up to three immunizations are given at 3-week intervals (i.e., at weeks 0, 3, 6, and 9), and sera are collected after each

immunization until weeks 33-51. Serum antibody titers against MeV HA protein or MeV F protein are determined by ELISA.

Example 26: MeV Rodent Challenge

The instant study is designed to test the efficacy in transgenic mice of candidate MeV vaccines against a lethal challenge using a MeV vaccine comprising mRNA encoding MeV HA protein or MeV F protein. The transgenic mice 10 express human receptor CD46 or signaling lymphocyte activation molecule (SLAM) (also referred to as CD150). Humans are the only natural host for MeV infection, thus transgenic lines are required for this study. CD46 is a complement regulatory protein that protects host tissue from 15 complement deposition by binding to complement components C3b and C4b. Its expression on murine fibroblast and lymphoid cell lines renders these otherwise refractory cells permissive for MeV infection, and the expression of CD46 on primate cells parallels the clinical tropism of MeV 20 infection in humans and nonhuman primates (Rall G F et al. PNAS USA 1997; 94(9):4659-63). SLAM is a type 1 membrane glycoprotein belonging to the immunoglobulin super-

family. It is expressed on the surface of activated lymphocytes, macrophages, and dendritic cells and is thought to play an important role in lymphocyte signaling. SLAM is a receptor for both wild-type and vaccine MeV strains (Sellin C I et al. *J Virol.* 2006; 80(13):6420-29).

CD46 or SLAM/CD150 transgenic mice are challenged with a lethal dose of the MeV. Animals are immunized intravenously (IV), intramuscularly (IM), or intradermally (ID) at week 0 and week 3 with candidate MeV vaccines with and without adjuvant. The animals are then challenged with a lethal dose of MeV on week 7 via IV, IM or ID. Endpoint is day 13 post infection, death or euthanasia. Animals displaying severe illness as determined by >30% weight loss, extreme lethargy or paralysis are euthanized. Body temperature and weight are assessed and recorded daily.

In experiments where a lipid nanoparticle (LNP) formulation is used, the formulation may include a cationic lipid, non-cationic lipid, PEG lipid and structural lipid in the ratios 50:10:1.5:38.5. The cationic lipid is DLin-KC2-DMA (50 mol %), the non-cationic lipid is DSPC (10 mol %), the PEG lipid is PEG-DOMG (1.5 mol %) and the structural lipid is cholesterol (38.5 mol %), for example.

TABLE 1

	Animal		111111	minia	10 gennent y	studios t	leeding schedul			
	groups						Day			
	(n = 8)	vaccine	-2	0	7	14	21	28	35	56
Placebo	Group $1 (n = 8)$	PBS) (IM)	Pre-Bleed	Prime	Bleeds	Bleeds	Bleeds/Boost	Bleeds	Bleeds	Harvest Spleens/Term
10 µg	Group									inal Bleeds
Dose	2(n = 8)									
2 μg	Group	2 µg								
Dose	3(n = 8)) (IM)								

Total n = 24

40 Each of the sequences described herein encompasses a chemically modified sequence or an unmodified sequence which includes no nucleotide modifications.

TABLE 2	2
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		SEQ II
Description	Sequence	NO:
gi 122891979 gb EF051124.1	ATGAGCTGGAAGGTGGTGATTATCTTCAGCCTGCTGATTA	1
Human	CACCTCAACACGGCCTGAAGGAGAGCTACCTGGAAGAGA	
metapneumovirus	GCTGCTCCACCATCACCGAGGGCTACCTGAGCGTGCTGC	
isolate TN/92-4	GGACCGGCTGGTACACCAACGTGTTCACCCTGGAGGTGG	
fusion protein gene,	GCGACGTGGAGAACCTGACCTGCAGCGACGGCCCTAGCC	
complete genome	TGATCAAGACCGAGCTGGACCTGACCAAGAGCGCTCTGA	
	GAGAGCTGAAGACCGTGTCCGCCGACCAGCTGGCCAGAG	
	AGGAACAGATCGAGAACCCTCGGCAGAGCAGATTCGTGC	
	TGGGCGCCATCGCTCTGGGAGTCGCCGCTGCCGCTGCAG	
	TGACAGCTGGAGTGGCCATTGCTAAGACCATCAGACTGG	
	AAAGCGAGGTGACAGCCATCAACAATGCCCTGAAGAAG	
	ACCAACGAGGCCGTGAGCACCCTGGGCAATGGAGTGAGA	
	GTGCTGGCCACAGCCGTGCGGGAGCTGAAGGACTTCGTG	
	AGCAAGAACCTGACCAGAGCCATCAACAAGAACAAGTG	
	CGACATCGATGACCTGAAGATGGCCGTGAGCTTCTCCCA	
	GTTCAACAGACGGTTCCTGAACGTGGTGAGACAGTTCTC	
	CGACAACGCTGGAATCACACCTGCCATTAGCCTGGACCT	
	GATGACCGACGCCGAGCTGGCTAGAGCCGTGCCCAACAT	
	GCCCACCAGCGCTGGCCAGATCAAGCTGATGCTGGAGAA	
	CAGAGCCATGGTGCGGAGAAAGGGCTTCGGCATCCTGAT	
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	GCCCATCTTCGGCGTGATCGACACCCCTGCTGGATCGTG	

TABLE 2-continued

Description	Sequence	SEQ II NO:
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	GCCTGTCTGCTGAGAGAGGACCAGGGCTGGTACTGCCAG	
	AACGCCGGAAGCACAGTGTACTATCCCAACGAGAAGGAC	
	TGCGAGACCAGAGGCGACCACGTGTTCTGCGACACCGCT	
	GCCGGAATCAACGTGGCCGAGCAGAGCAAGGAGTGCAA	
	CATCAACATCAGCACAACCAACTACCCCTGCAAGGTGAG CACCGGACGGCACCCCATCAGCATGGTGGCTCTGAGCCC	
	TCTGGGCGCTCTGGTGGCCTGCTATAAGGGCGTGTCCTGT	
	AGCATCGGCAGCAATCGGGTGGGCATCATCAAGCAGCTG	
	AACAAGGGATGCTCCTACATCACCAACCAGGACGCCGAC	
	ACCGTGACCATCGACAACACCGTGTACCAGCTGAGCAAG	
	GTGGAGGGCGAGCAGCACGTGATCAAGGGCAGACCCGT	
	GAGCTCCAGCTTCGACCCCATCAAGTTCCCTGAGGACCA GTTCAACGTGGCCCTGGACCAGGTGTTTGAGAACATCGA	
	GAACAGCCAGGCCCTGGTGGACCAGGTGTTTGAGAACATCGA	
	GTCCAGCGCTGAGAAGGGCAACACCGGCTTCATCATTGT	
	GATCATTCTGATCGCCGTGCTGGGCAGCTCCATGATCCTG	
	GTGAGCATCTTCATCATTATCAAGAAGACCAAGAAACCC	
	ACCGGAGCCCCTCCTGAGCTGAGCGGCGTGACCAACAAT	
	GGCTTCATTCCCCACAACTGA	
jb AY525843.1 : 3065-4684 Juman	ATGTCTTGGAAAGTGATGATCATCATTTCGTTACTCATAA CACCCCAGCACGGGCTAAAGGAGAGTTATTTGGAAGAAT	2
netapneumovirus	CATGTAGTACTATAACTGAGGGATACCTCAGTGTTTTAAG	
lsolate NL/1/99,	AACAGGCTGGTACACTAATGTCTTCACATTAGAAGTTGGT	
complete genome	GATGTTGAAAATCTTACATGTACTGATGGACCTAGCTTAA	
	TCAAAACAGAACTTGATCTAACAAAAAGTGCTTTAAGGG	
	AACTCAAAACAGTCTCTGCTGATCAGTTGGCGAGAGAGG	
	AGCAAATTGAAAATCCCAGACAATCAAGATTTGTCTTAG	
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	GTGAGGTGAATGCAATTAAAGGTGCTCTCAAACAAACTA	
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	AAAACCTGACTAGTGCAATCAACAGGAACAAATGTGACA	
	TTGCTGATCTGAAGATGGCTGTCAGCTTCAGTCAATTCAA	
	CAGAAGATTTCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGACT GATGCTGAGTTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCACGGCAGATAAAACTGATGTTGGAGAACCGCGCA	
	ATGGTAAGGAGAAAAGGATTTGGAATCCTGATAGGGGTC	
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	CACCCTATAAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTGGCTTGCTATAAAGGGGTAAGCTGCTCGATTGGCA	
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	CGTGTATCAACTAAGCAAAGTTGAAGGTGAACAGCATGT	
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	GTCTTCGAAAGCATTGAGAACAGTCAGGCACTAGTGGAC	
	CAGTCAAACAAAATTCTAAACAGTGCAGAAAAAGGAAA	
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	GTCTAACCATGATTTCAGTGAGCATCATCATCATAATCAA GAAAACAAGGAAGCCCACAGGAGCACCTCCAGAGCTGA	
	ATGGTGTCACCAACGGCGGTTTCATACCACATAGTTA	
b KJ627414.1 : 3015-4634	ATGTCTTGGAAAGTGATGATTATCATTTCGTTACTCATAA	3
luman	CACCTCAGCATGGACTAAAAGAAAGTTATTTAGAAGAAT	
netapneumovirus	CATGTAGTACTATAACTGAAGGATATCTCAGTGTTTTAAG	
strain hMPV/Homo	AACAGGTTGGTACACCAATGTCTTTACATTAGAAGTTGGT	
sapiens/PER/CFI0497/ 2010/B,	GATGTTGAAAATCTTACATGTACTGATGGACCTAGCTTAA TCAAAACAGAACTTGACCTAACCAAAAGTGCTTTAAGAG	
complete genome	AACTCAAAACAGTTTCTGCTGATCAGTTAGCGAGAGAAG	
	AACAAATTGAAAAATCCCAGACAATCAAGGTTTGTCCTAG	
	GTGCAATAGCTCTTGGAGTTGCCACAGCAGCAGCAGTCA	
	CAGCAGGCATTGCAATAGCCAAAACTATAAGGCTTGAGA	

TABLE 2-continued

Description	Sequence	SEQ II NO:
Jeacription	sequence	NO:
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	TTGCTGATTTGAAGATGGCTGTCAGCTTCAGTCAGTTCAA	
	CAGAAGATTCCTAAATGTTGTGCGGCAGTTTTCAGACAAT	
	GCAGGGATAACACCAGCAATATCATTGGACCTGATGAAT	
	GATGCTGAGCTGGCCAGAGCTGTATCATACATGCCAACA	
	TCTGCAGGACAGATAAAACTAATGTTAGAGAACCGTGCA ATGGTGAGGAGAAAAGGATTTGGAATCTTGATAGGGGTC	
	TACGGAAGCTCTGTGATTTACATGGTCCAGCTGCCGATCT	
	TTGGTGTCATAAATACACCTTGTTGGATAATCAAGGCAGC	
	TCCCTCTTGTTCAGAAAAAGATGGAAATTATGCTTGCCTC	
	CTAAGAGAGGATCAAGGGTGGTATTGTAAAAATGCAGGA	
	TCCACTGTTTACTACCCAAATGAAAAAGACTGCGAAACA AGAGGTGATCATGTTTTTTGTGACACAGCAGCAGGGATC	
	AATGTTGCTGAGCAATCAAGAGAATGCAACATCAACATCAACATCAACATCAACATCAACATA	
	TCTACCACCAACTACCCATGCAAAGTCAGCACAGGAAGA	
	CACCCTATCAGCATGGTTGCACTATCACCTCTCGGTGCTT	
	TGGTAGCTTGCTACAAAGGGGTTAGCTGCTCGACTGGCA	
	GTAATCAGGTTGGAATAATCAAACAACTACCTAAAGGCT	
	GCTCATACATAACTAACCAGGACGCAGACACTGTAACAA TTGACAACACTGTGTATCAACTAAGCAAAGTTGAGGGTG	
	AACAGCATGTAATAAAAGGGAGACCAGTTTCAAGCAGTT	
	TTGATCCAATCAGGTTTCCTGAGGATCAGTTCAATGTTGC	
	GCTTGATCAAGTCTTTGAAAGCATTGAAAACAGTCAAGC	
	ACTAGTGGACCAGTCAAACAAAATTCTGAACAGTGCAGA	
	AAAAGGAAACACTGGT TTCATTATTGTAATAATTTTGATTGCTGTTCTTGGGTTAAC	
	CATGATTTCAGTGAGCATCATCATCATCAAAAAAAAAC	
	AAGGAAGCCCACAGGGGCACCTCCGGAGCTGAATGGTGT	
	TACCAACGGCGGTTTCATACCGCATAGTTAG	
gb KJ723483.1 : 5586-7310	ATGGAGTTGCCAATCCTCAAAACAAATGCAATTACCACA	4
Human	ATCCTTGCTGCAGTCACACTCTGTTTCGCTTCCAGTCAAA	
respiratory	ACATCACTGAAGAATTTTATCAATCAACATGCAGTGCAG	
syncytial virus	TTAGCAAAGGCTATCTTAGTGCTCTAAGAACTGGTTGGTA	
strain RSVA/Homo	TACTAGTGTTATAACTATAGAATTAAGTAATATCAAGGA	
sapiens/USA/841-	AAATAAGTGTAATGGAACAGATGCTAAGGTAAAATTGAT AAAACAAGAATTAGATAAATATAAAAATGCTGTAACAGA	
215A-01/1984, complete genome	ATTGCAGTTGCTCATGCAAAGCACACCAGCAGCCAACAA	
somprete genome	TCGAGCCAGAAGAGAACTACCAAGGTTTATGAATTATAC	
	ACTCAATAATACCAAAAATACCAATGTAACATTAAGCAA	
	GAAAAGGAAAAGAAGATTTCTTGGCTTTTTGTTAGGTGTT	
	GGATCTGCAATCGCCAGTGGCATTGCTGTATCTAAGGTCC	
	TACTATCCACAAACAAGGCTGTAGTCAGCTTATCAAATG GAGTTAGTGTCTTAACCAGCAAAGTGTTAGACCTCAAAA	
	ACTATATAGATAAACAGTTGTTACCTATTGTGAACAAGC	
	AAAGCTGCAGCATATCAAACATTGAAACTGTGATAGAGT	
	TCCAACAAAAGAACAACAGACTACTAGAGATTACCAGGG	
	AATTTAGTGTTAATGCAGGTGTAACTACACCTGTAAGCAC	
	TTATATGTTAACTAATAGTGAATTATTATCATTAATCAAT	
	GATATGCCTATAACAAATGATCAGAAAAAGTTAATGTCC AACAATGTTCAAATAGTTAGACAGCAAAGTTACTCTATC	
	ATGTCCATAATAAAGGAGGAAGTCTTAGCATATGTAGTA	
	CAATTACCACTATATGGTGTAATAGATACACCCTGTTGGA	
	AACTGCACACATCCCCTCTATGTACAACCAACACAAAGG	
	AAGGGTCCAACATCTGCTTAACAAGAACCGACAGAGGAT	
	GGTATTGTGACAATGCAGGATCAGTATCTTTCTTCCCACA	
	AGCTGAAACATGTAAAGTTCAATCGAATCGGGTATTTTGT	
	GACACAATGAACAGTTTAACATTACCAAGTGAAGTAAAT CTCTGCAACATTGACATATTCAACCCCAAATATGATTGCA	
	AAATTATGACTTCAAAAACAGATGTAAGCAGCTCCGTTA	
	TCACATCTCTAGGAGCCATTGTGTCATGCTATGGCAAAAC	
	TAAATGTACAGCATCCAATAAAAATCGTGGGATCATAAA	
	GACATTTTCTAACGGGTGTGATTATGTATCAAATAAGGG	
	AATAAGCAAGAAGGCAAAAGTCTCTATGTAAAAGGTGAA	
	CCAATAATAAATTTCTATGACCCATTAGTGTTCCCCCTCTG ATGAATTTGATGCATCAATATCTCAAGTCAATGAGAAGA	
	TTAACCAGAGCCTAGCATTTATTCGTAAATCCGATGAATT	
	TTAACCAGAGCCTAGCATTTATTCGTAAATCCGATGAATT ATTACATAATGTAAATGCTGGTAAATCCACCACAAATAT	

TABLE 2-continued

		SEQ I
Description	Sequence	NO:
	GTGGTATAAATAATATTGCATTTAGTAACTGA	
	hMPV mRNA Sequences	
gi 122891979 gb EF051124.1 Human	AUGAGCUGGAAGGUGGUGAUUAUCUUCAGCCUGCUGAU UACACCUCAACACGGCCUGAAGGAGAGCUACCUGGAAG	57
netapneumo virus	AGAGCUGCUCCACCAUCACCGAGGGCUACCUGAGCGUG	
isolate TN/92-4	CUGCGGACCGGCUGGUACACCAACGUGUUCACCCUGGA	
fusion protein gene,	GGUGGGCGACGUGGAGAACCUGACCUGCAGCGACGGCC	
complete genome	CUAGCCUGAUCAAGACCGAGCUGGACCUGACCAAGAGC GCUCUGAGAGAGCUGAAGACCGUGUCCGCCGACCAGCU	
	GCCCAGAGAGAGCCGAGACCGGGCAGAGCCGGCGGCAGAGCA	
	GAUUCGUGCUGGGCGCCAUCGCUCUGGGAGUCGCCGCU	
	GCCGCUGCAGUGACAGCUGGAGUGGCCAUUGCUAAGAC	
	CAUCAGACUGGAAAGCGAGGUGACAGCCAUCAACAAUG CCCUGAAGAAGACCAACGAGGCCGUGAGCACCCUGGGC	
	AAUGGAGUGAGAGUGCUGGCCACACCGUGAGCACCCUGGGC	
	GAAGGACUUCGUGAGCAAGAACCUGACCAGAGCCAUCA	
	ACAAGAACAAGUGCGACAUCGAUGACCUGAAGAUGGCC	
	GUGAGCUUCUCCCAGUUCAACAGACGGUUCCUGAACGU	
	GGUGAGACAGUUCUCCGACAACGCUGGAAUCACACCUG CCAUUAGCCUGGACCUGAUGACCGACGCCGAGCUGGCU	
	AGAGCCGUGCCCAACAUGCCCACCAGCGCUGGCCAGAU	
	CAAGCUGAUGCUGGAGAACAGAGCCAUGGUGCGGAGAA	
	AGGGCUUCGGCAUCCUGAUUGGGGUGUAUGGAAGCUCC	
	GUGAUCUACAUGGUGCAGCUGCCCAUCUUCGGCGUGAU	
	CGACACACCCUGCUGGAUCGUGAAGGCCGCUCCUAGCU GCUCCGAGAAGAAAGGAAACUAUGCCUGUCUGCUGAGA	
	GAGGACCAGGGCUGGUACUGCCAGAACGCCGGAAGCAC	
	AGUGUACUAUCCCAACGAGAAGGACUGCGAGACCAGAG	
	GCGACCACGUGUUCUGCGACACCGCUGCCGGAAUCAAC	
	GUGGCCGAGCAGAGCAAGGAGUGCAACAUCAACAUCAG CACAACCAACUACCCCUGCAAGGUGAGCACCGGACGGC	
	ACCCCAUCAGCAUGGUGGCUCUGAGCCCUCUGGGCGCU	
	CUGGUGGCCUGCUAUAAGGGCGUGUCCUGUAGCAUCGG	
	CAGCAAUCGGGUGGGCAUCAUCAAGCAGCUGAACAAGG	
	GAUGCUCCUACAUCACCAACCAGGACGCCGACACCGUG ACCAUCGACAACACCGUGUACCAGCUGAGCAAGGUGGA	
	GGGCGAGCAGCACCGUGAUCAAGGGCAGACCCGUGAGCU	
	CCAGCUUCGACCCCAUCAAGUUCCCUGAGGACCAGUUC	
	AACGUGGCCCUGGACCAGGUGUUUGAGAACAUCGAGAA	
	CCAGCGCUGAGAAGGGCAACACCGGCUUCAUCAUUGUG AUCAUUCUGAUCGCCGUGCUGGGCAGCUCCAUGAUCCU	
	GGUGAGCAUCUUCAUCAUUAUCAAGAAGACCAAGAAAC	
	CCACCGGAGCCCCUCCUGAGCUGAGCGGCGUGACCAAC AAUGGCUUCAUUCCCCACAACUGA	
b AY525843.1 : 3065-4684 Juman	AUGUCUUGGAAAGUGAUGAUCAUCAUUUCGUUACUCAU AACACCCCAGCACGGGCUAAAGGAGAGUUAUUUGGAAG	58
etapneumovirus	AAUCAUGUAGUACUAUAACUGAGGGAUACCUCAGUGUU	
solate NL/1/99,	UUAAGAACAGGCUGGUACACUAAUGUCUUCACAUUAGA	
omplete genome	AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA CCUAGCUUAAUCAAAACAGAACUUGAUCUAACAAAAAG	
	UGCUUUAAGGGAACUCAAAACAGUCUCUGCUGAUCAGU	
	UGGCGAGAGAGGAGCAAAUUGAAAAUCCCAGACAAUCA	
	AGAUUUGUCUUAGGUGCGAUAGCUCUCGGAGUUGCUAC	
	AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA	
	CCAUAAGGCUUGAGAGUGAGGUGAAUGCAAUUAAAGG UGCUCUCAAACAAACUAAUGAAGCAGUAUCCACAUUAG	
	GGAAUGGUGUGCGGGUCCUAGCCACUGCAGUGAGAGAG	
	CUAAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCAAU	
	CAACAGGAACAAAUGUGACAUUGCUGAUCUGAAGAUGG	
	CUGUCAGCUUCAGUCAAUUCAACAGAAGAUUUCUAAAU GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC	
	AGCAAUAUCAUUGGACCUGAUGACUGAUGCUGAGUUGG	
	CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGGCAG	
	AUAAAACUGAUGUUGGAGAACCGCGCAAUGGUAAGGAG	
	AAAAGGAUUUGGAAUCCUGAUAGGGGUCUACGGAAGCU CUGUGAUUUACAUGGUUCAAUUGCCGAUCUUUGGUGUC	
	CUGUGAUUUACAUGUUCAAUUGUUGAUUUUGGUGUC	
	AUAGAUACACCUUGUUGGAUCAUCAAGGCAGCUCCCUC UUGCUCAGAAAAAAACGGGAAUUAUGCUUGCCUCCUAA	
	AUAGAUACACCUUGUUGGAUCAUCAAGGCAGCUCCCUC	

TABLE 2-continued

Deservite	Service en	SEQ ID
Description	Sequence	NO :
	AAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAACAU AUCUACUACCAACUACCCAUGCAAAGUCAGCACAGGAA	
	GACACCCUAUAAGCAUGGUUGCACUAUCACCUCUCGGU	
	GCUUUGGUGGCUUGCUAUAAAGGGGUAAGCUGCUCGAU	
	UGGCAGCAAUUGGGU	
	UGGAAUCAUCAAACAAUUACCCAAAGGCUGCUCAUACA	
	UAACCAACCAGGAUGCAGACACUGUAACAAUUGACAAU	
	ACCGUGUAUCAACUAAGCAAAGUUGAAGGUGAACAGCA	
	UGUAAUAAAAGGGAGACCAGUUUCAAGCAGUUUUGAUC	
	CAAUCAAGUUUCCUGAGGAUCAGUUCAAUGUUGCGCUU	
	GAUCAAGUCUUCGAAAGCAUUGAGAACAGUCAGGCACU	
	AGUGGACCAGUCAAACAAAAUUCUAAACAGUGCAGAAA	
	AAGGAAACACUGGUUUCAUUAUCGUAGUAAUUUUGGU UGCUGUUCUUGGUCUAACCAUGAUUUCAGUGAGCAUCA	
	UCAUCAUAAUCAAGAAAACAAGGAAGCCCACAGGAGCA	
	CCUCCAGAGCUGAAUGGUGUCACCAACGGCGGUUUCAU	
	ACCACAUAGUUAG	
gb KJ627414.1 : 3015-4634	AUGUCUUGGAAAGUGAUGAUUAUCAUUUCGUUACUCAU	59
Juman	AACACCUCAGCAUGGACUAAAAGAAAGUUAUUUAGAAG	
netapneumovirus	AAUCAUGUAGUACUAUAACUGAAGGAUAUCUCAGUGUU	
strain hMPV/Homo	UUAAGAACAGGUUGGUACACCAAUGUCUUUACAUUAGA	
sapiens/PER/CFI0497/	AGUUGGUGAUGUUGAAAAUCUUACAUGUACUGAUGGA	
2010/B,	CCUAGCUUAAUCAAAACAGAACUUGACCUAACCAAAAG	
complete genome	UGCUUUAAGAGAACUCAAAACAGUUUCUGCUGAUCAGU	
	UAGCGAGAGAAGAACAAAUUGAAAAUCCCAGACAAUCA	
	AGGUUUGUCCUAGGUGCAAUAGCUCUUGGAGUUGCCAC	
	AGCAGCAGCAGUCACAGCAGGCAUUGCAAUAGCCAAAA CUAUAAGGCUUGAGAGUGAAGUGA	
	UGCUCUCAAAACAACCAAUGAGGGAGGGAGUGCAAUCAAAGG	
	GAAAUGGAGUGCGGGUCCUAGCCACUGCAGUAAGAGAG	
	CUGAAAGAAUUUGUGAGCAAAAACCUGACUAGUGCGAU	
	CAACAAGAACAAGUGUGACAUUGCUGAUUUGAAGAUGG	
	CUGUCAGCUUCAGUCAGUUCAACAGAAGAUUCCUAAAU	
	GUUGUGCGGCAGUUUUCAGACAAUGCAGGGAUAACACC	
	AGCAAUAUCAUUGGACCUGAUGAAUGAUGCUGAGCUGG	
	CCAGAGCUGUAUCAUACAUGCCAACAUCUGCAGGACAG	
	AUAAAACUAAUGUUAGAGAACCGUGCAAUGGUGAGGA	
	GAAAAGGAUUUGGAAUCUUGAUAGGGGUCUACGGAAG	
	CUCUGUGAUUUACAUGGUCCAGCUGCCGAUCUUUGGUG UCAUAAAUACACCUUGUUGGAUAAUCAAGGCAGCUCCC	
	UCUUGUUCAGAAAAAGAUGGAAAAUUAUGCUUGCCUCCU	
	AAGAGAGGAUCAAGGGUGGUAUUGUAAAAAUGCAGGA	
	UCCACUGUUUACUACCCAAAUGAAAAAGACUGCGAAAC	
	AAGAGGUGAUCAUGUUUUUUGUGACACAGCAGCAGGGA	
	UCAAUGUUGCUGAGCAAUCAAGAGAAUGCAACAUCAAC	
	AUAUCUACCACCAACUACCCAUGCAAAGUCAGCACAGG	
	AAGACACCCUAUCAGCAUGGUUGCACUAUCACCUCUCG	
	GUGCUUUGGUAGCUUGCUACAAAGGGGUUAGCUGCUCG	
	ACUGGCAGUAAUCAGGUUGGAAUAAUCAAACAACUACC	
	UAAAGGCUGCUCAUACAUAACUAACCAGGACGCAGACA	
	CUGUAACAAUUGACAACACUGUGUAUCAACUAAGCAAA	
	GUUGAGGGUGAACAGCAUGUAAUAAAAGGGAGACCAG UUUCAAGCAGUUUUGAUCCAAUCAGGUUUCCUGAGGAU	
	CAGUUCAAUGUUGCGCUUGAUCCAAUCAGGUUUCCUGAGGAU	
	UGAAAACAGUCAAGCACUAGUGGACCAGUCAAACAAA	
	UUCUGAACAGUGCAGAAAAAGGAAACACUGGU	
	UUCAUUAUUGUAAUAAUUUUGAUUGCUGUUCUUGGGU	
	UAACCAUGAUUUCAGUGAGCAUCAUCAUCAUAAUCAAA	
	AAAACAAGGAAGCCCACAGGGGCACCUCCGGAGCUGAA	
	UGGUGUUACCAACGGCGGUUUCAUACCGCAUAGUUAG	
b KJ723483.1 : 5586-7310	AUGGAGUUGCCAAUCCUCAAAACAAAUGCAAUUACCAC	60
luman	AAUCCUUGCUGCAGUCACACUCUGUUUCGCUUCCAGUC	
respiratory	AAAACAUCACUGAAGAAUUUUUAUCAAUCAACAUGCAGU	
syncytial virus strain RSVA/Homo	GCAGUUAGCAAAGGCUAUCUUAGUGCUCUAAGAACUGG UUGGUAUACUAGUGUUAUAACUAUAGAAUUAAGUAAU	
sapiens/USA/841-	AUCAAGGAAAAUAAGUGUAAACUAUAGAAUUAAGUAAU	
215A-01/1984,	UAAAAUUGAUAAAACAAGAAUUAGAUAAAUAUAAAAA	
complete genome	UGCUGUAACAGAAUUGCAGUUGCUCAUGCAAAGCACAC	
	CAGCAGCCAACAAUCGAGCCAGAAGAGAACUACCAAGG	
	UUUAUGAAUUAUACACUCAAUAAUACCAAAAAUACCAA	
	UGUAACAUUAAGCAAGAAAAGGAAAAGAAGAUUUCUU	
	GGCUUUUUGUUAGGUGUUGGAUCUGCAAUCGCCAGUGG	
	CALIFICATION AND CALCOLLACE CONTRACT ACCOUNTS	

CAUUGCUGUAUCUAAGGUCCUGCACCUAGAAGGGGAAG

TABLE 2-continued

SEQ ID NO:	Sequence	Description
	UGAACAAAAUCAAAAGUGCUCUACUAUCCACAAACAAG	
	GCUGUAGUCAGCUUAUCAAAUGGAGUUAGUGUCUUAAC	
	CAGCAAAGUGUUAGACCUCAAAAACUAUAUAGAUAAAC	
	AGUUGUUACCUAUUGUGAACAAGCAAAGCUGCAGCAUA	
	UCAAACAUUGAAACUGUGAUAGAGUUCCAACAAAAGAA	
	CAACAGACUACUAGAGAUUACCAGGGAAUUUAGUGUUA	
	AUGCAGGUGUAACUACACCUGUAAGCACUUAUAUGUUA	
	ACUAAUAGUGAAUUAUUAUCAUUAAUCAAUGAUAUGCC	
	UAUAACAAAUGAUCAGAAAAAGUUAAUGUCCAACAAUG	
	UUCAAAUAGUUAGACAGCAAAGUUACUCUAUCAUGUCC	
	AUAAUAAAGGAGGAAGUCUUAGCAUAUGUAGUACAAU	
	UACCACUAUAUGGUGUAAUAGAUACACCCUGUUGGAAA	
	CUGCACACAUCCCCUCUAUGUACAACCAACACAAAGGA	
	AGGGUCCAACAUCUGCUUAACAAGAACCGACAGAGGAU	
	GGUAUUGUGACAAUGCAGGAUCAGUAUCUUUCUUCCCA	
	CAAGCUGAAACAUGUAAAGUUCAAUCGAAUCGGGUAUU	
	UUGUGACACAAUGAACAGUUUAACAUUACCAAGUGAAG	
	UAAAUCUCUGCAACAUUGACAUAUUCAACCCCAAAUAU	
	GAUUGCAAAAUUAUGACUUCAAAAACAGAUGUAAGCAG	
	CUCCGUUAUCACAUCUCUAGGAGCCAUUGUGUCAUGCU	
	AUGGCAAAACUAAAUGUACAGCAUCCAAUAAAAAUCGU	
	GGGAUCAUAAAGACAUUUUCUAACGGGUGUGAUUAUG	
	UAUCAAAUAAGGGGGUGGAUACUGUGUCUGUAGGUAA	
	UACAUUAUAUUAUGUAAAUAAGCAAGAAGGCAAAAGU	
	CUCUAUGUAAAAGGUGAACCAAUAAUAAAUUUCUAUGA	
	CCCAUUAGUGUUCCCCUCUGAUGAAUUUGAUGCAUCAA	
	UAUCUCAAGUCAAUGAGAAGAUUAACCAGAGCCUAGCA	
	UUUAUUCGUAAAUCCGAUGAAUUAUUACAUAAUGUAA	
	AUGCUGGUAAAUCCACCACAAAUAUCAUGAUAACUACU	
	AUGEUGGUARAUCEACEACAMAUAUGUUAUGUUAUCAUUAA	
	UUGCAGUUGGACUGCUCCUAUACUGCAAGGCCAGAAGC	
	ACACCAGUCACACUAAGUAAGGAUCAACUGAGUGGUAU AAAUAAUAUUGCAUUUAGUAACUGA	

TABLE	3
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	hMPV Amino Acid Sequences	
Description	Sequence	SEQ II NO:
gi 122891979 gb EF051124.1	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGW	5
Human	YTNVFTLEVGDVENLTCSDGPSLIKTELDLTKSALRELKTVS	
metapneumovirus	ADQLAREEQIENPRQSRFVLGAIALGVAAAAAVTAGVAIAK	
isolate TN/92-4	TIRLESEVTAINNALKKTNEAVSTLGNGVRVLATAVRELKD	
fusion protein gene,	FVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS	
complete cds	DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRA	
	MVRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPS	
	CSEKKGNYACLLREDQGWYCQNAGSTVYYPNEKDCETRG	
	DHVFCDTAAGINVAEQSKECNINISTTNYPCKVSTGRHPISM	
	VALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD	
	ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQF	
	NVALDQVFENIENSQALVDQSNRILSSAEKGNTGFIIVIILIAV	
	LGSSMILVSIFIIIKKTKKPTGAPPELSGVTNNGFIPHN	
gb AY525843.1 : 3065-4684	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW	6
Human	YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS	
metapneumovirus	ADQLAREEQIENPRQSRFVLGAIALGVATAAAVTAGIAIAKT	
isolate NL/1/99,	IRLESEVNAIKGALKQTNEAVSTLGNGVRVLATAVRELKEF	
complete cds	VSKNLTSAINRNKCDIADLKMAVSFSQFNRRFLNVVRQFSD	
-	NAGI TPAI SLDLMTDAELARAVSYMPTSAGQI KLMLENRAM	
	VRRKGFGILIGVYGSSVIYMVQLPIFGVIDTPCWIIKAAPSCS	
	EKNGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH	
	VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA	
	LSPLGALVACYKGVSCSIGSNWVGIIKQLPKGCSYITNQDAD	
	TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNV	
	ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVVILVAVL	
	GLTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	
gb KJ627414.1 : 3015-4634	MSWKVMIIISLLITPQHGLKESYLEESCSTITEGYLSVLRTGW	7
Human	YTNVFTLEVGDVENLTCTDGPSLIKTELDLTKSALRELKTVS	
metapneumovirus	ADQLAREEQIENPROSRFVLGAIALGVATAAAVTAGIAIAKT	

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TABLE	3-continued

hMPV Amino Acid Sequences		
Description	Sequence	SEQ II NO:
strain hMPV/Homo	IRLESEVNAIKGALKTTNEAVSTLGNGVRVLATAVRELKEF	
sapiens/PER/CFI0497/	VSKNLTSAINKNKCDIADLKMAVSFSQFNRRFLNVVRQFSD	
2010/B,	NAGITPAISLDLMNDAELARAVSYMPTSAGQIKLMLENRAM	
complete cds	VRRKGFGILIGVYGSSVIYMVQLPIFGVINTPCWIIKAAPSCS	
	EKDGNYACLLREDQGWYCKNAGSTVYYPNEKDCETRGDH	
	VFCDTAAGINVAEQSRECNINISTTNYPCKVSTGRHPISMVA	
	LSPLGALVACYKGVSCSTGSNQVGIIKQLPKGCSYITNQDAD	
	TVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIRFPEDQFNV	
	ALDQVFESIENSQALVDQSNKILNSAEKGNTGFIIVIILIAVLG	
	LTMISVSIIIIIKKTRKPTGAPPELNGVTNGGFIPHS	
gb KJ723483.1 : 5586-7310	MELPILKTNAITTILAAVTLCFASSQNITEEFYQSTCSAVSKG	8
Human	YLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDK	
respiratory	YKNAVTELQLLMQSTPAANNRARRELPRFMNYTLNNTKNT	
syncytial virus	NVTLSKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGEVNKI	
strain RSVA/Homo	KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVN	
sapiens/USA/841-	KOSCSISNIETVIEFOOKNNRLLEITREFSVNAGVTTPVSTYM	
215A-01/1984.	LTNSELLSLINDMPITNDOKKLMSNNVOIVROOSYSIMSIIKE	
complete cds	EVLAYVVOLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTR	
	TDRGWYCDNAGSVSFFPOAETCKVOSNRVFCDTMNSLTLP	
	SEVNLCNIDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGK	
	TKCTASNKNRGIIKTFSNGCDYVSNKGVDTVSVGNTLYYVN	
	KQEGKSLYVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSL	
	AFIRKSDELLHNVNAGKSTTNIMITTIIIVIIVILLSLIAVGLLL	
	YCKARSTPVTLSKDQLSGINNIAFSN	

TABLE 4

hMPV NCBI Accession Numbers (Amino Acid Sequences)		
Virus	GenBank Accession	
F [Human metapneumovirus] [Human metapneumovirus]	AEK26895.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53565.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53566.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53569.1	
fusion protein [Human metapneumovirus]	AEZ52347.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53574.1	
fusion glycoprotein [Human metapneumovirus]	AHV79473.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53570.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53567.1	
fusion protein [Human metapneumovirus]	AAS22125.1	
fusion glycoprotein [Human metapneumovirus]	AHV79795.1	
fusion glycoprotein [Human metapneumovirus]	AHV79455.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53568.1	
fusion protein [Human metapneumovirus]	AAS22109.1	
fusion glycoprotein [Human metapneumovirus]	AGU68417.1	
fusion glycoprotein [Human metapneumovirus]	AGJ74228.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53575.1	
fusion protein [Human metapneumovirus]	AAU25820.1	
fusion glycoprotein [Human metapneumovirus]	AGU68377.1	
fusion glycoprotein [Human metapneumovirus]	AGU68371.1	
fusion glycoprotein [Human metapneumovirus]	AGJ74087.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53560.1	
fusion glycoprotein [Human metapneumovirus]	AHV79858.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53577.1	
fusion protein [Human metapneumovirus]	AAS22085.1	
fusion protein [Human metapneumovirus]	AEZ52348.1	
fusion glycoprotein [Human metapneumovirus]	AGJ74044.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53563.1	
fusion glycoprotein precursor [Human metapneumovirus]	YP_012608.1	
fusion glycoprotein [Human metapneumovirus]	AGJ74053.1	
fusion protein [Human metapneumovirus]	BAM37562.1	
fusion glycoprotein [Human metapneumovirus]	ACJ53561.1	
fusion glycoprotein [Human metapneumovirus]	AGU68387.1	
fusion [Human metapneumovirus]	AGL74060.1	
fusion glycoprotein precursor [Human metapneumovirus]	AAV88364.1	
fusion protein [Human metapneumovirus]	AAN52910.1	
fusion protein [Human metapneumovirus]	AAN52915.1	
fusion protein [Human metapneumovirus]	BAM37564.1	
fusion glycoprotein precursor [Human metapneumovirus]	BAH59618.1	
fusion protein [Human metapneumovirus]	AAQ90144.1	
italea protein filunian metaphetinovirub]	7 E 1 X 2 V 1 TT 1	

TABLE 4-continued

	d Sequences)
Virus	GenBank Accession
fusion glycoprotein [Human metapneumovirus]	AHV79446.1
fusion protein [Human metapneumovirus]	AEL87260.1
fusion glycoprotein [Human metapneumovirus]	AHV79867.1 ABO66027.2
fusion protein [Human metapneumovirus] fusion glycoprotein [Human metapneumovirus]	AGQ00027.2 ACJ53621.1
fusion protein [Human metapneumovirus]	AAN52911.1
fusion glycoprotein [Human metapneumovirus]	AHV79536.1
fusion glycoprotein [Human metapneumovirus]	AGU68411.1
fusion protein [Human metapneumovirus]	AEZ52346.1
fusion protein [Human metapneumovirus]	AAN52913.1
fusion protein [Human metapneumovirus]	AAN52908.1
fusion glycoprotein [Human metapneumovirus]	ACJ53553.1
fusion glycoprotein [Human metapneumovirus] fusion protein [Human metapneumovirus]	AIY25727.1 ABM67072.1
fusion protein [Human metapheumovirus]	AEZ52361.1
fusion protein [Human metapneumovirus]	AAS22093.1
fusion glycoprotein [Human metapneumovirus]	AGH27049.1
fusion protein [Human metapneumovirus]	AAK62968.2
fusion glycoprotein [Human metapneumovirus]	ACJ53556.1
fusion glycoprotein [Human metapneumovirus]	ACJ53620.1
fusion protein [Human metapneumovirus]	ABQ58820.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26886.1
fusion glycoprotein [Human metapneumovirus]	ACJ53619.1
fusion glycoprotein [Human metapneumovirus]	ACJ53555.1
fusion [Human metapneumovirus] fusion protein [Human metapneumovirus]	AGL74057.1 ABD27850.1
fusion protein [Human metapheumovirus]	AEZ52349.1
fusion protein [Human metapneumovirus]	ABD27848.1
fusion protein [Human metapneumovirus]	ABD27846.1
fusion protein [Human metapneumovirus]	ABQ66021.1
fusion protein [Human metapneumovirus]	AFM57710.1
fusion protein [Human metapneumovirus]	AFM57709.1
fusion protein [Human metapneumovirus]	ABH05968.1
fusion protein [Human metapneumovirus]	AEZ52350.1
fusion protein [Human metapneumovirus]	AFM57712.1
fusion protein [Human metapneumovirus] fusion protein [Human metapneumovirus]	AEZ52364.1 AAN52912.1
fusion protein [Human metapneumovirus]	AEZ52363.1
fusion [Human metapneumovirus]	AGL74059.1
fusion glycoprotein [Human metapneumovirus]	ACJ53583.1
fusion protein [Human metapneumovirus]	AEZ52356.1
fusion protein [Human metapneumovirus]	AEZ52353.1
fusion glycoprotein [Human metapneumovirus]	ACJ53581.1
fusion glycoprotein [Human metapneumovirus]	ACJ53578.1
fusion protein [Human metapneumovirus]	AAS22117.1 BAN75965.1
fusion protein [Human metapneumovirus] fusion protein [Human metapneumovirus]	AGF92105.1
fusion protein [Human metapneumovirus]	AAS22077.1
fusion protein [Human metapheumovirus]	AAN52909.1
fusion glycoprotein [Human metapneumovirus]	ACJ53586.1
fusion protein [Human metapneumovirus]	AAQ90145.1
fusion glycoprotein [Human metapneumovirus]	AGT75042.1
fusion [Human metapneumovirus]	AGL74058.1
fusion protein [Human metapneumovirus]	AEL87263.1
fusion glycoprotein [Human metapneumovirus]	AGH27057.1
fusion glycoprotein [Human metapneumovirus]	AHV79491.1
F [Human metapneumovirus] [Human metapneumovirus]	AEK26906.1
fusion glycoprotein [Human metapneumovirus] fusion protein [Human metapneumovirus]	ACJ53580.1 AEZ52354.1
fusion protein [Human metapheumovirus]	AAN52914.1
G [Human metapneumovirus] [Human metapneumovirus]	AEK26901.1
glycoprotein [Human metapneumovirus]	AFI56738.1
lycoprotein [Human metapneumovirus]	AFI56739.1
glycoprotein [Human metapneumovirus]	AFI56745.1
G protein [Human metapneumovirus]	AAQ62718.1
G protein [Human metapneumovirus]	AAQ62719.1
attachment glycoprotein G [Human metapneumovirus]	AGH27104.1
G protein [Human metapneumovirus]	AAQ62729.1
G protein [Human metapneumovirus]	AAQ62728.1
glycoprotein [Human metapneumovirus]	AFI56753.1
glycoprotein [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AFI56746.1 AFI56750.1
glycoprotein [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AFI56750.1 AFI56747.1
G protein [Human metapneumovirus]	AAQ62721.1
glycoprotein [Human metapneumovirus]	AAT46573.1
glycoprotein [Human metapneumovirus]	AFI56748.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid	GenBank Accession
glycoprotein [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AFI56736.1 AFI56749.1
attachment glycoprotein G [Human metapneumovirus]	AGH27131.1
attachment glycoprotein G [Human metapneumovirus]	AHV79558.1
glycoprotein [Human metapneumovirus]	AFI56740.1
glycoprotein [Human metapneumovirus]	AFI56741.1 AFI56744.1
glycoprotein [Human metapneumovirus] attachment glycoprotein G [Human metapneumovirus]	AHV79790.1
attachment glycoprotein G [Human metapneumovirus]	AGH27122.1
attachment glycoprotein G [Human metapneumovirus]	AHV79763.1
attachment glycoprotein G [Human metapneumovirus]	AGZ48849.1
glycoprotein [Human metapneumovirus] attachment glycoprotein G [Human metapneumovirus]	AFI56743.1 AHV79450.1
glycoprotein [Human metapneumovirus]	AFI56751.1
attachment glycoprotein [Human metapneumovirus]	AAS48482.1
attachment glycoprotein G [Human metapneumovirus]	AHV79889.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43050.1
glycoprotein [Human metapneumovirus]	AFI56754.1
attachment glycoprotein G [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AHV79601.1 AFI56752.1
attachment glycoprotein G [Human metapneumovirus]	AHV79871.1
G protein [Human metapneumovirus]	AEZ68099.1
attachment glycoprotein G [Human metapneumovirus]	AHV79817.1
attachment glycoprotein G [Human metapneumovirus]	AHV79943.1
attachment glycoprotein G [Human metapneumovirus]	BAN75968.1 AGW43045.1
attachment surface glycoprotein [Human metapneumovirus] attachment glycoprotein G [Human metapneumovirus]	AGW43045.1 AHV79628.1
attachment glycoprotein [Human metapneumovirus]	AFK49783.1
G protein [Human metapneumovirus]	AAQ62723.1
attachment glycoprotein [Human metapneumovirus]	ABD27839.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43046.1
G protein [Human metapneumovirus]	AAQ62717.1 AFI56742.1
glycoprotein [Human metapneumovirus] attachment protein [Human metapneumovirus]	ABQ44522.1
glycoprotein [Human metapneumovirus]	AFI56735.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43065.1
G protein [Human metapneumovirus]	AAQ62724.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43075.1
attachment surface glycoprotein [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AGW43062.1 AAT46579.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43064.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43054.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43042.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43078.1
attachment surface glycoprotein [Human metapneumovirus] G protein [Human metapneumovirus]	AGW43067.1 AAQ62722.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43063.1
glycoprotein [Human metapneumovirus]	AAT46571.1
glycoprotein [Human metapneumovirus]	AAT46578.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74232.1
glycoprotein [Human metapneumovirus]	AAT46580.1
glycoprotein [Human metapneumovirus] attachment surface glycoprotein [Human metapneumovirus]	AAT46574.1 AGW43061.1
attachment glycoprotein [Human metapneumovirus]	AFK49791.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43047.1
glycoprotein [Human metapneumovirus]	ABC26386.1
attachment glycoprotein [Human metapneumovirus]	AAS48466.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43048.1
attachment glycoprotein G [Human metapneumovirus] attachment surface glycoprotein [Human metapneumovirus]	AGH27140.1 AGW43049.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74082.1
attachment glycoprotein G [Human metapneumovirus]	AHV79442.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74091.1
attachment glycoprotein G [Human metapneumovirus]	AHV79477.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43056.1
attachment protein [Human metapneumovirus] attachment glycoprotein G [Human metapneumovirus]	ABQ44523.1 BAH59622.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43070.1
glycoprotein [Human metapneumovirus]	AAT46585.1
attachment glycoprotein G [Human metapneumovirus]	AGU68409.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74223.1
attachment glycoprotein [Human metapneumovirus]	AAS22129.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74048.1
G protein [Human metanasumovinue]	
G protein [Human metapneumovirus] glycoprotein [Human metapneumovirus]	AAQ62725.1 ABC26384.1

TABLE 4-continued

hMPV NCBI Accession Numbers (Amino Acid	Sequences)
Virus	GenBank Accession
attachment glycoprotein G [Human metapneumovirus]	YP_012612.1
attachment surface glycoprotein [Human metapneumovirus]	AGW43071.1
attachment glycoprotein G [Human metapneumovirus]	AGJ74162.1
attachment glycoprotein G [Human metapneumovirus]	AGH27095.1
attachment glycoprotein G [Human metapneumovirus]	AHV79531.1
G protein [Human metapneumovirus] attachment glycoprotein [Human metapneumovirus]	AAQ62726.1 AAS48465.1
attachment givcoprotein [runnan metaphetiniovirus]	AGW43058.1
P [Human metapneumovirus] [Human metapneumovirus]	AEK26894.1
phosphoprotein [Human metapneumovirus]	AHV79631.1
phosphoprotein [Human metapneumovirus]	AHV79901.1
phosphoprotein [Human metapneumovirus]	AHV79570.1
phosphoprotein [Human metapneumovirus]	AGJ74076.1
phosphoprotein [Human metapneumovirus]	AA\$22123.1
phosphoprotein [Human metapneumovirus]	ABB16895.1
phosphoprotein [Human metapneumovirus]	AHV79579.1
phosphoprotein [Human metapneumovirus]	AGJ74244.1
phosphoprotein [Human metapneumovirus]	AHV79856.1
phosphoprotein [Human metapneumovirus]	ACJ70113.1
phosphoprotein [Human metapneumovirus]	AGZ48843.1
phosphoprotein [Human metapneumovirus]	AHV79498.1
phosphoprotein [Human metapneumovirus]	AHV79480.1
phosphoprotein [Human metapneumovirus]	ABQ43382.1 AAS22107.1
phosphoprotein [Human metapneumovirus] phosphoprotein [Human metapneumovirus]	ABB16898.1
phosphoprotein [Human metapheumovirus]	AGH27134.1
phosphoprotein [Human metapheumovirus]	ABB16899.1
phosphoprotein [Human metapneumovirus]	AGH27098.1
phosphoprotein [Human metapneumovirus]	AAN52866.1
phosphoprotein [Human metapneumovirus]	AAS22083.1
phosphoprotein [Human metapneumovirus]	YP_012606.1
phosphoprotein [Human metapneumovirus]	AHV79973.1
phosphoprotein [Human metapneumovirus]	AHV79462.1
phosphoprotein [Human metapneumovirus]	AGJ74042.1
phosphoprotein [Human metapneumovirus]	AAV88362.1
P [Human metapneumovirus] [Human metapneumovirus]	AIL23591.1
phosphoprotein [Human metapneumovirus]	AHV79453.1
phosphoprotein [Human metapneumovirus]	AGJ74261.1
phosphoprotein [Human metapneumovirus]	AGH27116.1
phosphoprotein [Human metapneumovirus]	ABB16444.1
phosphoprotein [Human metapneumovirus]	ABB16445.1
phosphoprotein [Human metapneumovirus]	AHV79507.1
phosphoprotein [Human metapneumovirus]	BAH59616.1
phosphoprotein [Human metapneumovirus]	ABB16443.1 ABO43388.1
phosphoprotein [Human metapneumovirus] phosphoprotein [Human metapneumovirus]	ABQ43389.1 ABQ43389.1
phosphoprotein [Human metapheumovirus]	ABQ43395.1 ABQ43395.1
phosphoprotein [Human metapheunovirus]	ABO43385.1
phosphoprotein [Human metapneumovirus]	AAP84042.1
phosphoprotein [Human metaphounovirus]	AAN52868.1
phosphoprotein [Human metapneumovirus]	AAP84041.1
phosphoprotein [Human metapneumovirus]	AGH27080.1
phosphoprotein [Human metapneumovirus]	ABQ43387.1
phosphoprotein [Human metapneumovirus]	AAS22099.1
phosphoprotein [Human metapneumovirus]	ABB16896.1
phosphoprotein [Human metapneumovirus]	AGJ74094.1
phosphoprotein [Human metapneumovirus]	AEZ68089.1
phosphoprotein [Human metapneumovirus]	ABK97002.1
phosphoprotein [Human metapneumovirus]	AAP13486.1
phosphoprotein [Human metapneumovirus]	AHV79444.1
phosphoprotein [Human metapneumovirus]	AHV79865.1
phosphoprotein [Human metapneumovirus]	AGJ74226.1
phosphoprotein [Human metapneumovirus]	ABQ43383.1
phosphoprotein [Human metapneumovirus]	AAN52863.1
phosphoprotein [Human metapneumovirus]	AHV79775.1
phosphoprotein [Human metapneumovirus]	AEZ68094.1
phosphoprotein [Human metapneumovirus]	AHV79883.1
phosphoprotein [Human metapneumovirus]	AEZ68092.1
phosphoprotein [Human metapneumovirus]	ABQ43390.1
phosphoprotein [Human metapneumovirus]	ABQ43386.1
phosphoprotein [Human metapneumovirus]	ABQ43391.1 ACS16062.1
phosphoprotein [Human metapneumovirus]	
phosphoprotein [Human metapneumovirus]	AEZ68090.1
phosphoprotein [Human metapneumovirus]	AAK62967.1
phosphoprotein [Human metapneumovirus]	AEZ68093.1
phosphoprotein [Human metapneumovirus]	AEZ68088.1

TABLE 4-continued

Virus	GenBank Accession
phosphoprotein [Human metapneumovirus]	ABQ43392.1
hosphoprotein [Human metapneumovirus]	ABQ43393.1
hosphoprotein [Human metapneumovirus]	ABQ43384.1
hosphoprotein [Human metapneumovirus] hosphoprotein [Human metapneumovirus]	ABQ43394.1 ABK96999.1
hosphoprotein [Human metapneumovirus]	AHV79489.1
hosphoprotein [Human metapneumovirus]	AGJ74235.1
hosphoprotein [Human metapneumovirus]	AAS22075.1
hosphoprotein [Human metapneumovirus]	AAS22115.1
hosphoprotein [Human metapneumovirus]	AII17601.1
hosphoprotein [Human metapneumovirus]	ABK97000.1
hosphoprotein [Human metapneumovirus]	AHV79561.1
hosphoprotein [Human metapneumovirus] hosphoprotein [Human metapneumovirus]	AGT75040.1 AAN52864.1
hosphoprotein [Human metapneumovirus]	ABK97001.1
phosphoprotein [Human metapneumovirus]	AGT74979.1
bhosphoprotein [Human metapneumovirus]	AHV79955.1
hosphoprotein [Human metapneumovirus]	AGH27055.1
hosphoprotein [Human metapneumovirus]	AAV88361.1
hosphoprotein [Human metapneumovirus]	ABQ43397.1
hosphoprotein [Human metapneumovirus]	AGJ74173.1
[Human metapneumovirus] [Human metapneumovirus]	AEK26904.1
hosphoprotein [Human metapneumovirus]	ACJ70104.1
phosphoprotein [Human metapneumovirus] phosphoprotein [Human metapneumovirus]	ABK97003.1 AGT74955.1
phosphoprotein [Human metapneumovirus]	AG174955.1 AAN52856.1
phosphoprotein [Human metapheumovirus]	AAN52862.1
bhosphoprotein [Human metapneumovirus]	AGJ74138.1
bhosphoprotein [Human metapneumovirus]	AHV79613.1
hosphoprotein [Human metapneumovirus]	AGJ74060.1
hosphoprotein [Human metapneumovirus]	AAQ67684.1
hosphoprotein [Human metapneumovirus]	AEA02278.1
I [Human metapneumovirus] [Human metapneumovirus]	AEK26899.1
nucleoprotein [Human metapneumovirus]	ACS16061.1 AAS88425.1
nucleoprotein [Human metapneumovirus] nucleoprotein [Human metapneumovirus]	YP_012605.1
nucleoprotein [Human metapheumovirus]	AHV79882.1
nucleoprotein [Human metapheumovirus]	AHV79774.1
nucleocapsid protein [Human metapneumovirus]	AAN52886.1
ucleoprotein [Human metapneumovirus]	AAS22082.1
ucleoprotein [Human metapneumovirus]	AHV79864.1
ucleoprotein [Human metapneumovirus]	AHV79828.1
ucleoprotein [Human metapneumovirus]	AGJ74084.1
nucleocapsid protein [Human metapneumovirus]	AAN52888.1
J [Human metapneumovirus] [Human metapneumovirus] ucleoprotein [Human metapneumovirus]	AIL23590.1 AAK62966.1
ucleoprotein [Human metapneumovirus]	AHV79972.1
ucleoprotein [Human metapneumovirus]	AHV79470.1
ucleoprotein [Human metapheumovirus]	AHV79452.1
ucleoprotein [Human metapneumovirus]	AGJ74243.1
ucleoprotein [Human metapneumovirus]	AHV79533.1
ucleoprotein [Human metapneumovirus]	AGJ74181.1
ucleoprotein [Human metapneumovirus]	AHV79497.1
ucleoprotein [Human metapneumovirus]	AHV79702.1
ucleoprotein [Human metapneumovirus]	AHV79648.1
ucleoprotein [Human metapneumovirus]	AHV79435.1
utative nucleoprotein [Human metapneumovirus] nucleocapsid protein [Human metapneumovirus]	AGJ74260.1 AAN52887.1
ucleoprotein [Human metapneumovirus]	AGU68386.1
nucleocapsid protein [Human metapheumovirus]	AAN52899.1
ucleoprotein [Human metapneumovirus]	AAR17673.1
ucleocapsid protein [Human metapneumovirus]	AAN52898.1
ucleoprotein [Human metapneumovirus]	AEA02277.1
ucleoprotein [Human metapneumovirus]	AHV79612.1
ucleoprotein [Human metapneumovirus]	AGU68416.1
ucleoprotein [Human metapneumovirus]	AGU68408.1
ucleoprotein [Human metapneumovirus]	AGU68370.1
nucleoprotein [Human metapneumovirus]	AAQ67683.1
ucleoprotein [Human metapneumovirus]	AGJ74137.1
uucleoprotein [Human metapneumovirus] uucleocapsid protein [Human metapneumovirus]	AGU68344.1 ABK96997.1
ucleoprotein [Human metapneumovirus]	AGU68413.1
ucleocapsid protein [Human metapneumovirus]	AAN52891.1
ucleoprotein [Human metapneumovirus]	AGU68360.1
nucleoprotein [Human metapneumovirus]	AGU68353.1
ucleocapsid protein [Human metapneumovirus]	ABK96996.1

TABLE 4-continued

Virus	GenBank Accession
nucleoprotein [Human metapneumovirus]	AAR17666.1
N [Human metapneumovirus] [Human metapneumovirus]	AEK26903.1
nucleoprotein [Human metapneumovirus]	AGT75039.1
nucleoprotein [Human metapneumovirus]	AGU68410.1
nucleoprotein [Human metapneumovirus]	AAS22074.1
nucleoprotein [Human metapneumovirus]	AHV79560.1
nucleoprotein [Human metapneumovirus]	AGT74978.1
nucleoprotein [Human metapneumovirus]	AGJ74128.1
nucleoprotein [Human metapneumovirus]	AAR17663.1
nucleoprotein [Human metapneumovirus]	AAR17662.1
nucleoprotein [Human metapneumovirus]	AAR17664.1
nucleoprotein [Human metapneumovirus]	AAR17657.1
nucleoprotein [Human metapneumovirus]	AAR17659.1
nucleoprotein [Human metapneumovirus]	AAR17661.1
nucleoprotein [Human metapneumovirus]	AGU68352.1
nucleoprotein [Human metapneumovirus]	AGU68373.1
nucleoprotein [Human metapneumovirus]	AGU68376.1
nucleoprotein [Human metapneumovirus]	AGU68342.1
nucleoprotein [Human metapneumovirus]	AGU68365.1
nucleoprotein [Human metapneumovirus]	AGU68363.1
nucleoprotein [Human metapneumovirus]	AGU68398.1
nucleoprotein [Human metapneumovirus]	AGU68348.1
nucleoprotein [Human metapneumovirus]	AGU68354.1
nucleoprotein [Human metapneumovirus]	AGU68391.1
nucleoprotein [Human metapneumovirus]	AGU68389.1 AGU68399.1
nucleoprotein [Human metapneumovirus] nucleoprotein [Human metapneumovirus]	AGU68337.1
nucleoprotein [Human metapheumovirus]	AGC08557.1 AAR17660.1
nucleoprotein [Human metapneumovirus]	AAR17667.1
nucleoprotein [Human metapneumovirus]	AGU68402.1
nucleoprotein [Avian metapneumovirus type C]	CDN30025.1
nucleoprotein [Avian metapneumovirus]	AGZ87947.1
Nucleoprotein [Avian metapneumovirus type C]	CAL25113.1
nucleocapsid protein [Avian metapneumovirus]	ABO42286.1
nucleocapsid protein [Avian metapneumovirus]	AAK38430.1
nucleocapsid protein [Avian metapneumovirus]	AAK54155.1
nucleocapsid protein [Avian metapneumovirus]	AAK38426.1
nucleocapsid protein [Avian metapneumovirus]	AAK38425.1
nucleocapsid protein [Avian metapneumovirus]	AAK38424.1
nucleocapsid protein [Avian metapneumovirus]	AAF05909.1
nucleocapsid protein [Avian metapneumovirus]	AAK38435.1
nucleocapsid protein [Avian metapneumovirus]	AAK38428.1
nucleoprotein [Human metapneumovirus]	AAR17669.1
nucleocapsid protein [Avian metapneumovirus]	AAK38429.1
nucleocapsid protein [Avian metapneumovirus]	AAK38427.1
nucleocapsid protein [Avian metapneumovirus]	AAK38423.1
nucleocapsid protein [Avian metapneumovirus]	AAK38434.1
nucleoprotein [Human metapneumovirus]	AGU68338.1
nucleoprotein [Avian metapneumovirus]	YP_443837.1
nucleoprotein [Human metapneumovirus]	AGU68384.1
nucleocapsid protein [Avian metapneumovirus]	AAK38431.1
nucleoprotein [Human metapneumovirus]	AGU68405.1
nucleoprotein [Human metapneumovirus]	AGU68382.1
nucleoprotein [Human metapneumovirus]	AGU68395.1
nucleocapsid [Human metapneumovirus]	AAL35389.3
nucleoprotein [Human metapneumovirus]	AEZ68064.1

TABLE 5

PI	V3 Nucleic Acid Sequences	
Description	Sequence	SEQ ID NO:
>gb KJ672601.1 : 4990-6609 Human parainfluenza virus 3 strain HPIV3/Homo sapiens/PER/FLA4815/ 2008[fusion glycoprotein F0]	ATGCCAATTTCAATACTGTTAATTATTACAACCATGATC ATGCCATCACACTGCCAAATAGACATCACAAAACTACA GCATGTAGGTGTATTGGTCAACAGTCCCAAAGGGATGA AGATATCACAAAACTTCGAAACAAGATATCTAATCCTGA GTCTCATACCAAAAATAGAAGATTCTAACTCTTGTGGTG ACCAACAGATCAAGCAATACAAGAGGTTATTGGATGAA CTGATCATCCTTTATATGATGGACTAAGATTACAGAAA GATGGATAGTGACTAACTAAGAATCCAATGAAACAC TGATCCCAGAACAGAA	9

TABLE 5-continued

	3 Nucleic Acid Sequences	anc
Description	Sequence	SEQ ID NO:
Description	AACTATTGCTCTAGGAGTAGCAACCTCAGCACAAATTAC AGCAGCAGTTGCTCTGGTTGAAGCCAAGCAGCAGGACAGA CAGACATTGAAAAACTCAGGAAGCAAGCAGCAGGACAATCAGGGACACA AATAAAGCAGTGCAGT	NU:
gi 612507167 gb AHX22430.1 hemagglutinin- neuraminidase [Human parainfluenza virus 3]	CAAAATGATAAGCCGTATGTATTAACAAACAAG ATGGAATACTGGAAGCACACCAACCACGGAAAGGATGC TGGTAATGAGCTGGAGAGCACCCACCACGGAAAGGATGC ACAAGCTCACCAACAAGATAACATATATATTGTGGACG ATAACCCTGGTGTTATTATCAATAGTCTTCATCATAGTG CTAACTAATTCCATCAAAAGTGAAAAGGCCGCGGAATC ATGCTACAAGACCAAAATGAAAAGGCCTCTTACCAATGC AGAAAAGATCCAAGTGGCATCGGATAATACTAATGATC TAATACAGTCAGGAGTGAATACAAGGCTTCTTACAATTC AGAATACGGTCATGGCATCGGATAATACTATGATGAT CAATTACAGTCAGGAGTGTATAAATGAATCAATGGACA AACAATATCGGATCTTAGGAAATCAATTGATGAAATTA CAATTAGAAATGGATGTTAGGAATTAATGATGA ATAACACATGATGTGGGTATAAAAACCTTTAAATCCAGAT GATTTCTGGAGATGGCGCTCTGGTCTTCCACCTTGAGA ATAACACATGATGTGGGGTATAAAACCTTTAATCCAGAT GATTTCTGGAGATGCGCACCGGCATGGCAAGAA ATAACCCATGATGTGGGGTATAAAACCTTTAATCCAGAT GATTTCTGGAGATGCGCGCTCTGGTCTCCACCTTGATG AAAACTCCAAAATAAGAATAATGACCGGGACAAGGAA ATCATGCCAACAACGACGTTGTGATGGGGCATAGGAA ATCATATCAAGTATTACCGAGGTTGCCAGGACTTAAGGAA ATCATATCAAGTATTACGGAGTATAAGGGATAATAGGGAA ATCATATCAAGTATTACGGAGTATATAGGGATAATAGGGA ATCATATCAAGTATTACGGAGTATATAGGAGTAATAAGG CCCAAAGTTGGTACCTGAGTTTAAGGACTAAGTCTCCA CCCAAAAGTTGATGACTGGATATTAGCACCGTCTCCA CCCAAAGTTGGTACCTGAGTTTAAGGACTAATACGGACTATGC GCCAAAGTTGATGACAGAGACTAGATAATGCCACAGG GCTCAAACCAACAGAACTTGGATATAGCACCACGG GCTCAAACCAACAGGACTTGAATATGCCACACGA GGGTAAGGAGGATGGTCACGAAAAATAAATTATAA GTTTGGACCACCAACAGGGATTATACCACCGGGACAAGAA GAGACTGTAATCAAGACACCGAAAATAAATTGCC CCCAAAGGGTCTGGAAACACACGAA GAGACTGAACCAACTGGGTCCTGAGGAAAACACAGA GCTGAACCAACTGGGTCCTGAAGGAAAAACACAGA GCTGAACCAAACTGGGACTCAATAAATGGGAATAA CATTACTGAACCAACTGGGGTCCAGAAGAACCACAG GCTGAACCAAACTGGGATCACACAAAAAGGAATAA CTTCTACTAGGACACAAGAGACTCACAAAAATGGAAAT CTTCTACTAGGACACAGAGATTAACCAATGGAGATAA CATAGGACAAAAATTACTGGGGCTCAGAAGAAAACAAGA GCATAGGACACAAAATTACCGGAGTCACAAAAAAGGACAT GCATAAGGACAACAAGACTCACACAAGAAAAAAGGACT CAAGGGAAACCAACAGGACTACCACAAAAAAAGGACT GCATAAGGGACATCCACACAGGAAACAAAAAAGGACT GCATAAGGGACATCCACACAGGAAAAAAAGGACT GCATAAGGGACATCCACACAGGAACAAAAACGACT GCATAGGGACATCCACACACGAAACCACGAAA GGGTAAACGACGGCGCATAACCACACAAAAAACCACTCACCACAAAAAACAACCACT	10

TABLE 5-continued

Description	Sequence	SEQ ID NO:
	GCTGGGTACACAACAACAAGCTGCATTACACACTATAA CAAAGGGTATTGTTTTCATATAGTAGAAATAAATCATAA AAGCTTAAACACATTTCAACCCATGTTGTTCAAAACAGA GATTCCAAAAAGCTGCAGT	
HPIV3_HN_Codon Optimized	ATGGAATACTGGAAGCACCACCACCACGGCAAGGACGC CGGCAACGAGCTGGAAACCAGCACACCACGACGACGAC ACAAGCTGACCAACAAGAGCACAACGCACACACGACG CTGACCCATAGCATCAACAACGAGTTCATCATCGTG CTGACCAATAGCATCAAGGCGACAACACCAACGAC CCGACGAGACCCAGGCGTGAACACCAACGACCACCAACGAC CTGATCCAGGACGTCACGACACCACGACCACCACCAC CAGAGACACCAGGGCGTGAACACCAGGACGTCATCAGCCCCGCAGACACCACGACACCACGAC CAGCATCAGCGACCTGCGGAACTACATCCACCACCACCAC CAGCACTCCGGAACGACCACGAACGTCCAGGCCTGACCAC CACCATCCGGAACGACCACGGAAGTCCATCAGCCCCCGA GAATCAACCCACGACGTGGGCATCAAGCCCCTGAACCCC GACGATTTCTGGCGGGTGTACAAGCGGCCTGGCCCGG ACTGCTGGCCATGCCTAACCACGATGCTGGCCCGG GACCCCCCAGGCTCGCTAACCACGGACGTGATCATCAG GCACGCCCCGGCGTCACCACGGTGATCCACGCCTG CACCAGCAACCTGATCAACCGCCGGGCATCATCACC GTGAACTCCGGCCTGGTGCCCGACCTGAACCATCGGCCTG CAGCCACCTTCAACGATCGGCCTGAACCATCGGCC CAGCCACCCTCGCGTGACCAACGAACGAAGAAGACCG CAGCCCCCCCAAGGTGGACGACGACGACCACGGACT CAGCCACCCTCGCGCGCCCGACCTGAACCACGACGGC CAGCCCCCCCAAGGTGGACGACGACGACCACGGCATCG CAGCCCCCCCAAGGTGGACGACGACGACCACGGCG CAGCCCCCCCAAGGTGGCGCGACCACGGCGTGACCAGCGCG CAGCCCCCCCAAGGTGGACGACGACGACCACGGCCTG CAGCCCCCCCAAGGTGGCCGACCACGGCGTCAAGAACAA CAACATCAGCTTCGACGACCACCCGGCTGCAAGAACAA CAACATCAGCTTCGACGACCCCCGGCTGCAAGAACAA CAACATCAGCTTCGACCACCCGGCTGCAAGAACCACCCC TTCTGTGGGCCCGGCGCAGAACCACCCCCGGTCACGACAACAA CAACATCAGCATCGGCCGCGCACAACCCCCCGGCTGGAACATC CTCCCGGGCATCGGCCACACCCCGGCTGCAAGAACCACC CCCAGAGAGCTGCAACACCCCCCGGCTGCAAGAACACC CCCAGAGAGCTGCAACACCCCCCGGCTGCAAGAACCACC TTCTGGGGCCCGGCCAGAACCCCCCAGCCCTGG GACAACTCCGCCAGAACGCCCACACGCCCTGG GACAACTCCGGCCAGAACGCCCCCCGGGCACACCCCCTGG GACAACTCCGCCCGGCCTACACCGGCACACCCCCGGGAACAAC CCCGGGCCGCGCACAACGCCCACACGCCCCCGGACACACACACACACACACACCCCCC	11
HPIV3_F_Codon Optimized	ATGCCCATCAGCATCCTGCTGATCATCACCACAATGATC ATGGCCAGCCACTGCCAGATCGACATCACCAAGCTGCA GCACGTGGGCGTGCTCGTGAACAGCCCCAAGGGCATGA AGATCAGCCAGAACTTCGAGACAGCCACCAGCTGCTGGACAG GCCTGATCCCCAAGATCGAGGACAGCAACAGCTGCGGC GACCAGCAGATCAAGCAGTACAAGCGGCTGCTGGACAG ACTGATCATCCCCCTGTACGACGGCAGCAGGAACAA CCGACCCCCGGACCGACGAGAGACAACGAGGACAG GCACAATCGCCCTGGGAGTGGCACAAGCGACGAGAACA CCGACCCCCGGACCGAGAGAGTCGTCGGGCGCGAGATT ACAGCGCCTGTGGCCCTGGTGGAAGCAACGAGGCCAG AATCGGCCTGTGGCCTGGTGGAAGCCAAGCGAGGCCAG AAGCGTCATCGAGAAGCGAGGCCACAAGCGAGGCCAG AAGCGGCCTGTGGCCCTGGTGGAAGCCAAGCGAGGCCAG AAGCGACATCGAGAAGCCGAGGCCAGGCC	12

TABLE 5-continued

	3 Nucleic Acid Sequences	
Description	Sequence	SEQ ID NO:
	TGGTACATCCCTCTGCCCAGCCACATTATGACCAAGGGC GCCTTTCTGGGCGGAGCCGACGTGAAAGAGTGCATCGA GGCCTTCAGCAGCTACATCTGCCCCAGCGACCCTGGCT CGTGCTGAACCACGGATGGAAAGCTGCCTGGGCGCCA ACATCAGCCAGTGCCCCAGAACCACCGTGACCGCGCA ATCGTGCCCAGATACGCCTCCGGAATGGCGGCGTGGT GCCAACTGCATCACCACCACCGTGTACCTGCAACGGCATC GGCAACCGGATCAACCACCACCGTGTACCTGCGACGCGCAC ACGGCATGCTTCAATACCACCAACAGAGGGCATCCA ACGGCATGCTTCAATACCACCAACAGAGGGCACCCTG GCCTTCTACACCCCCGACGACTATCACCCTGAACAACTCC GTGGCTCTGGACCCCCCGACGAGGCACCCTG GCCTTCTGGCCCCGACGACATCTCCATCGAGCTGAAC AAGGCCAAGAGCGACCTGGAAGAGCCCCAGGGCATC GGCACCGGAGCAACCAGAAGAGTGGAACCCATGGGCATCA AAGGCCAAGAGCGACCACCACCATCATCGGCAGCT GGCACCAGAGCAGCACCACCATCATCGGCAGCT GGCACCAGAGCAGCACCACCATCATCGGCAGCT GGCACCAGAGCAGCACCACCATCATCGTGATCATCAC TATCGCCATTAAGTACTACCGGATCCAGAAACGGAACC CAGGTGGCCCAGAATGACAAGCCCACACACTGCGAACGAA	
	PIV3 mRNA Sequences	
>gb KJ672601.1 : 4990-6609 Human parainfluenza virus 3 strain HPIV3/Homo sapiens/PER/FL44815/ 2008[fusion glycoprotein F0]	AUGCCAAUUUCAAUACUGUUAAUUAUUACAACCAUGA UCAUGCAUUCAAUACUGCCAAUAGACAUCACAAACU ACAGCAUGUAGGUGUAUUGUCAACAGUCCCAAAGGG AUGAAGAUAUCACAAAACUUCGAAACAAGUUUCUAACUC UUGUGUGACCAACAGAUCAAGAAUAUCAAGGUUA UUGGUGUGACCAACAGAUCAAGCAAUACAAGAGUUCUAACUC UUGUGUGACCAACAGAUCAUCAAGCAAUACAAGAGUUCUUA GAUUACAGAAGGAUGUGAUUAUUCAUACUACUAGUAUCCAAGAAUC CAAUGAAAACACUGAUCCCUUUUAUAUGAUGACUAACAAG GAUUACAGAAGGAUGUGAUUAUUCUUCUAGGAGUAGCAA CCUCAGCACAAUUACAGCAGCAGUUGCUUGGUUGA AGCCAACCAGCAAGAUCCAGCAGUUGCUUGGUUGA AGCCAACCAGGCAAGAUCCAACAUUGAAAAACUCAAG GAAGCAAUCAGGGACACAUUGAUAUGCUCUGGUUGA AUCAGUCCAGGAUUAUGCUCACAAGAAUUCCAAG GAAGCAAUCAGGGACACAAUAAAAGCAGUGCCA UUCAGAGCUCUGUAGGAUAUUGAUAGUACCAAUUAA AUCAGUCCAGGAUUAUGUUCAACAAAGAAAUCGUGCCA UCCAGACUCGGAGACUAGGUUGUGAAGCAACAUUAA AUCAGUCCAGGAUUAUGUUGAACAAAGAAAUCGUGCCA UCCAAUUCGGGACUAGGUUGUGAAGCAAGCAGCAGGACAUUC AGUUGCGAGACUAGGUUGUGAAGCAAGCACAUCAA GAAAAGGAAUAAAUUUCACAGGUAUUACUCAGAAUU AACAAAUAUAUUUGGUGAUAACAAGGUACUUACUACAAC AGUUGCACAAAUAUCACAGGAAUUACUCAGAAUU AACAAAUUAAUUUGGUGAUACAAGGUACUUCAAACAUCAAC AGUUGACAAAUAAUCACAGGAAUUUAACACACUCCAAC AGUUGACAAAUAAUCACAGAAAUAUCUACAACAUCAAC AGUUGACAAAUAAUCACAGAAUAUCUACUACUACAAC AGUUGACAAAUAACCUCCAAGUCCCUUU AUUGACCAACUGCUGAACACUCAAAUCUACAAGAA GAAUCAAUAAAGGUGAGAGUUCAAAUCUACAAGGAAUGGU AUUCCUCUUCCCAGCCUUCAAAUCUACAAGAAGAG AUUCCAUAUCAAGAAUUAUCCAAAAUCUACAAGAAGAA GCAUUCAGACUGCUGAACACUCAAAUUCUACAAGGA AUUCCUAGUUCUAGGAGACGUUCUAUCAAG AAACAUAUCCCAAUGUCCAAGUACUACAAGGAAUGGU AUAUCCCAAUUGCCAAGUACAUCUAAAGGAAUGGU AUAUCCCAAUUGCAAUGUACAACAUCUACAAGGAAUGGU AUAUCCCAAUUGCAAUGUACAACACUCAAUGAACACACAAUCAA GAAUUCUAAACCAUGAAUGAACCAACACACACUCAAGGA AACAUAUUCCUAGGUAAUGAAUCAACCAACACACAUCAA GAGUUCCAAAUUGUUCAACAACCAACACUAGGA AUCAAAAUUGUAUAACAACUACAACACUACAAGAA GAGUUCCAAAUUGUUGAAUCAACCAACACACACACACACA	61
gi 612507167 gb AHX22430.1 hemagglutinin- neuraminidase Human parainfluenza virus 3]	AUGGAAUACUGGAAGCACACCAACCACGGAAAGGAUG CUGGUAAUGAGCUGGAGACAUCCACAGCCACUCAUGG CAACAAGCUCACCAACAAGAUAACAUAUAUAUUGUGG ACGAUAACCCUGGUGUUAUUAUCAAUAGUCUUCAUCA UAGUGCUAACUAAUUCCAUCAAAAGUGAAAAGGCCCG GAAGUCAUUGCUACAAGACAUAAAUAAUGAGUUUAUG GAAGUUACAGAAAAGAUCCAAGUGGCAUCGGAUAAUA CUAAUGAUCUAAUACAGUCAGGAGUGAAUACAAGGCU	62

TABLE 5-continued

		SEQ II
escription	Sequence	NO:
	UCUUACAAUUCAGAGUCAUGUCCAGAAUUAUAUACCA	
	AUAUCAUUGACACAACAAAUAUCGGAUCUUAGGAAAU	
	UCAUUAGUGAAAUUACAAUUAGAAAUGAUAAUCAAGA AGUGCCACCACAAAGAAUAACACAUGAUGUGGGUAUA	
	AAACCUUUAAAUCCAGAUGAUUUCUGGAGAUGCACGU	
	CUGGUCUUCCAUCUUUGAUGAAAACUCCAAAAAUAAG	
	AUUAAUGCCGGGACCAGGAUUAUUAGCUAUGCCAACG	
	ACUGUUGAUGGCUGUGUCAGAACCCCGUCCUUAGUGA	
	UAAAUGAUCUGAUUUAUGCUUACACCUCAAAUCUAAU UACUCGAGGUUGCCAGGAUAUAGGGAAAUCAUAUCAA	
	GUAUUACAGAUAGGGAUAAUAACUGUAAACUCAGACU	
	UGGUACCUGACUUAAAUCCUAGGAUCUCUCAUACCUU	
	CAACAUAAAUGACAAUAGAAAGUCAUGUUCUCUAGCA	
	CUCCUAAAUACAGAUGUAUAUCAACUGUGUUCAACCC	
	CAAAAGUUGAUGAAAGAUCAGAUUAUGCAUCAUCAGG	
	CAUAGAAGAUAUUGUACUUGAUAUUGUCAAUUAUGAU GGCUCAAUCUCGACAACAAGAUUUAAGAAUAAUAAUA	
	UAAGUUUUGAUCAACCAUAUGCGGCAUUAUACCCAUC	
	UGUUGGACCAGGGAUAUACUACAAAGGCAAAAUAAUA	
	UUUCUCGGGUAUGGAGGUCUUGAACAUCCAAUAAAUG	
	AGAAUGCAAUCUGCAACACAACUGGGUGUCCUGGGAA	
	AACACAGAGAGACUGUAAUCAAGCAUCUCAUAGUCCA	
	UGGUUUUCAGAUAGAAGGAUGGUCAACUCUAUAAUUG UUGUUGACAAGGGCUUGAACUCAGUUCCAAAAUUGAA	
	GGUAUGGACGAUAUCUAUGAGACAAAAUUACUGGGGG	
	UCAGAAGGAAGAUUACUUCUACUAGGUAACAAGAUCU	
	ACAUAUACACAAGAUCUACAAGUUGGCACAGCAAGUU	
	ACAAUUAGGAAUAAUUGACAUUACUGACUACAGUGAU	
	AUAAGGAUAAAAUGGACAUGGCAUAAUGUGCUAUCAA	
	GACCAGGAAACAAUGAAUGUCCAUGGGGACAUUCAUG UCCGGAUGGAUGUAUAACGGGAGUAUAUACCGAUGCA	
	UAUCCACUCAAUCCCACAGGAAGCAUUGUAUCAUCUG	
	UCAUAUUGGACUCACAAAAAUCGAGAGUCAACCCAGU	
	CAUAACUUACUCAACAGCAACCGAAAGGGUAAACGAG	
	CUGGCUAUCCGAAACAAAACACUCUCAGCUGGGUACA	
	CAACAACAAGCUGCAUUACACACUAUAACAAAGGGUA	
	UUGUUUUCAUAUAGUAGAAAUAAAUCAUAAAAGCUUA	
	AACACAUUUCAACCCAUGUUGUUCAAAACAGAGAUUC CAAAAAGCUGCAGU	
PIV3 HN Codon	AUGGAAUACUGGAAGCACACCAACCACGGCAAGGACG	63
timized	CCGGCAACGAGCUGGAAACCAGCACAGCCACACGCGC	0.5
-	AACAAGCUGACCAACAAGAUCACCUACAUCCUGUGGA	
	CCAUCACCCUGGUGCUGCUGAGCAUCGUGUUCAUCAUC	
	GUGCUGACCAAUAGCAUCAAGAGCGAGAAGGCCAGAG	
	AGAGCCUGCUGCAGGACAUCAACAACGAGUUCAUGGA	
	AGUGACCGAGAAGAUCCAGGUGGCCAGCGACAACACC AACGACCUGAUCCAGAGCGGCGUGAACACCCGGCUGCU	
	GACCAUCCAGAGCCACGUGCAGAACUACAUCCCCAUCA	
	GCCUGACCCAGCAGAUCAGCGACCUGCGGAAGUUCAUC	
	AGCGAGAUCACCAUCCGGAACGACAACCAGGAAGUGC	
	CCCCCCAGAGAAUCACCCACGACGUGGGCAUCAAGCCC	
	CUGAACCCCGACGAUUUCUGGCGGUGUACAAGCGGCC	
	UGCCCAGCCUGAUGAAGACCCCCCAAGAUCCGGCUGAUG CCUGGCCCUGGACUGCCGCCAUGCCUACCACAGUGGA	
	CCUGGCCCUGGACUGCUGGCCAUGCCUACCACAGUGGA UGGCUGUGUGCGGACCCCCAGCCUCGUGAUCAACGAUC	
	UGAUCUACGCCUACACCAGCAUCUGAUCAACCGGGGC	
	UGCCAGGAUAUCGGCAAGAGCUACCAGGUGCUGCAGA	
	UCGGCAUCAUCACCGUGAACUCCGACCUGGUGCCCGAC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAAGAGCUGCAGCCUGGCUCUGCUGAACACCC GACGUGUACCAGCUGUGCAGCACCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCAGCAUCAGC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGCUCCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGCGCAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUACGCCGCCUGUACCCUUCUGUGGGCCCUGGCA	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACACCC GACGUGUACCAGCUGUGCAGCACCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCGAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUACGCCGCCUGUAACUACCUUCGUGGGCCCUGGCA UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG CGGCCUGGAACACCACAUCAACGACAUCGAC	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGCUUCCUGCUGAACACC GACGUGUACCAGCUGUGCAGCACCCCCCAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGCGCGCAUCGAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUGAGCGCCCUGGACCUUCUUCCUGGGCCCCUGGCA UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG CGGCCUGGAACACCCCAUCAACGAGAACGCCAUCUGCA ACACCACCGGCUGCCUGGCAAGAACCGCAGG	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACAUC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCGAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUACGCCGCCUUGUACCUUCUGUGGGCCCUGGCA UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG CGGCCUGGAACACCCAUCAACGAGAACGCCAUCUGCA ACACCACCGGCUGCCCUGGCAAGAGACGCCAUCUGC AAUCAGGCCAGCCACGCCCUGGUCAGCGACCGCAG AAUCAGGCCAGCCACGCCCUGGUCAGCGACCGCAG AAUCAGCCACGCCUGAUCAUCGUGGUCGACAAGGGCCUG	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACAUC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUACGCCGCCUUGUACCUUUCUUGUGGGCCCUGGCA UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG CGGCCUGGAACACCCCUUCAACGAGAACGCCAUCUGCA ACACCACCGGCUGCCCUGGCAAGACCCAGGAGACUCGC AAUCAGCCACCCCAUCACCAGGACCACGCAG AAUCAGCCACCCACACCCCUGGUUCAGCGACCGCAG AAUCAGCCACCCAACACCUGGUUCAGCGACCGCAG AAUGGUCAACUCUAUCAUCGUGGUGACCAAUCAGCA	
	CUGAACCCUCGGAUCAGCCACACCUUCAACAUCAACGA CAACAGAAAGAGCUGCAGCCUGGCUCUGCUGAACAUC GACGUGUACCAGCUGUGCAGCACCCCCAAGGUGGACG AGAGAAGCGACUACGCCAGCAGCGCAUCGAGGAUAU CGUGCUGGACAUCGUGAACUACGACGGCGAGCAUCAGC ACCACCCGGUUCAAGAACAACAACAUCAGCUUCGACCA GCCCUACGCCGCCUUGUACCUUCUGUGGGCCCUGGCA UCUACUACAAGGGCAAGAUCAUCUUCCUGGGCUACGG CGGCCUGGAACACCCAUCAACGAGAACGCCAUCUGCA ACACCACCGGCUGCCCUGGCAAGAGACGCCAUCUGC AAUCAGGCCAGCCACGCCCUGGUCAGCGACCGCAG AAUCAGGCCAGCCACGCCCUGGUCAGCGACCGCAG AAUCAGCCACGCCUGAUCAUCGUGGUCGACAAGGGCCUG	

TABLE 5-continued

-	
ACAUCACCGACUACAGGACAUCCGAUCAAGUGGACC UGGCACAACGUGCUGAGCAGACCCGGCAACAAUGAGU GCCCUUGGGGCCACAGCUGCCCCGAUGGAUGUAUCACC GGCGUGUACACCGACGCUACCCCGGAGAUCUACCGG CUCCAUCGUGUCCAGCGUGAUCCUGGACAGCCAGAAA AGCAGAGUGAACCACGGCCAUCAGAACACAGCC CGAGAGGGAGUGAACGAACUGGCCAUCAGAACC CUGAGCGCCGGCUACACCACCACAAGCUGCAUCACACA	
CUACAACAAGGGCUACUGCUUCCACAUCGUGGAAAUC AACCACAAGUCCCUGAACACCUUCCAGCCCAUGCUGUU CAAGACCGAGAUCCCCAAGAGCUGCUCC	
AUGCCCAUCAGCAUCCUGCUGAUCAUCACCACAAUGAU CAUGGCCAGCAUGCCAGAUCGACAUCACCAAGCUGC AGCACGUGGGCUGUGUGUGAACAGCCCCAAGGCUU GAAGAUCAGCCAGAACUUCGAGACACCCUACCUGAUC UUGAGCCUGAUCCCCAAGAUCGAGACACGCUACCUGAUC GCGCCGACUGAUCAUCCCCCUGUACGACGCCUGCU GGACAGACUGAUCAUCCCCCUGUACGACGCCUGCUG GGCAGAAGACCUGAUCAUCCCCUGUACGACGCCUGCGC UGCAGAAGACCUGAUCGUGACCAACAGGAUUCUUCGGCG GCGUGAUCGGCACAAUCGCCUGGAGAGUUCUUCGGCG GCGUGAUCGGCACAAUCGACAUCGAGAGGUGCACAAG CGCCCAGAUUCAGCCCUUGUGCAGAGCGUGCAGA AGCAGGCCAGAAUCGACAUCGAGAGCUGCAGAGCGU UCCAGCGUGGGCAAUCUGAUCGUGCCGUGUGGAAGGCC AGCCGGCUGGCCAUCUGAUCGUGCCGUGUGGAAGCUG GGCUGGGCCUGCACAACAGCGUGCAGAGCUGCAG UCCAGCGUGGGCAUCUGAUCGUGCGCUGUAU CGCCCGGCUGGCCUGUGAACAAGAGUGCCGCUCUAU CGCCCGGCUGGCCUGUGAACGACGCUGCAGGCUGCACAA CAUCUUCGGCGACAACAUCGGCAGCCUGCAGCUGCAGAU GGCAUUGACCGAGAUCUGCGCCGCUGUACCGCA CCAACAUCACCGGAGAUCGACCGCAGCUGCAGCA CAUCUUCGGCGACAACAUCGGCAGCCUGCAGGAAAAG GGCAUUAAGUGCACGGGAUCGCCAGCAU CAACAUCACCGAGAUCUUCACCACCAGCACCGUGAU AAGUACGACAUCUUCGACGCUGCUGUCACCGA GACUGCUGAACACCCCAGAUCUACCGCAGCUU CUCCUACAACAUCCAGAAGCGGCUGCCCUGUGACCA CAACUCACCCUGCAGGUGUGACCGCACUA CAGCAUCACCCUGCAGGUGCGCCUGACCACACU CUCCUACACACCCCAGAUCUACAGAGGGCCUUCUCGGC GACUGCUGAACACCCCAGAUCUACAGAGCA CCACGCCUGAACACCCCGCAGUGGUCCACCA GACUGCUGAACACCCCAGAUCUACAGAGCCA CCACGCUGACACCCCGGACCCUGGCCUUCUGGCC AGUUCCACACCACGUGACCUCGACCUUCUGGCC AGUACCCCACAUUAUGACCACAGGCGCUUUCUGGCC AGUACCCCCCCCCC	64
	GGCGUGUACACCGACGCUACCCCUGAAUCCUACAGAA AGCAGAQUGAACCCCGUGAUCACGACAGCACGACAA AGCAGAQUGAACGCCCGUGAUCACGACAGCACCGCC CUGAGCGCCGGCUACACCACCACAGCCUGCAUCAAACAAGACC CUACAACAAGGCCCGUACACCACCACAAGCUGCAUCAACAA CUACAACAAGGCCUGAACACCUUCCACACACAAGCU CAAGACCGAGAUCCCCUGAUCAUCACCACACAAGAU CAAGACCGAGAUCCCCGAGAUCGACAUCACCACAAGGU GACGCUGGGCGUGCUGUGAUCAUCACCACAAGCUG CUGAGCCUGGCCAGAUCGGCAUCACCACAAGCUG CUGAGCCUGGCCGGCUGUGAUCAUCACCACAAGCUG CGGCGGCCAGAACUUCGAGACAGCAUCACCAAGCUG CUGAGCCUGAUCCCCCAGAUCGAGACAGCAACCAGCU CGGCGGACCAGCAGAUCGAGACAGCAACAGCU CGGGCGACCAGCAGAUCGAGGACAGCAACAGCU CGGGCGACCAGCAGAUCGAGGACAGCAACAGCU CGGGCGACCAGCAGAUCGAGGACGACAACCAGCU GGGACAACUGAUCAUCCCCCUGUGAGCAGCAACGACAA CGAGAACACCGACCCCCGGGACCGAGAGUUCUUCGGGG GCGUGAUCGGCACAAUCGCCCUGGGGGUGGCCACAAG CGCCCAGAUUACAGCCCUUGUGGCCCUGGUGAAGCCA AGCAGGCCAGAAGCGACAUCGAGAGAGUACCAA GGCCAGAUUACAGCCCUUGGAGCGAGAGCCAAG CGCCCGGCUGGCCACAAUCGAGAGAGUGCCACAAG CGCCCGGCUGGCCACACAGGCCUGGUGGAAGCCA AGCAGGCCAGAACGACAACAGGCGUGCAG UCCAGGCUAGGCACAUCGAGAGAGCGCAAGGCC GGCUUGGCCGGACACCAACAGGCGUGGCCACAAG CGCCUGGGCACACCAACAGGCCUGCGGCGGCG GGCUUGGGCCGGACACCGCGGCGGCCGCCUCUUU CGCCCGGCUGGCUGUGAACGCGGCCGCCUCUUU CGCCCGGCUGGCUGGAGAUCUGCGCGCCUCUUU CGCCCGGCUGGCUGGCGCGGCGGCGCAGCCAA CAUCUUCGCGGACAACAGCACUGCGGCGCGCCCUCUUU CGCCCGGCUGGCUGGCGGCGGCGCGCCGCCUGGAGU GGCAUUGACGCGCGAGAUCUGCGCGCGCCGCCGCAGACGA CAUCUCCGGGACAACCAGCCUGCUGCAGCCAA CAUCUUCGCGCAAAUCGGCGGCUGCCCGAGACGA CCAACAUCACCGAGAUCUGACCCACGGCGUGCCCAAGCCA CCAACAUCACCGAGAUCGCGCGCGCCUGGAGACAACACCA CACGACCACCCUGCAAGUGGCGCGCCCCUGGCGCCGCCUUCUGGC GAACAGCUGGAAGACCCAGGACUGAGCCCACACCA GCUACAUCUGCCCAGAACCGCGAGUGGCACACUCGCC CACGACGCGUGAACACCCAGGACCUGGACCCCUCCGCU CCCCACAACACCCCGGACCUGGCCUUCAGCC AGUACCACCCCCGGACCUCCGACAUCCGCCCU CCCACAACACCCCGGACCUCGACAUCCGCCC AGUACCACCACCACCACGGCAUCCGCCCU CCCACAACACCCCGGACCUCGACAUCCGCCCU CCCCCACAACACCCCGGAUCCCCGGCAUCAGCCCU CCCCCACAACCACCCGGCAUCCGCGCUUCGGCCCU UCUACACCCCCGACAUCCCCGACAUCCGCCU CCCCCACAACACCCGGAUCCCCGGCCUUCGGCCCU CUCACCCCCGACGACUCCGACUCCGACCUCGGCCUUCGCCCU CUCACCCCCGACGACCUCCGACUCCGACCUCGGCCUU CCCCCACAAGCCCCGACAUCCCCGACCUCGGCCUU

TABLE 6

	PIV3 Amino Acid Sequences	
Description	Sequence	SEQ ID NO:
>gi 612507166 gb AHX22429.1 fusion glycoprotein	MPISILLIITTMIMASHCQIDITKLQHVGVLVNSPKGMKISQ NFETRYLILSLIPKIEDSNSCGDQQIKQYKRLLDRLIIPLYDG LRLQKDVIVTNQESNENTDPRTERFFGGVIGTIALGVATSA	13
FO [Human] parainfluenza virus 3]	QITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSVG NLIVAIKSVQDYVNKEIVPSIARLGCEAAGLQLGIALTQHYS ELTNIFGDNIGSLQEKGIKLQGIASLYRTNITEIFTTSTVDKY	
-1	DIYDLLFTESIKVRVIDVDLNDYSITLQVRLPLLTRLLNTQIY	

TABLE 6-continued

	PIV3 Amino Acid Sequences	
Description	Sequence	SEQ II NO:
gi 612507167 gb AHX22430.1 hemagglutinin- neuraminidase [Human parainfluenza virus 3]	KVDSISYNIQNREWYIPLPSHIMTKGAFLGGADVKECIEAFS SYICPSDPGFVLNHEMESCLSGNISQCPRTTVTSDIVPRYAF VNGGVVANCITTTCTCNGIGNRINQPPDQGVKIITHKECNTI GINGMLFNTNKEGTLAFYTPDDITLNNSVALDPIDISIELNK AKSDLEESKEWIRRSNQKLDSIGSWHQSSTTIIVILIMMIILFI INITIITIAIKYYRIQKRNRVDQNDKPYVLTNK MEYWKHTNHGKDAGNELETSTATHGNKLTNKITYILWTIT LVLLSIVFIIVLTNSIKSEKARESLLQDINNEFMEVTEKIQVA SDNTNDLIQSGVNTRLLTIQSHVQNYIPISLTQQISDLRKFIS EITIRNDNQEVPPQRITHDVGIKPLNPDDFWRCTSGLPSLMK TPKIRLMPGPGLLAMPTTVDGCVRTPSLVINDLIYAYTSNLI TRGCQDIGKSYQVLQIGIITVNSDLVPDLNPRISHTPNINDN	14
	RKSCSLALLNTDVYQLCSTPKVDERSDYASSGIEDIVLDIV NYDGSISTTRFKNNNISFDQPYAALYPSVGPGIYYKGKIIPL GYGGLEHPINENAICNTTGCPGKVTQRCNQASHSPWFSDR RMVNSIIVVDKGLNSVPKLKVMTISMRQNYWGSEGRLLLL GNKIYIYTRSTSWHSKLQLGIIDITDYSDIRIKWTWHNVLSR PGNNECPWGHSCPDGCITGVYTDAYPLNPTGSIVSSVILDS QKSRVNPVITYSTATERVNELAIRNKTLSAGYTTTSCITHY NKGYCFHIVEINHKSLNTFQPMLFKTEIPKSCS	

TABLE 7

PIV3 NCBI Accession Numbers (Nucleic Acid and Amino Acid Sequences)				
Description	GenBank Accession			
Fusion glycoprotein F0 [Human parainfluenza virus 3]	KJ672601.11:			
HPIV3/Homo sapiens/PER/FLA4815/2008	4990-6609			
	AHX22429			
	(Fusion protein)			
hemagglutinin-neuraminidase [Human parainfluenza virus 3]	KJ672601.1 :			
HPIV3/Homo sapiens/PER/FLA4815/2008	6724-8442			
	AHX22430			
	(HN protein)			
Recombinant PIV3/PIV1 virus fusion glycoprotein (F)	AF016281			
and hemagglutinin (HN) genes, complete cds; and RNA	AAC23947			
dependent RNA polymerase (L) gene, partial eds.	(hemagglutinin)			
Recombinant PIV3/PIV1 virus fusion glycoprotein (F)	AF016281			
and hemagglutinin (HN) genes, complete cds; and RNA	AAC23947			
lependent RNA polymerase (L) gene, partial cds.	(fusion protein)			
nemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32044.1			
nemagglutinin-neuraminidase [Human parainfluenza virus 3]	BAO32051.1			
C protein [Human parainfluenza virus 3]	NP_599251.1			
C protein [Human parainfluenza virus 3]	ABZ85670.1			
C protein [Human parainfluenza virus 3]	AGT75164.1			
C protein [Human parainfluenza virus 3]	AAB48686.1			
C protein [Human parainfluenza virus 3]	AHX22115.1			
C protein [Human parainfluenza virus 3]	AGW51066.1			
C protein [Human parainfluenza virus 3]	AGW51162.1			
C protein [Human parainfluenza virus 3]	AGT75252.1			
C protein [Human parainfluenza virus 3]	AGT75188.1			
C protein [Human parainfluenza virus 3]	AGW51218.1			
C protein [Human parainfluenza virus 3]	AGW51074.1			
C protein [Human parainfluenza virus 3]	AGT75323.1			
C protein [Human parainfluenza virus 3]	AGT75307.1			
C protein [Human parainfluenza virus 3]	AHX22131.1			
C protein [Human parainfluenza virus 3]	AGW51243.1			
C protein [Human parainfluenza virus 3]	AGT75180.1			
C protein [Human parainfluenza virus 3]	AGT75212.1			
C protein [Human parainfluenza virus 3]	AGW51186.1			
C protein [Human parainfluenza virus 3]	AHX22075.1			
C protein [Human parainfluenza virus 3]	AHX22163.1			
C protein [Human parainfluenza virus 3]	AGT75196.1			
C protein [Human parainfluenza virus 3]	AHX22491.1			
C protein [Human parainfluenza virus 3]	AHX22139.1			
C protein [Human parainfluenza virus 3]	AGW51138.1			
C protein [Human parainfluenza virus 3]	AGW51114.1			
C protein [Human parainfluenza virus 3]	AGT75220.1			
C protein [Human parainfluenza virus 3]	AHX22251.1			
RecName: Full = Protein C; AltName: Full = VP18 protein	P06165.1			

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TABLE 7-continued

Description	GenBank Accession
C protein [Human parainfluenza virus 3]	AHX22187.1
C protein [Human parainfluenza virus 3]	AGT75228.1
C protein [Human parainfluenza virus 3]	AHX22179.1
C protein [Human parainfluenza virus 3] C protein [Human parainfluenza virus 3]	AHX22427.1 AGW51210.1
nonstructural protein C [Human parainfluenza virus 3]	BAA00922.1
C protein [Human parainfluenza virus 3]	AHX22315.1
C protein [Human parainfluenza virus 3]	AGW51259.1
C protein [Human parainfluenza virus 3]	AHX22435.1
C protein [Human parainfluenza virus 3]	AHX22123.1
C protein [Human parainfluenza virus 3]	AHX22299.1
C protein [Human parainfluenza virus 3]	AGW51267.1 CAA28430.1
unnamed protein product [Human parainfluenza virus 3] C protein [Human parainfluenza virus 3]	AGW51178.1
C protein [Human parainfluenza virus 3]	AHX22411.1
RecName: Full = Protein C	P06164.1
phosphoprotein [Human parainfluenza virus 3]	NP_067149.1
phosphoprotein [Human parainfluenza virus 3]	AAB48685.1
phosphoprotein [Human parainfluenza virus 3]	AHX22498.1
phosphoprotein [Human parainfluenza virus 3]	AHX22490.1
phosphoprotein [Human parainfluenza virus 3]	AGT75259.1
phosphoprotein [Human parainfluenza virus 3]	AGW51137.1 AGW51145.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51145.1 AGT75298.1
phosphoprotein [Human parainfluenza virus 3]	AGW51113.1
phosphoprotein [Human parainfluenza virus 3]	AGT75203.1
phosphoprotein [Human parainfluenza virus 3]	AGT75163.1
phosphoprotein [Human parainfluenza virus 3]	AHX22506.1
phosphoprotein [Human parainfluenza virus 3]	AGW51129.1
phosphoprotein [Human parainfluenza virus 3]	AHX22194.1
phosphoprotein [Human parainfluenza virus 3]	AGT75211.1
phosphoprotein [Human parainfluenza virus 3]	AHX22258.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51121.1 AGT75282.1
phosphoprotein [Human parainfluenza virus 3]	AHX22146.1
phosphoprotein [Human parainfluenza virus 3]	AHX22138.1
phosphoprotein [Human parainfluenza virus 3]	AHX22322.1
phosphoprotein [Human parainfluenza virus 3]	AHX22370.1
phosphoprotein [Human parainfluenza virus 3]	AHX22098.1
phosphoprotein [Human parainfluenza virus 3]	AHX22130.1
phosphoprotein [Human parainfluenza virus 3]	AHX22418.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AHX22114.1 AHX22410.1
phosphoprotein [Human parainfluenza virus 3]	AGT75306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22170.1
phosphoprotein [Human parainfluenza virus 3]	AHX22266.1
phosphoprotein [Human parainfluenza virus 3]	AHX22090.1
phosphoprotein [Human parainfluenza virus 3]	AGT75195.1
phosphoprotein [Human parainfluenza virus 3]	AHX22226.1
phosphoprotein [Human parainfluenza virus 3]	AHX22178.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AHX22122.1 AHX22186.1
phosphoprotein [Human parainfluenza virus 3]	AHX22066.1
phosphoprotein [Human parainfluenza virus 3]	AHX22522.1
phosphoprotein [Human parainfluenza virus 3]	AGW51225.1
phosphoprotein [Human parainfluenza virus 3]	BAN29032.1
phosphoprotein [Human parainfluenza virus 3]	ABZ85669.1
phosphoprotein [Human parainfluenza virus 3]	AHX22426.1
phosphoprotein [Human parainfluenza virus 3]	AHX22058.1
phosphoprotein [Simian Agent 10]	ADR00400.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AHX22250.1 AHX22434.1
phosphoprotein [Human parainfluenza virus 3]	AHX22454.1 AHX22298.1
phosphoprotein [Human parainfluenza virus 3]	AHX22442.1
phosphoprotein [Human parainfluenza virus 3]	AHX22074.1
phosphoprotein [Human parainfluenza virus 3]	AGW51153.1
phosphoprotein [Human parainfluenza virus 3]	AGW51241.1
phosphoprotein [Human parainfluenza virus 3]	AHX22210.1
phosphoprotein [Human parainfluenza virus 3]	AGW51105.1
phosphoprotein [Human parainfluenza virus 3]	AGT75251.1
phosphoprotein [Human parainfluenza virus 3]	AHX22362.1 AHX22474.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51217.1
phosphoprotein [Human parainfluenza virus 3]	AIG60038.1
phosphoprotein [Human parainfluenza virus 3]	AHX22378.1

TABLE 7-continued

Description	GenBank Accession
phosphoprotein [Human parainfluenza virus 3]	AGT75187.1
phosphoprotein [Human parainfluenza virus 3]	AGW51233.1
phosphoprotein [Human parainfluenza virus 3]	AHX22482.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51161.1 AHX22306.1
phosphoprotein [Human parainfluenza virus 3]	AHX22162.1
phosphoprotein [Human parainfluenza virus 3]	ACJ70087.1
phosphoprotein [Human parainfluenza virus 3]	AHX22466.1
phosphoprotein [Human parainfluenza virus 3]	AHX22346.1
phosphoprotein [Human parainfluenza virus 3]	AGW51089.1 AGW51073.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51075.1 AGW51185.1
phosphoprotein [Human parainfluenza virus 3]	AGW51065.1
phosphoprotein [Human parainfluenza virus 3]	ABY47603.1
phosphoprotein [Human parainfluenza virus 3]	AGW51049.1
phosphoprotein [Human parainfluenza virus 3]	AHX22330.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51250.1 AGT75227.1
phosphoprotein [Human parainfluenza virus 3]	AGW51282.1
phosphoprotein [Human parainfluenza virus 3]	AGW51209.1
phosphoprotein [Human parainfluenza virus 3]	AGW51193.1
phosphoprotein [Human parainfluenza virus 3]	AGT75322.1
phosphoprotein [Human parainfluenza virus 3]	AGT75219.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51258.1 AGW51041.1
phosphoprotein [Human parainfluenza virus 3]	ACD99698.1
phosphoprotein [Human parainfluenza virus 3]	AGW51266.1
phosphoprotein [Human parainfluenza virus 3]	AGT75179.1
phosphoprotein [Human parainfluenza virus 3]	AHX22282.1
phosphoprotein [Human parainfluenza virus 3] phosphoprotein [Human parainfluenza virus 3]	AGW51169.1 AGW51274.1
phosphoprotein [Human parainfluenza virus 3]	AGW51274.1 AGW51201.1
phosphoprotein [Human parainfluenza virus 3]	AGW5120111 AGW51177.1
RecName: Full = Phosphoprotein; Short = Protein P	P06162.1
P protein [Human parainfluenza virus 3]	AAA66818.1
phosphoprotein [Human parainfluenza virus 3]	AAA46866.1
phosphoprotein [Human parainfluenza virus 3] polymerase-associated nucleocapsid phosphoprotein	BAA00031.1 RRNZP5
(version 2) - parainfluenza virus type 3	
[Human parainfluenza virus 3]	
phosphoprotein [Human parainfluenza virus 3]	AGT75171.1
phosphoprotein [Human parainfluenza virus 3]	BAA00921.1 NP_599250.1
D protein [Human parainfluenza virus 3] D protein [Human parainfluenza virus 3]	AHX22377.1
D protein [Human parainfluenza virus 3]	AHX22121.1
D protein [Human parainfluenza virus 3]	AGT75297.1
D protein [Human parainfluenza virus 3]	AGW51136.1
D protein [Human parainfluenza virus 3]	AGW51242.1
D protein [Human parainfluenza virus 3] D protein [Human parainfluenza virus 3]	AGW51112.1 AHX22497.1
D protein [Human parainfluenza virus 3]	AHX22145.1
D protein [Human parainfluenza virus 3]	AGT75202.1
D protein [Human parainfluenza virus 3]	AHX22385.1
D protein [Human parainfluenza virus 3]	AGW51216.1
D protein [Human parainfluenza virus 3]	AGT75281.1
D protein [Human parainfluenza virus 3] D protein [Human parainfluenza virus 3]	AGT75194.1 AHX22521.1
D protein [Human parainfluenza virus 3]	AGW51120.1
D protein [Human parainfluenza virus 3]	AGT75313.1
D protein [Human parainfluenza virus 3]	AHX22249.1
D protein [Human parainfluenza virus 3]	AHX22097.1
D protein [Human parainfluenza virus 3]	AGW51144.1
D protein [Human parainfluenza virus 3]	AHX22089.1 AHX22225.1
D protein [Human parainfluenza virus 3] D protein [Human parainfluenza virus 3]	AHX22223.1 AHX22137.1
D protein [Human parainfluenza virus 3]	AHX22065.1
D protein [Human parainfluenza virus 3]	AGW51224.1
D protein [Human parainfluenza virus 3]	AGT75210.1
D protein [Human parainfluenza virus 3]	AHX22393.1
D protein [Human parainfluenza virus 3]	AGT75258.1
D protein [Human parainfluenza virus 3] D protein [Human parainfluenza virus 3]	AHX22345.1 AGT75250.1
D protein [Human parainfluenza virus 3]	AHX22113.1
D protein [Human parainfluenza virus 3]	AGW51232.1
D protein [Human parainfluenza virus 3]	AHX22057.1
D protein [Human parainfluenza virus 3]	AHX22209.1

TABLE 7-continued

Description	GenBank Accession
D protein [Human parainfluenza virus 3]	AGW51056.1
D protein [Human parainfluenza virus 3]	AHX22161.1
D protein [Simian Agent 10]	ADR00402.1
D protein [Human parainfluenza virus 3]	AHX22361.1
D protein [Human parainfluenza virus 3]	AGW51281.1
D protein [Human parainfluenza virus 3]	AGW51184.1
D protein [Human parainfluenza virus 3]	AGW51160.1
D protein [Human parainfluenza virus 3]	AHX22465.1
D protein [Human parainfluenza virus 3]	AHX22329.1
D protein [Human parainfluenza virus 3]	AGW51064.1
D protein [Human parainfluenza virus 3]	AGW51040.1
D protein [Human parainfluenza virus 3]	AGT75226.1
D protein [Human parainfluenza virus 3]	AG175220.1 AHX22425.1
D protein [Human parainfluenza virus 3]	AHX22305.1
D protein [Human parainfluenza virus 3]	AGW51249.1
D protein [Human parainfluenza virus 3]	AHX22481.1
D protein [Human parainfluenza virus 3]	AHX22281.1
D protein [Human parainfluenza virus 3]	AGW51048.1
D protein [Human parainfluenza virus 3]	AHX22297.1
D protein [Human parainfluenza virus 3]	AGW51088.1
D protein [Human parainfluenza virus 3]	AGT75305.1
D protein [Human parainfluenza virus 3]	AHX22185.1
D protein [Human parainfluenza virus 3]	AGW51104.1
D protein [Human parainfluenza virus 3]	AHX22081.1
D protein [Human parainfluenza virus 3]	AGW51192.1
D protein [Human parainfluenza virus 3]	AHX22489.1
D protein [Human parainfluenza virus 3]	AHX22441.1
D protein [Human parainfluenza virus 3]	AHX22409.1
D protein [Human parainfluenza virus 3]	AHX22369.1
D protein [Human parainfluenza virus 3]	AHX22303.1 AHX22321.1
D protein [Human parainfluenza virus 3]	AHX22073.1
D protein [Human parainfluenza virus 3]	AGW51152.1
D protein [Human parainfluenza virus 3]	AGW51072.1
D protein [Human parainfluenza virus 3]	AGT75321.1
D protein [Human parainfluenza virus 3]	AHX22257.1
D protein [Human parainfluenza virus 3]	AHX22129.1
D protein [Human parainfluenza virus 3]	AHX22417.1
D protein [Human parainfluenza virus 3]	AGT75218.1
D protein [Human parainfluenza virus 3]	AHX22265.1
D protein [Human parainfluenza virus 3]	AGT75178.1
D protein [Human parainfluenza virus 3]	AHX22433.1
D protein [Human parainfluenza virus 3]	AGW51273.1
D protein [Human parainfluenza virus 3]	AGW51208.1
D protein [Human parainfluenza virus 3]	AGT75170.1
D protein [Human parainfluenza virus 3]	AGT75162.1
D protein [Human parainfluenza virus 3]	AGW51257.1
D protein [Human parainfluenza virus 3]	AGW51257.1 AGW51200.1
D protein [Human parainfluenza virus 3]	AGW51176.1
D protein [Human parainfluenza virus 3]	AGT75186.1
D protein [Human parainfluenza virus 3]	AGW51265.1
D protein [Human parainfluenza virus 3]	AGW51168.1

TABLE 8

TABLE 8-continued

	Signal Peptides		50	30		
Description	Sequence	SEQ ID NO:		Descript	ion	
HuIgG _k signal peptide	METPAQLLFLLLLWLPDTTG	15	55	Japanese encephal		
IgE heavy chain epsilon-1 signal peptide	MDWTWILFLVAAATRVHS	16		signal s		
Japanese encephalitis PRM signal sequence	MLGSNSGQRVVFTILLLLVAPAYS	17	60		hM	
VSVq protein	MKCLLYLAFLFIGVNCA	18		Group	n	
signal sequence			65	1	5	

_____ 50 _____

		Signal Peptides	
	Description	Sequence	SEQ ID NO:
	Japanese encephalitis JEV signal sequence	MWLVSLAIVTACAGA	19
)		TABLE 9	

-	hMPV/PIV Cotton Rat Challenge Study Design					
_	Group	n	Test Article	[conc]/µg	Route	Challenge
	1		Placebo	n/a	IM	hMPV/A2
	2	5	hMPV vaccine mRNA	30	IM	hMPV/A2

TABLE 9-continued

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 $[conc]/\mu g$ Route Challenge

PIV3

PIV3

PIV3

_				innaea						nunaça		
_		hl	MPV/PIV Cotton Rat Chall	enge Study	Design		-		hMPV/PIV Cotton Rat Cha	illenge Study I	Design	
_	Group	n	Test Article	[conc]/µg	Route	Challenge	. 5	Group	n Test Article	[conc]/µg	Route	(
	3	5	hMPV vaccine mRNA	15	IM	hMPV/A2		10	5 PIV3 vaccine mRNA	10	IM	<u> </u>
	4	5	hMPV vaccine mRNA	10	IM	hMPV/A2			5 hMPV/PIV3 vaccine	30	IM	
	5	5	hMPV/PIV3 vaccine mRNA (15/15)	30	IM	hMPV/A2		11	mRNA (15/15)	30	1111	1
	6	5	FI-hMPV	n/a	IM	hMPV/A2		12	5 FI-PIV3	n/a	IM	J
	7	5	Placebo	n/a	IM	PIV3	10					
	8	5	PIV3 vaccine mRNA	30	IM	PIV3	r.		60			
	9	5	PIV3 vaccine mRNA	15	IM	PIV3						_

TABLE 1	0
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Strain	Nucleic Acid Sequence	SEQ I NO:
gb KJ156934.1 : 21405-25466	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC	20
Middle	TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG	
East respiratory	TCTGCTTGTATTGAGGTTGATATACAACAGACCTTCTTTGA	
syndrome	TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC	
oronavirus	GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA	
isolate	CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT	
Riyadh 14 2013,	GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA	
pike protein	CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA	
(nucleotide)	CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA	
	GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC	
	TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC	
	TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG	
	CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCGATGGAT	
	GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTAGAGCCT	
	CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC	
	TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG	
	GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA	
	GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA	
	ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC	
	ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG	
	TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG	
	CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA	
	CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT	
	GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT	
	GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT	
	GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA	
	TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT	
	CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA	
	GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC	
	TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT	
	GCAATTATAATCTTACCAAATTGCTTTCACTTTTTTCTGTG AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC	
	TAGCAACTGTTATTCTTCACTGATTTTGGATTATTTTTCAT	
	ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT	
	GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA	
	TCCCACATGTTTGATCTTAGCGACTGTTCCTCATAACCTTA	
	CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA	
	GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCTC	
	AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT	
	GTCCCATCCACTGTGTGGGGAAGACGGTGATTATTATAGGA	
	AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC	
	TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG	
	GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA	
	GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT	
	TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG	
	GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA	
	GGTGTTCGACAGCAGCGCCTTTGTTTATGATGCGTACCAGA	
	ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT	
	CTGCGTGCTTGTGTTGTGTTGTGTTCCTGTCTGTCATCTATGA	
	TAAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTT	
	GCATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCG	
	TTCTACGCGATCAATGCTTAAACGGCGAGATTCTACATAT	
	GGCCCCCTTCAGACACCTGTTGGTTGTGTGTCCTAGGACTTGT	
	TAATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTCG	
	GTCAATCTCTCTGTGCTCTTCCTGACACCCTAGTACTCTC	
	ACACCTCGCAGTGTGCGCTCTGTGCCAGGTGAAATGCGCT	
	TGGCATCCATTGCTTTTAATCATCCCATTCAGGTTGATCAA	
	CTTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTT	

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TABLE 10-continued

B	etacoronavirus Nucleic Acid Sequence	
Strain	Nucleic Acid Sequence	SEQ II NO:
	TTCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC	
	AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG	
	TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG	
	TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT	
	ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG	
	AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG GTGACTTTAATTTGACACTTCTAGAACCTGTTTCTATATCT	
	ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC	
	TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA	
	AGGTTACGATGATTGTATGCAGCAAGGTCCAGCATCAGCT	
	CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTATAAAGT	
	ATTACCTCCTCTTATGGATGTTAATATGGAAGCCGCGTATA	
	CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT	
	GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG TATVTTTTATATCCTCCTTTGCTGCTATTCCATTTGCACAGAG	
	TATYTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAG GTTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTA	
	ATCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAAC	
	TAATGAAGCTTTTCCGGAAGGTTCAGGATGCTGTGAACAAC	
	AATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTA	
	ATACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATA	
	CAACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACA	
	GACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTT	
	GCACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGC	
	TCAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCA CAATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATA	
	TAGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTACTTT	
	ATGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGT	
	TTCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATT	
	GTATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAAC	
	ACTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTT	
	CTATGCACCTGAGCCCATCACCTCTCTTAATACTAAGTATG	
	TTGCACCACAGGTGACATACCAAAACATTTCTACTAACCT	
	CCCTCCTCCTCTCTCGGCAATTCCACCGGGATTGACTTCC AAGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAG	
	TATACCTAATTTTGGTTCTCTAACACAGATTAATACTACACAA	
	TACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTT	
	GTTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGC	
	TTGGCAATTATACTTATTACAACAAATGGCCGTGGTACAT	
	TTGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTAT	
	GCGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAAC	
	TGTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGAT	
	ACGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCA CTAA	
IERS S FL	ATGATACACTCAGTGTTTCTACTGATGTTCTTGTTAACACC	21
PIKE	TACAGAAAGTTACGTTGATGTAGGGCCAGATTCTGTTAAG	
CEMC/2012	TCTGCTTGTATTGAGGTTGATATACAACAGACTTTCTTTGA	
XBaI change(T to)) (nucleotide)	TAAAACTTGGCCTAGGCCAATTGATGTTTCTAAGGCTGAC GGTATTATATACCCTCAAGGCCGTACATATTCTAACATAA	
// (Indefeotine)	CTATCACTTATCAAGGTCTTTTTCCCTATCAGGGAGACCAT	
	GGTGATATGTATGTTTACTCTGCAGGACATGCTACAGGCA	
	CAACTCCACAAAAGTTGTTTGTAGCTAACTATTCTCAGGA	
	CGTCAAACAGTTTGCTAATGGGTTTGTCGTCCGTATAGGA	
	GCAGCTGCCAATTCCACTGGCACTGTTATTATTAGCCCATC	
	TACCAGCGCTACTATACGAAAAATTTACCCTGCTTTTATGC	
	TGGGTTCTTCAGTTGGTAATTTCTCAGATGGTAAAATGGG	
	CCGCTTCTTCAATCATACTCTAGTTCTTTTGCCCCGATGGAT GTGGCACTTTACTTAGAGCTTTTTATTGTATTCTGGAGCCT	
	CGCTCTGGAAATCATTGTCCTGCTGGCAATTCCTATACTTC	
	TTTTGCCACTTATCACACTCCTGCAACAGATTGTTCTGATG	
	GCAATTACAATCGTAATGCCAGTCTGAACTCTTTTAAGGA	
	GTATTTTAATTTACGTAACTGCACCTTTATGTACACTTATA	
	ACATTACCGAAGATGAGATTTTAGAGTGGTTTGGCATTAC	
	ACAAACTGCTCAAGGTGTTCACCTCTTCTCATCTCGGTATG	
	TTGATTTGTACGGCGGCAATATGTTTCAATTTGCCACCTTG	
	CCTGTTTATGATACTATTAAGTATTATTCTATCATTCCTCA CAGTATTCGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT	
	GCCTTCTACGTTCTATCCAAAGTGATAGAAAAGCTTGGGCT GCCTTCTACGTATATAAACTTCAACCGTTAACTTTCCTGTT	
	GGATTTTTCTGTTGATGGTTATATACGCAGAGCTATAGACT	
	GTGGTTTTAATGATTTGTCACAACTCCACTGCTCATATGAA	
	TCCTTCGATGTTGAATCTGGAGTTTATTCAGTTTCGTCTTT	
	CGAAGCAAAACCTTCTGGCTCAGTTGTGGAACAGGCTGAA	
	GGTGTTGAATGTGATTTTTCACCTCTTCTGTCTGGCACACC	
	TCCTCAGGTTTATAATTTCAAGCGTTTGGTTTTTACCAATT	

GCAATTATAATCTTACCAAATTGCTTTCACTTTTTCTGTG

TABLE 10-continued

Betacoro	navirus Nucleic Acid Sequence	
Strain	Nucleic Acid Sequence	SEQ I NO:
	AATGATTTTACTTGTAGTCAAATATCTCCAGCAGCAATTGC	
	TAGCAACTGTTATTCTTCACTGATTTTGGATTACTTTTCAT	
	ACCCACTTAGTATGAAATCCGATCTCAGTGTTAGTTCTGCT	
	GGTCCAATATCCCAGTTTAATTATAAACAGTCCTTTTCTAA	
	TCCCACATGTTTGATTTTAGCGACTGTTCCTCATAACCTTA CTACTATTACTAAGCCTCTTAAGTACAGCTATATTAACAA	
	GTGCTCTCGTCTTCTTTCTGATGATCGTACTGAAGTACCAG	
	AGTTAGTGAACGCTAATCAATACTCACCCTGTGTATCCATT	
	GTCCCATCCACTGTGTGGGAAGACGGTGATTATTATAGGA	
	AACAACTATCTCCACTTGAAGGTGGTGGCTGGCTTGTTGC	
	TAGTGGCTCAACTGTTGCCATGACTGAGCAATTACAGATG	
	GGCTTTGGTATTACAGTTCAATATGGTACAGACACCAATA	
	GTGTTTGCCCCAAGCTTGAATTTGCTAATGACACAAAAAT	
	TGCCTCTCAATTAGGCAATTGCGTGGAATATTCCCTCTATG	
	GTGTTTCGGGCCGTGGTGTTTTTCAGAATTGCACAGCTGTA	
	GGTGTTCGACAGCAGCGCTTTGTTTATGATGCGTACCAGA ATTTAGTTGGCTATTATTCTGATGATGGCAACTACTACTGT	
	TTGCGTGCTTGTGTTAGTGTTCCTGTTTCTGTCATCTACTAGT	
	AAAGAAACTAAAACCCACGCTACTCTATTTGGTAGTGTTG	
	CATGTGAACACATTTCTTCTACCATGTCTCAATACTCCCGT	
	TCTACGCGATCAATGCTTAAACGGCGAGATTCTACATATG	
	GCCCCCTTCAGACACCTGTTGGTTGTGTCCTAGGACTTGTT	
	AATTCCTCTTTGTTCGTAGAGGACTGCAAGTTGCCTCTTGG	
	TCAATCTCTCTGTGCTCTTCCTGACACCCCTAGTACTCTCA	
	CACCTCGCAGTGTGCGCTCTGTTCCAGGTGAAATGCGCTT	
	GGCATCCATTGCTTTTAATCATCCTATTCAGGTTGATCAAC	
	TTAATAGTAGTTATTTTAAATTAAGTATACCCACTAATTTT TCCTTTGGTGTGACTCAGGAGTACATTCAGACAACCATTC	
	AGAAAGTTACTGTTGATTGTAAACAGTACGTTTGCAATGG	
	TTTCCAGAAGTGTGAGCAATTACTGCGCGAGTATGGCCAG	
	TTTTGTTCCAAAATAAACCAGGCTCTCCATGGTGCCAATTT	
	ACGCCAGGATGATTCTGTACGTAATTTGTTTGCGAGCGTG	
	AAAAGCTCTCAATCATCTCCTATCATACCAGGTTTTGGAG	
	GTGACTTTAATTTGACACTTCTGGAACCTGTTTCTATATCT	
	ACTGGCAGTCGTAGTGCACGTAGTGCTATTGAGGATTTGC	
	TATTTGACAAAGTCACTATAGCTGATCCTGGTTATATGCA	
	AGGTTACGATGATTGCATGCAGCAAGGTCCAGCATCAGCT CGTGATCTTATTTGTGCTCAATATGTGGCTGGTTACAAAGT	
	ATTACCTCCTCTTATGGATGTTAATATGGGAAGCCGCGTATA	
	CTTCATCTTTGCTTGGCAGCATAGCAGGTGTTGGCTGGACT	
	GCTGGCTTATCCTCCTTTGCTGCTATTCCATTTGCACAGAG	
	TATCTTTTATAGGTTAAACGGTGTTGGCATTACTCAACAGG	
	TTCTTTCAGAGAACCAAAAGCTTATTGCCAATAAGTTTAA	
	TCAGGCTCTGGGAGCTATGCAAACAGGCTTCACTACAACT	
	AATGAAGCTTTTCAGAAGGTTCAGGATGCTGTGAACAACA	
	ATGCACAGGCTCTATCCAAATTAGCTAGCGAGCTATCTAA	
	TACTTTTGGTGCTATTTCCGCCTCTATTGGAGACATCATAC AACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACAG	
	ACGTCTTGATGTTCTCGAACAGGACGCCCAAATAGACAG ACTTATTAATGGCCGTTTGACAACACTAAATGCTTTTGTTG	
	CACAGCAGCTTGTTCGTTCCGAATCAGCTGCTCTTTCCGCT	
	CAATTGGCTAAAGATAAAGTCAATGAGTGTGTCAAGGCAC	
	AATCCAAGCGTTCTGGATTTTGCGGTCAAGGCACACATAT	
	AGTGTCCTTTGTTGTAAATGCCCCTAATGGCCTTTACTTCA	
	TGCATGTTGGTTATTACCCTAGCAACCACATTGAGGTTGTT	
	TCTGCTTATGGTCTTTGCGATGCAGCTAACCCTACTAATTG	
	TATAGCCCCTGTTAATGGCTACTTTATTAAAACTAATAACA	
	CTAGGATTGTTGATGAGTGGTCATATACTGGCTCGTCCTTC	
	TATGCACCTGAGCCCATTACCTCCCTTAATACTAAGTATGT TGCACCACAGGTGACATACCAAAACATTTCTACTAACCTC	
	CCTCCTCCTCTTCTCGGCAATTCCACCGGGATTGACCTCCA	
	AGATGAGTTGGATGAGTTTTTCAAAAATGTTAGCACCAGT	
	ATACCTAATTTTGGTTCCCTAACACAGATTAATACTACATT	
	ACTCGATCTTACCTACGAGATGTTGTCTCTTCAACAAGTTG	
	TTAAAGCCCTTAATGAGTCTTACATAGACCTTAAAGAGCT	
	TGGCAATTATACTTATTACAACAAATGGCCGTGGTACATT	
	TGGCTTGGTTTCATTGCTGGGCTTGTTGCCTTAGCTCTATG	
	CGTCTTCTTCATACTGTGCTGCACTGGTTGTGGCACAAACT	
	GTATGGGAAAACTTAAGTGTAATCGTTGTTGTGATAGATA	
	CGAGGAATACGACCTCGAGCCGCATAAGGTTCATGTTCAC TAA	
	Inn	
ovel MERS S2 subunit trimeric	ATGATCCACTCCGTGTTCCTCCTCATGTTCCTGTTGACCCC	22
accine	CACTGAGTCAGACTGCAAGCTCCCGCTGGGACAGTCCCTG	
nucleotide)	TGTGCGCTGCCTGACACTCCTAGCACTCTGACCCCACGCTC	
	CGTGCGGTCGGTGCCTGGCGAAATGCGGCTGGCCTCCATC	

CGTGCGGTCGGTGCCTGGCGAAATGCGGCTGGCCTCCATC

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TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ I NO:
	GCCTTCAATCACCCAATCCAAGTGGATCAGCTGAATAGCT	
	CGTATTTCAAGCTGTCCATCCCCACGAACTTCTCGTTCGGG	
	GTCACCCAGGAGTACATCCAGACCACAATTCAGAAGGTCA	
	CCGTCGATTGCAAGCAATACGTGTGCAACGGCTTCCAGAA	
	GTGCGAGCAGCTGCTGAGAGAATACGGGCAGTTTTGCAGC AAGATCAACCAGGCGCTGCATGGAGCTAACTTGCGCCAGG	
	ACGACTCCCGTGCGCAACCTCTTTGCCTCTGTGAAGTCATCC	
	CAGTCCTCCCCAATCATCCCCGGGATTCGGAGGGGGCTTCA	
	ACCTGACCCTCCTGGAGCCCGTGTCGATCAGCACCGGTAG	
	CAGATCGGCGCGCTCAGCCATTGAAGATCTTCTGTTCGAC	
	AAGGTCACCATCGCCGATCCGGGCTACATGCAGGGATACG	
	ACGACTGTATGCAGCAGGGACCAGCCTCCGCGAGGGACCT	
	CATCTGCGCGCAATACGTGGCCGGGTACAAAGTGCTGCCT CCTCTGATGGATGTGAACATGGAGGCCGCTTATACTTCGT	
	CCCTGCTCGGCTCTATCGCCGGCGTGGGGTGGACCGCCGG	
	CCTGTCCTCCTTCGCCGCTATCCCCTTTGCACAATCCATTT	
	TCTACCGGCTCAACGGCGTGGGCATTACTCAACAAGTCCT	
	GTCGGAGAACCAGAAGTTGATCGCAAACAAGTTCAATCA	
	GGCCCTGGGGGCCATGCAGACTGGATTCACTACGACTAAC	
	GAAGCGTTCCAGAAGGTCCAGGACGCTGTGAACAACAAC	
	GCCCAGGCGCTCTCAAAGCTGGCCTCCGAACTCAGCAACA	
	CCTTCGGAGCCATCAGCGCATCGATCGGTGACATAATTCA GCGGCTGGACGTGCTGGAGCAGGACGCCCAGATCGACCG	
	CCTCATCAACGGACGGCTGACCACCTTGAATGCCTTCGTG	
	GCACAACAGCTGGTCCGGAGCGAATCAGCGGCACTTTCCG	
	CCCAACTCGCCAAGGACAAAGTCAACGAATGCGTGAAGG	
	CCCAGTCCAAGAGGTCCGGTTTCTGCGGTCAAGGAACCCA	
	TATTGTGTCCTTCGTCGTGAACGCGCCCAACGGTCTGTACT	
	TTATGCACGTCGGCTACTACCCGAGCAATCATATCGAAGT	
	GGTGTCCGCCTACGGCCTGTGCGATGCCGCTAACCCCACT AACTGTATTGCCCCTGTGAACGGATATTTTATTAAGACCA	
	ACTGTATTGCCCCTGTGAACGGATATTTTATTAAGACCA ACAACACCCCGCATTGTGGACGAATGGTCATACACCGGTTC	
	GTCCTTCTACGCGCCCGAGCCCATCACTTCACTGAACACC	
	AAATACGTGGCTCCGCAAGTGACCTACCAGAACATCTCCA	
	CCAATTTGCCGCCGCCGCTGCTCGGAAACAGCACCGGAAT	
	TGATTTCCAAGATGAACTGGACGAATTCTTCAAGAACGTG	
	TCCACTTCCATTCCCAACTTCGGAAGCCTGACACAGATCA	
	ACACCACCCTTCTCGACCTGACCTACGAGATGCTGAGCCT	
	TCAACAAGTGGTCAAGGCCCTGAACGAGAGCTACATCGAC CTGAAGGAGCTGGGCAACTATACCTACTACAACAAGTGGC	
	CGGACAAGATTGAGGAGATTCTGTCGAAAAATCTACCACAAGTGGC	
	TGAAAACGAGATCGCCAGAATCAAGAAGCTTATCGGCGA	
	AGCC	
IERS SO Full-	ATGGAAACCCCTGCCCAGCTGCTGTTCCTGCTGCTGCTGTG	23
ength Spike	GCTGCCTGATACCACCGGCAGCTATGTGGACGTGGGCCCC	
rotein	GATAGCGTGAAGTCCGCCTGTATCGAAGTGGACATCCAGC	
nucleotide, codon	AGACCTTTTTCGACAAGACCTGGCCCAGACCCATCGACGT	
ptimized)	GTCCAAGGCCGACGGCATCATCTATCCACAAGGCCGGACC	
	TACAGCAACATCACCATTACCTACCAGGGCCTGTTCCCAT ATCAAGGCGACCACGGCGATATGTACGTGTACTCTGCCGG	
	CCACGCCACCGGCACCACCACCCCAGAAACTGTTCGTGGCC	
	AACTACAGCCAGGACGTGAAGCAGTTCGCCAACGGCTTCG	
	TCGTGCGGATTGGCGCCGCTGCCAATAGCACCGGCACAGT	
	GATCATCAGCCCCAGCACCAGCGCCACCATCCGGAAGATC	
	TACCCCGCCTTCATGCTGGGCAGCTCCGTGGGCAATTTCA	
	GCGACGGCAAGATGGGCCGGTTCTTCAACCACACCCTGGT	
	GCTGCTGCCCGATGGCTGTGGCACACTGCTGAGAGCCTTC	
	TACTGCATCCTGGAACCCAGAAGCGGCAACCACTGCCCTG CCGGCAATAGCTACACCAGCTTCGCCACCTACCACACACC	
	CCGGCAATAGCTACACCAGCTTCGCCACCTACCACACACC CGCCACCGATTGCTCCGACGGCAACTACAACCCGGAACGCC	
	AGCCTGAACAGCTTCAAAGAGTACTTCAACCTGCGGAACT	
	GCACCTTCATGTACACCTACAATATCACCGAGGACGAGAT	
	CCTGGAATGGTTCCGCATCACCCAGACCGCCCAGGGCGTG	
	CACCTGTTCAGCAGCAGATACGTGGACCTGTACGGCGGCA	
	ACATGTTCCAGTTTGCCACCCTGCCCGTGTACGACACCATC	
	AAGTACTACAGCATCATCCCCCACAGCATCCGGTCCATCC	
	AGAGCGACAGAAAAGCCTGGGCCGCCTTCTACGTGTACAA	
	GCTGCAGCCCCTGACCTTCCTGCTGGACTTCAGCGTGGAC GGCTACATCAGACGGGCCATCGACTGCGGCTTCAACGACC	
	GGCTACATCAGACGGGCCATCGACTGCGGCTTCAACGACC TGAGCCAGCTGCACTGCTCCTACGAGAGCTTCGACGTGGA	
	AAGCGGCGTGTACAGCGTGTCCAGCTTCGAGGCCAAGCCT	
	AGCGGCAGCGTGGTGGAACAGGCTGAGGGCGTGGAATGC	
	GACTTCAGCCCTCTGCTGAGCGGCACCCCTCCCCAGGTGT	

TABLE 10-continued

train	Nucleic Acid Sequence	SEQ I NO:
	CCTGACCAAGCTGCTGAGCCTGTTCTCCGTGAACGACTTC	
	ACCTGTAGCCAGATCAGCCCTGCCGCCATTGCCAGCAACT	
	GCTACAGCAGCCTGATCCTGGACTACTTCAGCTACCCCCT	
	GAGCATGAAGTCCGATCTGAGCGTGTCCTCCGCCGGACCC	
	ATCAGCCAGTTCAACTACAAGCAGAGCTTCAGCAACCCTA	
	CCTGCCTGATTCTGGCCACCGTGCCCCACAATCTGACCAC	
	CATCACCAAGCCCCTGAAGTACAGCTACATCAACAAGTGC	
	AGCAGACTGCTGTCCGACGACCGGACCGAAGTGCCCCAGC TCGTGAACGCCAACCAGTACAGCCCCTGCGTGTCCATCGT	
	GCCCAGCACCGTGTGGGAGGACGGCGACTACTACAGAAA	
	GCAGCTGAGCCCCCTGGAAGGCGGCGGATGGCTGGTGGCT	
	TCTGGAAGCACAGTGGCCATGACCGAGCAGCTGCAGATG	
	GGCTTTGGCATCACCGTGCAGTACGGCACCGACACCAACA	
	GCGTGTGCCCCAAGCTGGAATTCGCCAATGACACCAAGAT	
	CGCCAGCCAGCTGGGAAACTGCGTGGAATACTCCCTGTAT	
	GGCGTGTCCGGACGGGGCGTGTTCCAGAATTGCACAGCAG	
	TGGGAGTGCGGCAGCAGAGATTCGTGTACGATGCCTACCA	
	GAACCTCGTGGGCTACTACAGCGACGACGGCAATTACTAC	
	TGCCTGCGGGCCTGTGTGTCCGTGCCCGTGTCCGTGATCTA	
	CGACAAAGAGACAAAGACCCACGCCACACTGTTCGGCTCC CTCCCCCTCCCACACTGCCCCCCCCCC	
	GTGGCCTGCGAGCACATCAGCTCCACCATGAGCCAGTACT CCCGCTCCACCCGGTCCATGCTGAAGCGGAGAGATAGCAC	
	CTACGGCCCCCTGCAGACACCTGTGCGGATGTGTGCTGGGC	
	CTCGTGAACAGCTCCCTGTTTGTGGAAGATGCAAGCTGC	
	CCCTGGGCCAGAGCCTGTGTGCCCTGCCAGATACCCCTAG	
	CACCCTGACCCCTAGAAGCGTGCGCTCTGTGCCCGGCGAA	
	ATGCGGCTCGCCTCTATCGCCTTCAATCACCCCATCCAGGT	
	GGACCAGCTGAACTCCAGCTACTTCAAGCTGAGCATCCCC	
	ACCAACTTCAGCTTCGGCGTGACCCAGGAGTACATCCAGA	
	CCACAATCCAGAAAGTGACCGTGGACTGCAAGCAGTACGT	
	GTGCAACGGCTTTCAGAAGTGCGAACAGCTGCTGCGCGAG	
	TACGGCCAGTTCTGCAGCAAGATCAACCAGGCCCTGCACG	
	GCGCCAACCTGAGACAGGATGACAGCGTGCGGAACCTGTT	
	CGCCAGCGTGAAAAGCAGCCAGTCCAGCCCCATCATCCCT	
	GGCTTCGGCGGCGACTTTAACCTGACCCTGCTGGAACCTG TGTCCATCAGCACCGGCTCCAGAAGCGCCCAGATCCGCCAT	
	CGAGGACCTGCTGTTCGACAAGGGCCAGATCCGCCAT	
	GGCTACATGCAGGGCTACGACGATGCATGCAGCAGGGCC	
	CAGCCAGCGCCAGGGATCTGATCTGTGCCCCAGTATGTGGC	
	CGGCTACAAGGTGCTGCCCCCCTGATGGACGTGAACATG	
	GAAGCCGCCTACACCTCCAGCCTGCTGGGCTCTATTGCTG	
	GCGTGGGATGGACAGCCGGCCTGTCTAGCTTTGCCGCCAT	
	CCCTTTCGCCCAGAGCATCTTCTACCGGCTGAACGGCGTG	
	GGCATCACACAGGGGGGGGGGGGGGAGAACCAGAAGCTG	
	ATCGCCAACAAGTTTAACCAGGCACTGGGCGCCATGCAGA	
	CCGGCTTCACCACCACCAACGAGGCCTTCAGAAAGGTGCA	
	GGACGCCGTGAACAACGCCCAGGCTCTGAGCAAGCT GGCCTCCGAGCTGAGCAATACCTTCGGCGCCATCAGCGCC	
	TCCATCGGCGACATCATCCAGCGGCTGGACGTGCTGGAAC	
	AGGACGCCCAGATCGACCGGCTGATCAACGGCAGACTGA	
	CCACCCTGAACGCCTTCGTCGCACAGCAGCTCGTGCCGGAG	
	CGAATCTGCCGCTCTGTCTGCTCAGCTGGCCAAGGACAAA	
	GTGAACGAGTGCGTGAAGGCCCAGTCCAAGCGGAGCGGC	
	TTTTGTGGCCAGGGCACCCACATCGTGTCCTTCGTCGTGAA	
	TGCCCCCAACGGCCTGTACTTTATGCACGTGGGCTATTACC	
	CCAGCAACCACATCGAGGTGGTGTCCGCCTATGGCCTGTG	
	CGACGCCGCCAATCCTACCAACTGTATCGCCCCCGTGAAC	
	GGCTACTTCATCAAGACCAACAACACCCGGATCGTGGACG	
	AGTGGTCCTACACAGGCAGCAGCTTCTACGCCCCCGAGCC	
	CATCACCTCCCTGAACACCAAATACGTGGCCCCCCAAGTG	
	ACATACCAGAACATCTCCACCAACCTGCCCCCTCCACTGC TGGGAAATTCCACCGGCATCGACTTCCAGGACGAGCTGGA	
	TGGGAAATTCCACCGGCATCGACTTCCAGGACGAGCTGGA CGAGTTCTTCAAGAACGTGTCCACCTCCATCCCCAAGTTCG	
	GCAGCCTGACCCAGATCAACACCACCACCTGGCAGCCTGAC	
	CTACGAGATGCTGTCCCTGCAACAGGTCGTGAAAGCCCTG	
	AACGAGAGCTACATCGACCTGAAAGAGCTGGGGAACTAC	
	ACCTACTACAACAAGTGGCCTTGGTACATTTGGCTGGGCT	
	TTATCGCCGGCCTGGTGGCCCTGGCCCTGTGCGTGTTCTTC	
	ATCCTGTGCTGCACCGGCTGCGGCACCAATTGCATGGGCA	
	AGCTGAAATGCAACCGGTGCTGCGACAGATACGAGGAAT	

TABLE 10-continued

Strain	Nucleic Acid Sequence	SEQ NO :
;	Betacoronavirus mRNA Sequences	
gb KJ156934.1 : 21405-2546	6 AUGAUACACUCAGUGUUUCUACUGAUGUUCUUGUUAAC	65
Middle	ACCUACAGAAAGUUACGUUGAUGUAGGGCCAGAUUCUG	00
East respiratory	UUAAGUCUGCUUGUAUUGAGGUUGAUAUACAACAGACC	
syndrome	UUCUUUGAUAAAACUUGGCCUAGGCCAAUUGAUGUUUC	
coronavirus	UAAGGCUGACGGUAUUAUAUACCCUCAAGGCCGUACAU	
isolate	AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCCU	
Riyadh 14 2013,	AUCAGGGAGACCAUGGUGAUAUGUAUGUUUACUCUGCA	
spike protein	GGACAUGCUACAGGCACAACUCCACAAAAGUUGUUUGU	
(nucleotide)	AGCUAACUAUUCUCAGGACGUCAAACAGUUUGCUAAUG	
,	GGUUUGUCGUCCGUAUAGGAGCAGCUGCCAAUUCCACUG	
	GCACUGUUAUUAUUAGCCCAUCUACCAGCGCUACUAUAC	
	GAAAAAUUUACCCUGCUUUUAUGCUGGGUUCUUCAGUU	
	GGUAAUUUCUCAGAUGGUAAAAUGGGCCGCUUCUUCAA	
	UCAUACUCUAGUUCUUUUGCCCGAUGGAUGUGGCACUU	
	UACUUAGAGCUUUUUAUUGUAUUCUAGAGCCUCGCUCU	
	GGAAAUCAUUGUCCUGCUGGCAAUUCCUAUACUUCUUU	
	UGCCACUUAUCACACUCCUGCAACAGAUUGUUCUGAUGG	
	CAAUUACAAUCGUAAUGCCAGUCUGAACUCUUUUAAGG	
	AGUAUUUUAAUUUACGUAACUGCACCUUUAUGUACACU	
	UAUAACAUUACCGAAGAUGAGAUUUUAGAGUGGUUUGG	
	CAUUACACAAACUGCUCAAGGUGUUCACCUCUUCUCAUC	
	UCGGUAUGUUGAUUUGUACGGCGGCAAUAUGUUUCAAU	
	UUGCCACCUUGCCUGUUUAUGAUACUAUUAAGUAUUAU	
	UCUAUCAUUCCUCACAGUAUUCGUUCUAUCCAAAGUGAU	
	AGAAAAGCUUGGGCUGCCUUCUACGUAUAUAAACUUCA	
	ACCGUUAACUUUCCUGUUGGAUUUUUCUGUUGAUGGUU	
	AUAUACGCAGAGCUAUAGACUGUGGUUUUAAUGAUUUG	
	UCACAACUCCACUGCUCAUAUGAAUCCUUCGAUGUUGAA	
	UCUGGAGUUUAUUCAGUUUCGUCUUUCGAAGCAAAACC	
	UUCUGGCUCAGUUGUGGAACAGGCUGAAGGUGUUGAAU	
	GUGAUUUUUCACCUCUUCUGUCUGGCACACCUCCUCAGG	
	UUUAUAAUUUCAAGCGUUUGGUUUUUACCAAUUGCAAU	
	UAUAAUCUUACCAAAUUGCUUUCACUUUUUUCUGUGAA	
	UGAUUUUACUUGUAGUCAAAUAUCUCCAGCAGCAAUUG	
	CUAGCAACUGUUAUUCUUCACUGAUUUUUGGAUUAUUUU	
	UCAUACCCACUUAGUAUGAAAUCCGAUCUCAGUGUUAG	
	UUCUGCUGGUCCAAUAUCCCAGUUUAAUUAUAAACAGU	
	CCUUUUCUAAUCCCACAUGUUUGAUCUUAGCGACUGUUC	
	CUCAUAACCUUACUACUAUUACUAAGCCUCUUAAGUACA	
	GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU	
	CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA	
	CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA	
	AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG	
	AAGGUGGUGGCUGGCUUGUUGCUAGUGGCUCAACUGUU	
	GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA	
	AGCUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA	
	UUAGGCAAUUGCGUGGAAUAUUCCCUCUAUGGUGUUUC	
	GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG	
	UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU	
	UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG	
	UCUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU	
	AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU	
	AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA	
	AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA	
	UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU	
	CCUAGGACUUGUUAAUUCCUCUUUGUUCGUAGAGGACU	
	GCAAGUUGCCUCUCGGUCAAUCUCUCUGUGCUCUUCCUG	
	ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG	
	UGCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU	
	CAUCCCAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU	
	UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA	
	CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU	
	GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA	
	GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU	
	CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC	
	AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA	
	AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU	
	GACUUUAAUUUGACACUUCUAGAACCUGUUUCUAUAUC	
	UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU	
	UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU	
	AUGCAAGGUUACGAUGAUUGUAUGCAGCAAGGUCCAGC	

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TABLE 10-continued

Betacoronavirus Nucleic Acid Sequence		
Strain	Nucleic Acid Sequence	SEQ ID NO:
Strain	Nucleic Acid Sequence AUCAGCUCGUGAUUAUUUGUGUGCUCAAUAUGUGGCUG GUUAUAAAGUAUUACUUCAUCUUUGCUUGGAUGUUAAUAUG GAAGCCGCGUAUACUUCAUCUUUGCUUGGAGCAUAGCA GGUGUUGGCUGGACUGCUGCUUAUCCUCUUUGCUGCU AUUCCAUUUGCACAGAGUAUYUUUUAUAGGUUAAACGG UGUUGGCAUGCACAGAGUUCUUUCAGAGAACCAAA AGCUUAUUCCCAUACAGUUCUUUCAGAGAACCAAA AGCUUAUUCACGACUUCAUACAACUAAUGAAGCUUUUCG GAAGGUUCAGGAAUCAACUAAUGAAGCUUUUCG GAAGGUUCCGCCUCUUUGAGACAACACUAAUGCACAGGCUC UAUCCAAAUUAGCUGUCGAACACACUAAUACUUUUGGU GCUAUUUCCGCAUCAUAAGGCCCCAAAUAGACAGACUUAU UAAUGGCGUUUCGAUCAAACCUAAUGACUUUUGGU GAUGUUCCGAAUAAGUCAUACAACGACUUAU UAAUGGCGUUUGGACAACACUAAAUGACUUUUGUUGCAUGCC AAUUGGCCGUUUGGAUUAAUGAGUGUCCAAGGCA AAGCUUUGUUGUUGUAAAUGCCCUAAGGCACACAU AUUGGCUCUUUGUUGUUAAAUGCCCUAAGGCACACAU AUUGUUCUUUUGUUGUUAAAUGCCCCUAAUGGCUUUA CUUUAUUGUUGUUGUUAAAUGCCCUUUUGCGAUGACCUAU UUAAUACAAUAACCUACUUUUUGCGAUGACUAACC AAAACUUUUUUGUUGUUGUUGUUGAUAGGUGGCCAUUUUU AUACUAAUAACACUAGGUUUGUCCUUCAAGAGUUGGUCAU UUUUUCAAUAAUAACCUACUUUCAAAGAUUGUUGAUUAGCUUUUUUUU	
MERS S FL SPIKE 2cEMC/2012 (XBaI change(U to G)) (nucleotide)	UACGAGGAAAACUUAAGUGUAAUCGUUGUGUGUAUAA UACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGU UCACUAA AUGAUACACUCAGUCUUCACUCGAUGUUCUUCUUGUUAAC ACCUACAGAAAGUUACGUUGAUGUAGGUCCUUCUUCUU UUAAGUCUGCUUGUAUUGACGUUGAUGUACAACAGACU UUCUUUGAUAAAACUUUGCCUAAGCCCGUACAU AUUCUAACAUAACUAUCACUUAUCAAGGUCUUUUUCCU AUCAGGAGACCAUGGUGUAUAUACAACAGCUUUUUCCU AUCAGGAGACCAUGUUAUCACUUAUCAAGGUCUUUUUCCU AUCAGGAGACCAUGUUAUCACUUAUCAAGGUCUUUUUCCU GGACAUGCUACAGUCACACUCACAAAAGUUUUCACUGCA GGACAUGCUACAGUCACAACUCCACAAAAGUUUUCACUUGCA GGUUUGUUCGUCCGUAUAGAGCUGCAAUUCACUUG GACAUGUUAUUAUAGCCCUCUAACAGUUUUCACUUG GAAAAAUUUACCCUGCUUUUAUGCGGGUUCUUCAGUU GGUAAUUUCUCAGAUGUAAAAUGGGCCGCUUCUUCAA UCAUACUCUAGUUCUUUUGCCGAUGGAUGUGGACUUUUAGG GAAUUUUCUCAGAUGUGAAAAUGGGCCGCUUCUUCAA UCAUACUCUAGUUCUUUUGCUGGAUGUGGACUUUUAGG CAAUUACAUUGUCCUGCUGCAACAGAUUCUUUUUUU UGCCACUUUUUAUUGUAACGGCGCCUCUUUUAAGG CAAUUACAUUGUCCUGCUGCAACAGAUUGUUCUGAUGG AGUAUUUUAAUUUACGUAACGCGCGCUUCUUAAGG CAAUUACAAUGGUAUUUAUGUAACUUCUUU UGCCACCUUAUCACACUCUCAAGUUUUAAGG CAUUACAAUUGUCCUGCUGCAACAGAUUUUUAAGG AGUAUUUUAAUUUACGUAACGCGCGCCUCUUCAAU UUGCCACCUUACGUCAAGGUGUUCAACUUUUAAGG CAUUACACUGUCUCAAGGUGUUCAACUUUUAAGG CAUUACACUGUCUCAAGGUGUUCACCUUUUAAGG CAUUACACUUGCCUCAAGGUGUUCACCUUUUCAAU UUGCCACCUUGCUCAAGGUGUUCACCUCUUCCAUC UCGGUAUGUGGCUGCCUUCUACGUAUUAAAGUAUUAA UUGCCACUUGCCUCAAGGUGUUCACUUCUCAUCAAU UUGCGACUUGGCUGCUUUCAGUUUUAAAGUGUU AUAAACUUCCCUCUACGUAUUAAAGUGUUCAAUGAU AUAUACGCAGGCUAUAGAUUCUUCGUUCAAUGUU AUAUACCUCCUCUCAUAGAUUCUUCGAUGUUGAA UCUGGAGUUAUUCAGUUUCAGUUUUAAAGUGUU AUAUAACUUCCUCUUCGUUCUACGUUUCAAUGUUGAA UCUGGAGUUAUUCAGUUUCGUCUUCGAAGGGUGUAAACUUCA UUCUGGCCACUUCUUCGUCUUCGAAGGUGUUGAA UUCUACACUCCUCUUCGGCACACCUCCUCAGG UUUAUAAAUUUCACUUUCGUUUCG	66

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TABLE 10-continued Betacoronavirus Nucleic Acid Sequence

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GCUAUAUUAACAAGUGCUCUCGUCUUCUUUCUGAUGAU CGUACUGAAGUACCUCAGUUAGUGAACGCUAAUCAAUA	
	CUCACCCUGUGUAUCCAUUGUCCCAUCCACUGUGUGGGA	
	AGACGGUGAUUAUUAUAGGAAACAACUAUCUCCACUUG	
	AAGGUGGUGGCUUGCUUGUUGCUAGUGGCUCAACUGUU	
	GCCAUGACUGAGCAAUUACAGAUGGGCUUUGGUAUUAC AGUUCAAUAUGGUACAGACACCAAUAGUGUUUGCCCCA	
	AGUUGAAUUUGCUAAUGACACAAAAAUUGCCUCUCAA	
	UUAGGCAAUUGCGUGGAAUAUUCCCUCUAUGGUGUUUC	
	GGGCCGUGGUGUUUUUCAGAAUUGCACAGCUGUAGGUG	
	UUCGACAGCAGCGCUUUGUUUAUGAUGCGUACCAGAAU UUAGUUGGCUAUUAUUCUGAUGAUGGCAACUACUACUG	
	UUUGCGUGCUUGUGUUAGUGUUCCUGUUUCUGUCAUCU	
	AUGAUAAAGAAACUAAAACCCACGCUACUCUAUUUGGU	
	AGUGUUGCAUGUGAACACAUUUCUUCUACCAUGUCUCA	
	AUACUCCCGUUCUACGCGAUCAAUGCUUAAACGGCGAGA	
	UUCUACAUAUGGCCCCCUUCAGACACCUGUUGGUUGUGU CCUAGGACUUGUUAAUUCCUCUUUGUUCGUAGAGGACU	
	GCAAGUUGCCUCUUGGUCAAUCUCUCUGUGCUCUUCCUG	
	ACACACCUAGUACUCUCACACCUCGCAGUGUGCGCUCUG	
	UUCCAGGUGAAAUGCGCUUGGCAUCCAUUGCUUUUAAU	
	CAUCCUAUUCAGGUUGAUCAACUUAAUAGUAGUUAUUU	
	UAAAUUAAGUAUACCCACUAAUUUUUCCUUUGGUGUGA CUCAGGAGUACAUUCAGACAACCAUUCAGAAAGUUACU	
	GUUGAUUGUAAACAGUACGUUUGCAAUGGUUUCCAGAA	
	GUGUGAGCAAUUACUGCGCGAGUAUGGCCAGUUUUGUU	
	CCAAAAUAAACCAGGCUCUCCAUGGUGCCAAUUUACGCC	
	AGGAUGAUUCUGUACGUAAUUUGUUUGCGAGCGUGAAA AGCUCUCAAUCAUCUCCUAUCAUACCAGGUUUUGGAGGU	
	GACUJUJAAUJUGACACUUCUGGAACCUGUJUCUAUAUC	
	UACUGGCAGUCGUAGUGCACGUAGUGCUAUUGAGGAUU	
	UGCUAUUUGACAAAGUCACUAUAGCUGAUCCUGGUUAU	
	AUGCAAGGUUACGAUGAUUGCAUGCAGGCAAGGUCCAGC	
	AUCAGCUCGUGAUCUUAUUUGUGCUCAAUAUGUGGCUG GUUACAAAGUAUUACCUCCUCUUAUGGAUGUUAAUAUG	
	GAAGCCGCGUAUACUUCAUCUUUGCUUGGCAGCAUAGCA	
	GGUGUUGGCUGGACUGCUGGCUUAUCCUCCUUUGCUGCU	
	AUUCCAUUUGCACAGAGUAUCUUUUAUAGGUUAAACGG	
	UGUUGGCAUUACUCAACAGGUUCUUUCAGAGAACCAAA AGCUUAUUGCCAAUAAGUUUAAUCAGGCUCUGGGAGCU	
	AUGCAAACAGGCUUCACUACAACUAAUGAAGCUUUUCA	
	GAAGGUUCAGGAUGCUGUGAACAACAAUGCACAGGCUC	
	UAUCCAAAUUAGCUAGCGAGCUAUCUAAUACUUUUGGU	
	GCUAUUUCCGCCUCUAUUGGAGACAUCAUACAACGUCUU GAUGUUCUCGAACAGGACGCCCAAAUAGACAGACUUAU	
	UAAUGGCCGUUUGACAACACUAAAUGCUUUUGUUGCAC	
	AGCAGCUUGUUCGUUCCGAAUCAGCUGCUCUUUCCGCUC	
	AAUUGGCUAAAGAUAAAGUCAAUGAGUGUGUCAAGGCA	
	CAAUCCAAGCGUUCUGGAUUUUGCGGUCAAGGCACACAU AUAGUGUCCUUUGUUGUAAAUGCCCCUAAUGGCCUUUA	
	CUUCAUGCAUGUUGGUUAUUACCCUAGCAACCACAUUGA	
	GGUUGUUUCUGCUUAUGGUCUUUGCGAUGCAGCUAACC	
	CUACUAAUUGUAUAGCCCCUGUUAAUGGCUACUUUAUU	
	AAAACUAAUAACACUAGGAUUGUUGAUGAGUGGUCAUA	
	UACUGGCUCGUCCUUCUAUGCACCUGAGCCCAUUACCUC CCUUAAUACUAAGUAUGUUGCACCACAGGUGACAUACCA	
	AAACAUUUCUACUAACCUCCCUCCUCCUCUUCUCGGCAA	
	UUCCACCGGGAUUGACUUCCAAGAUGAGUUGGAUGAGU	
	UUUUCAAAAAUGUUAGCACCAGUAUACCUAAUUUUGGU	
	UCCCUAACACAGAUUAAUACUACAUUACUCGAUCUUACC	
	UACGAGAUGUUGUCUCUCAACAAGUUGUUAAAGCCCU UAAUGAGUCUUACAUAGACCUUAAAGAGCUUGGCAAUU	
	AUACUUAUUACAACAAAUGGCCGUGGUACAUUUGGCUU	
	GGUUUCAUUGCUGGGCUUGUUGCCUUAGCUCUAUGCGU	
	CUUCUUCAUACUGUGCUGCACUGGUUGUGGCACAAACUG	
	UAUGGGAAAACUUAAGUGUAAUCGUUGUUGUGAUAGAU ACGAGGAAUACGACCUCGAGCCGCAUAAGGUUCAUGUUC	
	ACGAGGAADACGACCUCGAGCCGCADAAGGUUCAUGUUC	
Novel_MERS_S2_subunit_trimeric	AUGAUCCACUCCGUGUUCCUCCUCAUGUUCCUGUUGACC	67
vaccine	CCCACUGAGUCAGACUGCAAGCUCCCGCUGGGACAGUCC	
(nucleotide)	CUGUGUGCGCUGCCUGACACUCCUAGCACUCUGACCCCA	
	CGCUCCGUGCGGUCGGUGCCUGGCGAAAUGCGGCUGGCC UCCAUCGCCUUCAAUCACCCAAUCCAAGUGGAUCAGCUG	
	CONTRACTOR CALCENATION CALCUNATION CALCUNA	

TABLE 10-continued

train	Nucleic Acid Sequence	SEQ NO :
	•	
	UCGUUCGGGGUCACCCAGGAGUACAUCCAGACCACAAUU CAGAAGGUCACCGUCGAUUGCAAGCAAUACGUGUGCAAC	
	GGCUUCCAGAAGUGCGAGCAGCUGCUGAGAGAAUACGG	
	GCAGUUUUGCAGCAAGAUCAACCAGGCGCUGCAUGGAGC	
	UAACUUGCGCCAGGACGACUCCGUGCGCAACCUCUUUGC	
	CUCUGUGAAGUCAUCCCAGUCCUCCCCAAUCAUCCCGGG	
	AUUCGGAGGGGACUUCAACCUGACCCUCCUGGAGCCCGU	
	GUCGAUCAGCACCGGUAGCAGAUCGGCGCGCUCAGCCAU	
	UGAAGAUCUUCUGUUCGACAAGGUCACCAUCGCCGAUCC GGGCUACAUGCAGGGAUACGACGACUGUAUGCAGCAGG	
	GGGCUACAUGCAGGGAUACGACGACUGUAUGCAGCAGG GACCAGCCUCCGCGAGGGACCUCAUCUGCGCGCAAUACG	
	UGGCCGGGUACAAAGUGCUGCCUCCUCUGAUGGAUGUG	
	AACAUGGAGGCCGCUUAUACUUCGUCCCUGCUCGGCUCU	
	AUCGCCGGCGUGGGGUGGACCGCCGGCCUGUCCUCCUUC	
	GCCGCUAUCCCCUUUGCACAAUCCAUUUUCUACCGGCUC	
	AACGGCGUGGGCAUUACUCAACAAGUCCUGUCGGAGAAC	
	CAGAAGUUGAUCGCAAACAAGUUCAAUCAGGCCCUGGG	
	GGCCAUGCAGACUGGAUUCACUACGACUAACGAAGCGUU	
	CCAGAAGGUCCAGGACGCUGUGAACAACAACGCCCAGGC GCUCUCAAAGCUGGCCUCCGAACUCAGCAACACCUUCGG	
	AGCCAUCAGCGCGAUCGGUCGGUGACAUAAUUCAGCGGCU	
	GGACGUGCUGGAGCAGGACGCCCAGAUCGACCGCCUCAU	
	CAACGGACGGCUGACCACCUUGAAUGCCUUCGUGGCACA	
	ACAGCUGGUCCGGAGCGAAUCAGCGGCACUUUCCGCCCA	
	ACUCGCCAAGGACAAAGUCAACGAAUGCGUGAAGGCCCA	
	GUCCAAGAGGUCCGGUUUCUGCGGUCAAGGAACCCAUAU	
	UAUGCACGUCGGCUACUACCCCGAGCAAUCAUAUCGAAGU GGUGUCCGCCUACGGCCUGUGCGAUGCCGCUAACCCCAC	
	UAACUGUAUUGCCCCUGUGAACGGAUAUUUUAUUAAGA	
	CCAACAACACCCGCAUUGUGGACGAAUGGUCAUACACCG	
	GUUCGUCCUUCUACGCGCCCGAGCCCAUCACUUCACUGA	
	ACACCAAAUACGUGGCUCCGCAAGUGACCUACCAGAACA	
	UCUCCACCAAUUUGCCGCCGCCGCUGCUCGGAAACAGCA	
	CCGGAAUUGAUUUCCAAGAUGAACUGGACGAAUUCUUC	
	AAGAACGUGUCCACUUCCAUUCCCAACUUCGGAAGCCUG	
	ACACAGAUCAACACCACCCUUCUCGACCUGACCUACGAG AUGCUGAGCCUUCAACAAGUGGUCAAGGCCCUGAACGAG	
	AUGUUGAGUUUGAGUUGAGUGUGGGUAAGGUUUGAGUAGG AGCUACAUCGACCUGAAGGAGCUGGGCAACUAUACCUAC	
	UACAACAAGUGGCCGGACAAGAUUGAGGAGAUUCUGUC	
	GAAAAUCUACCACAUUGAAAACGAGAUCGCCAGAAUCA	
	AGAAGCUUAUCGGCGAAGCC	
RS_S0_Full-	AUGGAAACCCCUGCCCAGCUGCUGCUGCUGCUGCUGCUG	68
ngth Spike	UGGCUGCCUGAUACCACCGGCAGCUAUGUGGACGUGGGC	
otein	CCCGAUAGCGUGAAGUCCGCCUGUAUCGAAGUGGACAUC	
ucleotide, codon	CAGCAGACCUUUUUCGACAAGACCUGGCCCAGACCCAUC	
timized)	GACGUGUCCAAGGCCGACGGCAUCAUCUAUCCACAAGGC	
	CGGACCUACAGCAACAUCACCAUUACCUACCAGGGCCUG UUCCCAUAUCAAGGCGACCACGGCGAUAUGUACGUGUAC	
	UCUGCCGGCCACGCCACCGGCACCACACCACACCACAGAAACUG	
	UUCGUGGCCAACUACAGCCAGGACGUGAAGCAGUUCGCC	
	AACGGCUUCGUCGUGCGGAUUGGCGCCCGCUGCCAAUAGC	
	ACCGGCACAGUGAUCAUCAGCCCCAGCACCAGCGCCACC	
	AUCCGGAAGAUCUACCCCGCCUUCAUGCUGGGCAGCUCC	
	GUGGGCAAUUUCAGCGACGGCAAGAUGGGCCGGUUCUU	
	CAACCACACCCUGGUGCUGCUGCCCGAUGGCUGUGGCAC	
	ACUGCUGAGAGCCUUCUACUGCAUCCUGGAACCCAGAAG	
	CGGCAACCACUGCCCUGCCGGCAAUAGCUACACCAGCUU CGCCACCUACCACACACCCGCCACCGAUUGCUCCGACGG	
	CAACUACAACCGGAACGCCAGCCUGAACAGCUUCAAAGA	
	GUACUUCAACCUGCGGAACUGCACCUUCAUGUACACCUA	
	CAAUAUCACCGAGGACGAGAUCCUGGAAUGGUUCGGCA	
	UCACCCAGACCGCCCAGGGCGUGCACCUGUUCAGCAGCA	
	GAUACGUGGACCUGUACGGCGGCAACAUGUUCCAGUUU	
	GCCACCCUGCCCGUGUACGACACCAUCAAGUACUACAGC	
	AUCAUCCCCCACAGCAUCCGGUCCAUCCAGAGCGACAGA	
	AAAGCCUGGGCCGCCUUCUACGUGUACAAGCUGCAGCCC CUGACCUUCCUGCUGGACUUCAGCGUGGACGGCUACAUC	
	CUGACCUUCCUGCUGGACUUCAGCGUGGACGGCUACAUC AGACGGGCCAUCGACUGCGGCUUCAACGACCUGAGCCAG	
	CUGCACUGCUCCUACGAGGCUUCGACGUGGAAAGCGGC	
	GUGUACAGCGUGUCCAGCUUCGAGGCCAAGCCUAGCGGC	
	AGCGUGGUGGAACAGGCUGAGGGCGUGGAAUGCGACUU	
	CAGCCCUCUGCUGAGCGGCACCCCUCCCCAGGUGUACAA	

TABLE 10-continued

		SEQ I
Strain	Nucleic Acid Sequence	NO :
	GACCAAGCUGCUGAGCCUGUUCUCCGUGAACGACUUCAC	
	CUGUAGCCAGAUCAGCCCUGCCGCCAUUGCCAGCAACUG	
	CUACAGCAGCCUGAUCCUGGACUACUUCAGCUACCCCCU	
	GAGCAUGAAGUCCGAUCUGAGCGUGUCCUCCGCCGGACC	
	CAUCAGCCAGUUCAACUACAAGCAGAGCUUCAGCAACCC	
	UACCUGCCUGAUUCUGGCCACCGUGCCCCACAAUCUGAC	
	CACCAUCACCAAGCCCCUGAAGUACAGCUACAUCAACAA	
	GUGCAGCAGACUGCUGUCCGACGACCGACCGAAGUGCC	
	CAUCGUGCCCAGCACCGUGUGGGAGGACGGCGACUACUA CAGAAAGCAGCUGAGCCCCCUGGAAGGCGGCGGAUGGCU	
	GGUGGCUUCUGGAAGCACAGUGGCCAUGACCGAGCAGCU	
	GCAGAUGGGCUUUGGCAUCACCGUGCAGUACGGCACCGA	
	CACCAACAGCGUGUGCCCCAAGCUGGAAUUCGCCAAUGA	
	CACCAAGAUCGCCAGCCAGCUGGGAAACUGCGUGGAAUA	
	CUCCCUGUAUGGCGUGUCCCGGACGGGGCGUGUUCCAGAA	
	UUGCACAGCAGUGGGAGUGCGGCAGCAGAGAUUCGUGU	
	ACGAUGCCUACCAGAACCUCGUGGGCUACUACAGCGACG	
	ACGGCAAUUACUACUGCCUGCGGGCCUGUGUGUCCGUGC	
	CCGUGUCCGUGAUCUACGACAAAGAGACAAAGACCCACG	
	CCACACUGUUCGGCUCCGUGGCCUGCGAGCACAUCAGCU	
	CCACCAUGAGCCAGUACUCCCGCUCCACCCGGUCCAUGC	
	UGAAGCGGAGAGAUAGCACCUACGGCCCCCUGCAGACAC	
	CUGUGGGAUGUGUGCUGGGCCUCGUGAACAGCUCCCUGU	
	UUGUGGAAGAUUGCAAGCUGCCCCUGGGCCAGAGCCUGU	
	GUGCCCUGCCAGAUACCCCUAGCACCCUGACCCCUAGAA	
	GCGUGCGCUCUGUGCCCGGCGAAAUGCGGCUGGCCUCUA	
	UCGCCUUCAAUCACCCCAUCCAGGUGGACCAGCUGAACU	
	CCAGCUACUUCAAGCUGAGCAUCCCCACCAACUUCAGCU	
	UCGGCGUGACCCAGGAGUACAUCCAGACCACAAUCCAGA	
	AAGUGACCGUGGACUGCAAGCAGUACGUGUGCAACGGC	
	UUUCAGAAGUGCGAACAGCUGCUGCGCGAGUACGGCCAG	
	UUCUGCAGCAAGAUCAACCAGGCCCUGCACGGCGCCAAC	
	CUGAGACAGGAUGACAGCGUGCGGAACCUGUUCGCCAGC	
	GUGAAAAGCAGCCAGUCCAGCCCCAUCAUCCCUGGCUUC	
	GGCGGCGACUUUAACCUGACCCUGCUGGAACCUGUGUCC	
	AUCAGCACCGGCUCCAGAAGCGCCAGAUCCGCCAUCGAG	
	GACCUGCUGUUCGACAAAGUGACCAUUGCCGACCCCGGC	
	UACAUGCAGGGCUACGACGAUUGCAUGCAGGAGGGCCCA	
	GCCAGCGCCAGGGAUCUGAUCUGUGCCCAGUAUGUGGCC	
	GGCUACAAGGUGCUGCCCCCCUGAUGGACGUGAACAUG	
	GAAGCCGCCUACACCUCCAGCCUGCUGGGCUCUAUUGCU	
	GGCGUGGGAUGGACAGCCGGCCUGUCUAGCUUUGCCGCC	
	GUGGGCAUCACACAACAGGUGCUGAGCGAGAACCAGAA	
	GCAGACCGGCUUCACCACCACCACGAGGCCUUCAGAAA	
	GGUGCAGGACGCCGUGAACAACACGCCCAGGCUCUGAG CAAGCUGGCCUCCGAGCUGAGCAAUACCUUCGGCGCCAU	
	CAGCGCCUCCAUCGGCGACAUCAUCCAGCGGCUGGACGU	
	GCUGGACAGGACGCCCAGAUCGACGGCUGGACGGCUGGACGG	
	CAGACUGAACAGGACGCCCAGAUCGACGGCUGAUCAACGG CAGACUGACCACCCCUGAACGCCUUCGUGGCACAGCAGCU	
	CGUGCGGAGCGAAUCUGCCGCUCUGUCUGCUCAGCUGGC	
	CAAGGACAAAGUGAACGAGUGCGUGAAGGCCCAGUCCA	
	AGCGGAGCGGCUUUUGUGGCCAGGGCACCCACAUCGUGU	
	CCUUCGUCGUGAAUGCCCCCAACGGCCUGUACUUUAUGC	
	ACGUGGGCUAUUACCCCAGCAACCACAUCGAGGUGGUGU	
	CCGCCUAUGGCCUGUGCGACGCCGCCAAUCCUACCAACU	
	GUAUCGCCCCCGUGAACGGCUACUUCAUCAAGACCAACA	
	ACACCCGGAUCGUGGACGAGUGGUCCUACACAGGCAGCA	
	GCUUCUACGCCCCCGAGCCCAUCACCUCCCUGAACACCA	
	UCGACUUCCAGGACGAGCUGGACGAGUUCUUCAAGAACG	
	UGUCCACCUCCAUCCCCAACUUCGGCAGCCUGACCCAGA	
	UCAACACCACUCUGCUGGACCUGACCUACGAGAUGCUGU	
	CCCUGCAACAGGUCGUGAAAGCCCUGAACGAGAGCUACA	
	UCGACCUGAAAGAGCUGGGGAACUACACCUACUACAACA	
	AGUGGCCUUGGUACAUUUGGCUGGGCUUUAUCGCCGGCC	
	NGENGGCCCNGGCCCNGNGCGNGNNCNNCANGCNGCA	
	GCACCGGCUGCGGCACCAAUUGCAUGGGCAAGCUGAAAU	
	GCAACCGGUGCUGCGACAGAUACGAGGAAUACGACCUGG	
	AACCUCACAAAGUGCAUGUGCAC	

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TABLE 11

		SEQ II
Strain	Amino Acid Sequence	NO:
gb KJ156934.1 : 21405-25466 Middle East respiratory syndrome coronavirus isolate Riyadh_14_2013, spike protein (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVHIGAAANS TGTVIISPSTSATIRKIYPAPMLGSSVGNFSDGKMGRPFNHTL VLLPDGCGTLLRAFYCILEPRSGNHCPACNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQPATLPVVDTIKYTSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQABGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFt CSGISPAAIASNCYSSILDYFSYVBLSMKSDLSVSSAGFISQFN YKQSFSNPTCLILATVPHNLTTITKPLKYSYINKCSRLSDDRT EVPQLVNNQYSPCVSIVPSTWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGMCVEYSLYGVSGRGVFQNCTAVGVRQQFFVDA YQNLVGYYSDGNYYCLRACVSVPSVIDVERTTHATLFG SVACHHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCULGL VNSSLFVEDCKLDLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAPNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQPCSKINGALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDPNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADFGYMQGYDDCMQQGPASARDLICAQVVA GYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTAGLSSFAAIFF AQSIFYLLNGVGITQQUSENQKLIANKNQALGAMQTGFTT TNEAFrKVQDAVNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQUVRSESAALSAQLA KDKVNECVKAQSKRSGFCQGTHIVSFVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVNGQFIKTNNTRIV DEWSYTGSSFYAPEPITSLNKKVVAPQVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIPNFSGTQUTISTNLPPLLG VSYCALNESYIDLKELGNYTYNKWPWIWLGFIAGLVA LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEVDLEPHKV HVH	24
MERS S FL SPIKE 2cEMC/2012 (XBaI change(T to G)) (amino acid)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WRPPIDVSKADGIIYPQGRTYSNITITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAPMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCLLEPRSGNHCPACNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYPNLRNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGMMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVBSGVYSVSSFEAKPSGSVVEQABGV ECDFSPLLSGTPPQVYNFKRLVFTNCNYNLTKLLSLFSVNDFT CSQISPAATASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQFN YKQSFSNFTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVFSTWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQFFVDA YQNLVGYYSDDGNYYCLRACVSVPVSVIDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLDLGQSLCALPDTPSTITPRSVRSVPGBMRLA SIAFNHPIQVDQLNSSYFKLSIPTNFFGVTQEYIQTTIQKVTV DCKQVVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADFGYMQGYDCMQGPASARDLCAQYVA GYKVLPPLMVNMEAAYTSSLLGSLAVFFALGAMQTGFT THEAFQKVQDAVNNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQDAQIDRLINGRLTTLNAFVAQQLVRSESAALSAQLA KDKVNECVKAQSKRSGCGQGTHIVSFVNAPNGLYFMW GYYPSNHIEVSAYGLCDAANPTNCIAPVNGYFIKTNNTRIV DEKSYTGSSFYAPEPITSLINFFGSLTQINTTILDLTYEMLS LQQVVALNESYIDLKELGNYTYNKWPYIWLGFIAGLVA LALCVFFILCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	25
Novel_MERS_S2_subunit_trimeric vaccine (amino acid)	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSVR SVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYI QTTIQKVTVDCKQYVCNGFQKCEQLLREYGQFCSKINQALH GANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSIS TGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASAR DLICAQYYAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTA GLSSFAAIPFAQSIFYRLMGVGITQQVLSENQKLIANKFNQAL	26

Betacoronavirus Amino Acid Sequences		
Strain	Amino Acid Sequence	SEQ ID NO:
	GAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTFG AISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRS ESAALSAQLAKDKVNECVKAQSKRSGFCGQGTHIVSFVVNA PNGLYFMHVGYYPSNHIEVVSAYGLCDAANPTNCIAPVNGY FIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNI STNLPPPLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTL LDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWPDKIE EILSKIYHIENEIARIKKLIGEA	
Isolate Al- Hasa_1_2013 (NCBI accession #AGN70962)	MIHSVFLLMFLLTPTESYVDVGPDSVKSACIEVDIQQTFFDKT WPRIDVSKADGIIYPQGRTYSNITIITYQGLFPYQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAPMLGSSVGNFSDGKMGRFFNHTL VLLPDGCGTLLRAFYCILBFRSGNHCPACMSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLFNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVVDTIKYYSII PHSIRSIQSDRKAWAAFYVYKLQPLTFLLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFEAKPSGSVVEQAEGV ECDFSPLLSGTPQVYNFKRLVFTNCNYNLTKLSLFSVNDFT CSQISPAAIASNCYSSLIDYFSYDLSMKSDLSVSSAGPISQFN YKQFFSNFTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTVWEDGDYYRKQLSPLEGGGW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLYGVSGRGVFQNCTAVGVRQQRFVYDA YQNLVGYSDDGNYYCLRACVSVPSVIVDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLCALPDTPSTLTPRSVRSVPGEMRLA SIAPNHPIQVDQLNSSYFKLSIPTNFSFGVTQEYIQTTIQKVTV DCKQYVCNGFQKCEQLLREYGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGDDNLTLLEPVSISTGSRSARSAI EDLLFDKVTIADFGYQQTDCMQQGPASARDLICAQYVA GYKVLPPLMDVNMEAAYTSSLGSIAGVGNTAGLSSFAAIFF AQSIFYRLMGVGITQQVLSENQKLIANKFNQALGANQTGFT TNEAFRKVQDAVNNAQALSKLASELSNTFGAISASIGDIIQR LDVLEQVAQSKRSGFCQGTHIVSFVNAPNGLYFMHV GYYFSNHIEVVSAYGLCDANPTNCIAPVMGYFIKNNTRIV DEWSYTGSSFYAPEPITSLNTKYVAPHVTYQNISTNLPPPLLG NSTGIDFQDELDEFFKNVSTSIDFNSLSTQINTTLLDFYELS LQQVVKALNESYIDLKELGNYTYNKWPWYIWLGFIAGLVA LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	27
Middle East respiratory syndrome coronavirus S protein UniProtKB- R9UQ53	MIHSVFLLMPLLTPTESYVDVGPDSVKSACIEVDIQQTFPDKT WPRPIDVSKADGIIYPQGRTYSNITITYQGLPPVQGDHGDMY VYSAGHATGTTPQKLFVANYSQDVKQFANGFVVRIGAAANS TGTVIISPSTSATIRKIYPAPMLGSSVGNFSDGKMGRFPNHTL VLLPGCGTLLRAFYCILEPRSGNHCPAGNSYTSFATYHTPA TDCSDGNYNRNASLNSFKEYFNLFNCTFMYTYNITEDEILEW FGITQTAQGVHLFSSRYVDLYGGNMFQFATLPVYDTIKYYSII PHSIRSIQSDRKAMAAFYYYKLQPLTFLDFSVDGYIRRAIDC GFNDLSQLHCSYESFDVESGVYSVSSFAKPSGSVVEQAEGV ECDFSPLLSGTPPQYNFRRLVFTNCNYNLTKLLSLFSVNDFT CSQISPAAIASNCYSSLILDYFSYPLSMKSDLSVSSAGPISQPN YKQFFSNFTCLILATVPHNLTTITKPLKYSYINKCSRLLSDDRT EVPQLVNANQYSPCVSIVPSTWEDGDYYRKQLSPLEGGBW LVASGSTVAMTEQLQMGFGITVQYGTDTNSVCPKLEFANDT KIASQLGNCVEYSLIGVSGRGVFQNCTAVGVRQQFFVDA YQNLVGYYSDDGNYYCLRACVSVPVSVIYDKETKTHATLFG SVACEHISSTMSQYSRSTRSMLKRRDSTYGPLQTPVGCVLGL VNSSLFVEDCKLPLGQSLREVGQFCSKINQALHGANLRQDDS VRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSISTGSRSARSAI EDLLFPKVQDANNNAQALSKLASELSNTFGAISASIGDIQR LVASGSTVAMTSQLGLREYGQFCSKINQALGAMQTGFTT TNEAFRKVQDAVNNAQALSKLASELSNTFGAISASIGDIQR LDVLGYYSDGGTUQVSENQKLIANKFNQALGAMQTGFTT TNEAFRKVQDAVNNAQALSKLASELSNTFGAISASIGDIQR LDVLFYSNGGTQQVLSENQKLIANKFNQALGAMQTGFTT TNEAFRKVQDAVNNAQALSKLASELSNTFGAISASIGDIQR LDVLEQDAQIDRLINGRITTLNAFVAQLVRSESAALSAQLA KDKVNECVKAQSKRSGFCQGTHIVSFVNAPNGLYFMHV GYYPSNHIEVVSAYGLCDAANPTNCIAPVMGYFIKTNNTRIV DEWSYTGSSFYAPEPITSLNYVNAPHYQNISTNLPPPLLG NSTGIDFQDELDEFFKNYSTSIPNFGSLQINTTLLDLTYEMLS LQQVVKALMESYIDLKELGNYTYNKWPWIWLGFIAGLVA	28

TABLE 11-continued

Betacoronavirus Amino Acid Sequences		
Strain	Amino Acid Sequence	SEQ II NO:
	LALCVFFILCCTGCGTNCMGKLKCNRCCDRYEEYDLEPHKV HVH	
Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus) Spike glycoprotein UniProtKB- P59594	MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYY PDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTGONPVIPFKDG IYFAATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRAC NFELCDNFFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAFSLD VSEKSGNFKHLREFVFKNKDGFLYVYKGYQFIDVVRDLPSGF NTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVGYL KPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGI YQTSNFRVVPSGDVVRPNITNLCPFGEVFNATKFPSVYAWE RKKISNCVADYSULYNSTFFSTFKCYGVSATKLNDLCFSNVY ADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCVLAW NTRNIDATSTGNYNYKYRYLRHGKLRPFERDISNVPFSPDGK PCTPPALNCYWPLNDYGFYTTGIGYQPYRVVUSFELLNAP ATVCGFKLSTDLIKNQCVNFNENGLTGTGVLTPSSKRFQPFQ QFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSE VAVLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAG CLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYT MSLGADSSIAYSNNTIAIFTNFSISITTEVMPVSMAKTSVDCN MYICGDSTECANLLQYGSFCTQLNRALSGIAAEQDRNTREV FAQVKQWKKTPTLKYFGGFNFSQILPDFLKPTKRSFIEDLLFN KVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLL TDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYR FNGIGUTQNVLYENXGLANGFKAISQIQESLTTTSTLGKL QDVNQNAQALNTLVKQLSNFGAISSVLNDILSRLDKVEAE VQLDRLITGRLQSLQTVTVQLLRAAEIRASANLAATKMSEC VLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQER NFTTAPAICHEGKAYFPREGVFVPNGTSWFITQNFFSQIITT DNTFVSGNCDVIGIINNTVDPLQPELDSFKEELDKYFKNH TSPDVDLGDISGINASVVNIQKEIDRLNEVFKHH TSPDVDLGDISGINASVVNIQKEIDRLNESKLDLJESLDLQE LGKYEQYIKWPYVLGFIAGLIAIVMVTILLCCMTSCCSCL KGACSCGSCCKFDEDDSEPVLKGVKLHYT	29
Human coronavirus OC43 (HCoV-OC43) Spike glycoprotein UniProtKB- P36334	MFLILLISLPTAFAVIGDLKCTSDNINDKDTGPPPISTDTVDVT NGLGTYVVLDRVYLNTTLFLNGYYPTSGSTYRNMALKGSVL LSRLWFKPPFLSDFINGIFAKVKNTKVIKDRVMYSEFPAITIGS TFVNTSYSVVVQPRTINSTQDGDNKLQGLLEVSVCQYNMCE YPQTICHPNLGNHRKELMHLDTGVVSCLYKRNFTYDVNAD YLYPHFYQEGGTFYAYFTDTGVVTKFLFNVYLGMALSHYV MPLTCNSKLTLEYWVTPLTSRQYLLAFNQDGIIPNAEDCMSD FMSEIKCKTQSIAPPTGVYELNGYTVQPIADVYRKKPNLPNC NIEAWLMDKSVPSPLNMERKTFSNCNFINSSLMSFIQADSFT CNNIDAKIYGMCFSSITIDKFAIPNGRKUDLQLGNLGYLQSF NYRIDTTATSCQLYYNLPAANVSVSRPNSTWNKRFGFIEDS VFKPRPAGVLTNHDVVYAQHCFKAPKNFCPCKLNGSCVGSG PGKNNGIGTCPAGTNYLTCDNLCTPQPITFTGTYKCPQTKSL VGIGEHCSGLAVKSDYCGGNSCTCRPQAFLGWSADSCLQED KCNIFANFILHDVNSQLLYSNGNLYGFRDYIJINRTFMI RSCYSGRVSAPHANSEPALLFRNIKCNYVFINSLTRQLQFI NYFDSYLGCVNAYNSTAISVQTCDLTVGSGYCVDYSKNRR SRGAITTGYRFTNFEPFTVNSVNDSLEPVGGLYHQIPSEFTIG NMVEFIQTSSPKVTIDCAAFVCGDYAACKSQLVEYGSFCDNI NAILTEVNELLDTQLQVANSLMNGVTLSTKLKDGVFRNVD DINFSPVLGCLGSECSKASSRSAIEDLLFDKVKLSDVGFVEAY NNCTGGAEIRDLICVQSYKGIKVLPPLLSENQISGYTLAATSA SLFPPWTAAAGVPFYLNVQYRINGLAVQSSRINFCGNGNHIIS LVQNAPYGLYFINFEPFTVKVTARVSPGLCIAGDRGHAVS QQLSDSTLVKFSAQAMEKVNECVKSQSSRINFCGNGNHIIS LVQNAPGLYFIHFSYVPTKYVTARVSPGLCIAGDRGIAPKS GYFVNVNNTWMYTGSGYYPEPITENNVVMSTCAVNYTK APYVMLNTSIPNLPDFKEELDQWFKNQTSVAPDLSLDYINVT FLDLQVEMNRLQEAIKVLNQSYINLKDIGTYEYVKWPWVV WLLICLAGVAMLVLEFFICCCTGGGTSCFKKCGGCCDDYTG YQELVIKTSHDD	30
Human coronavirus HKU1 (isolate N5) (HCoV- HKU1) Spike glycoprotein	MFLIIFILPTTLAVIGDFNCTNSFINDYNKTIPRISEDVVDVSLG LGTYYVLNRVYLNTTLLFTGYPFKSGANFRDLALKGSIVLST LWYKPPFLSDFNNGIFSKVKNTKLYVNNTLYSEFSTIVIGSVF VNTSYTIVVQPHNGILEITACQYTMCEYPHTVCKSKGSIRNES WHIDSSEPLCLFKKNFTYNVSADWLYFHFYQERGVFYAYYA DVGMPTTFLFSLYLGTILSHYYVMPLTCNAISSNTDNETLEY	31

TABLE 11-continued

Be	Betacoronavirus Amino Acid Sequences		
Strain	Amino Acid Sequence	SEQ ID NO:	
UniProtKB- Q0ZME7	WVTPLSRRQVLLNFDEHGVITNAVDCSSSFLSEIQCKTQSFAP NTGVYDLSGFTVKFVATVYRRIPNLPDCDIDNMLNNVSVPSP LNWERRIFSNCNFNLSTLLRLVHVDSFSCNNLDKSKIFGSCFN SITVDKFAIPNRRDDLQLGSSGFLQSSNYKIDISSSSCQLYYS LPLVNVTINNENPSSWNRRYGFGSFNLSSYDVVYSDHCFSVN SDFCPCADPSVVNSCAKSKPPSAICPAGTKYRHCDLDTTLYV KNWCRCSCLPDPISTYSPNTCPQKKVVVGIGEHCPGLGINEE KCGTQLNHSSCPCSPDAFLGWSPDSCISNNRCNIPSNFIFNGIN SGTTCSNDLLYSNTEISTGVCVNYDLYGITGQGIFKEVSAAY YNNWQNLLYDSNGNIIGFKDFLTNKTYTILPCYSGRVSAAFY QNSSSPALLYNNKCSYVLNISFISQPFYDSYLGCVLNAVN LTSYSVSSCDLRMGSGFCIDYALPSSRKRRGISSPYRPVTFEP FNVSFVNDSVETVGGLFEIQIPTNFTIAGHEEFIQTSSPKVTIDC SAFVCSNYAACHDLSEYGTFCDNINSILNEVNDLLDITQLQV ANALMQGVTLSSNLNTNLHSDVDNIDFKSLLGCLGSQCGSSS RSLLEDLFNKVKLSDVGFVEAYNNCTGGSEIRDLLCVQSFN GIKVLPPILSETQISGYTTAATVAAMPPWSAAAGVPFSLNVQ YRINGLGVTMANAQALNSLLQQLFNKFGAISSSLGEILSRLDNLE AQVQIDRLINGRTALNAYVSQLSDITLIKAGASRAIEKVNE CVKSQSPRINFCGNGNHILSLVQNAPYGLLFIHFSYKPTSFKT VLVSPGLCLSGDRGIAPKQGYFIKQNDSWMFTGSSYYYPEPIS DKNVVFMNSCSVNFTKAPFIVLNNSIFNLSDFEAELSLWFKN HTSIAPNLTFNSHINATFLDLYYEMVIQESIKSLNSSFINLKEI GTYEMYVKWPWYIWLLVILFIIFLMILFFICCCTGCGSACFSK CHNCCDEYGGHNDFVIKASHDD		
Novel_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGPNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVBAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAIC HEGKAYFPREGYFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEXKNLNESLIDLQELGKYEQYI KWPWYWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT	32	
Novel_MERS_S2	MIHSVFLLMFLLTPTESDCKLPLGQSLCALPDTPSTLTPRSVR SVPGEMRLASIAFNHPIQVDQLNSSYFKLSIPTNPSFGVTQEYI QTTIQKVTVDCKQYVCNGFQKCEQLLREYGQPCSKINQALH GANLRQDDSVRNLFASVKSSQSSPIIPGFGGDFNLTLLEPVSIS TGSRSARSAIEDLLFDKVTIADPGYMQGYDDCMQQGPASAR DLICAQYVAGYKVLPPLMDVNMEAAYTSSLLGSIAGVGWTA GLSSPAAIPFAQSIFYRLNGVGITQQVLSENQKLIANKFNQAL GAMQTGFTTTNEAFQKVQDAVNNNAQALSKLASELSNTFG AISASIGDIIQRLDVLEQDAQIDRLINGRLTTLNAFVAQQLVRS ESAALSAQLAKDKVNECVKAQSKRSGPCGQGTHIVSFVVNA PNGLYFMHVGYYPSNHIEVVSAYGLCDANPTNCIAFVNGY FIKTNNTRIVDEWSYTGSSFYAPEPITSLNTKYVAPQVTYQNI STNLPPPLLGNSTGIDFQDELDEFFKNVSTSIPNFGSLTQINTTL LDLTYEMLSLQQVVKALNESYIDLKELGNYTYYNKWP	33	
Novel_Trimeric_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTAPAIC HEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLESSLIDLQELGKYEQYI KWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT	34	

TABLE 12

enBank ccession	Country	Collection Date	Release Date	Virus Name
FY13307	United	2012 Sep. 11	2012 Dec. 5	Betacoronavirus England 1,
FS88936	Kingdom	2012 Jun. 13	2012 Sep. 27	complete genome Human betacoronavirus 2c
GG22542	United	2012 Sep. 19	2013 Feb. 27	EMC/2012, complete genome Human betacoronavirus 2c England-
HY21469	Kingdom Jordan	2012	2014 May 4	Qatar/2012, complete genome Human betacoronavirus 2c Jordan- N3/2012 isolate MG167, complete
GH58717	Jordan	2012 April	2013 Mar. 25	genome Human betacoronavirus 2c Jordan-
GV08444	Saudi Arabia	2013 May 7	2013 Sep. 17	N3/2012, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08546	Saudi Arabia	2013 May 11	2013 Sep. 17	Hasa_12_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08535	Saudi Arabia	2013 May 12	2013 Sep. 17	Hasa_15_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08558	Saudi Arabia	2013 May 15	2013 Sep. 17	Hasa_16_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08573	Saudi Arabia	2013 May 23	2013 Sep. 17	Hasa_17_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08480	Saudi Arabia	2013 May 23	2013 Sep. 17	Hasa_18_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GN70962	Saudi Arabia	2013 May 9	2013 Jun. 10	Hasa_19_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08492	Saudi Arabia	2013 May 30	2013 Sep. 17	Hasa_1_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
HI48517	Saudi Arabia	2013 May 2	2014 Feb. 6	Hasa_21_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GN70951	Saudi Arabia	2013 Apr. 21	2013 Jun. 10	Hasa_25_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GN70973	Saudi Arabia	2013 Apr. 22	2013 Jun. 10	Hasa_2_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GN70929	Saudi Arabia	2013 May 1	2013 Jun. 10	Hasa_3_2013, complete genome Middle East respiratory syndrome coronavirus isolate Al-
GV08408	Saudi Arabia	2012 Jun. 19	2013 Sep. 17	Hasa_4_2013, complete genome Middle East respiratory syndrome coronavirus isolate Bisha_1_2012,
GV08467	Saudi Arabia	2013 May 13	2013 Sep. 17	complete genome Middle East respiratory syndrome coronavirus isolate
ID50418	United Kingdom	2013 Feb. 10	2014 Jun. 18	Buraidah_1_2013, complete genome Middle East respiratory syndrome coronavirus isolate England/2/2013,
ID81451	United Kingdom	2013 Feb. 10	2015 Jan. 18	complete genome Middle East respiratory syndrome coronavirus isolate England/3/2013,
JD81440	United Kingdom	2013 Feb. 13	2015 Jan. 18	complete genome Middle East respiratory syndrome coronavirus isolate England/4/2013,
HB33326	France	2013 May 7	2013 Dec. 7	complete genome Middle East respiratory syndrome coronavirus isolate FRA/UAE,
Z48760	USA	2014 June	2014 Dec. 14	complete genome Middle East respiratory syndrome coronavirus isolate Florida/USA- 2_Saudi Arabia_2014, complete
GV08455	Saudi Arabia	2013 Jun. 4	2013 Sep. 17	genome Middle East respiratory syndrome coronavirus isolate Hafr-Al-
HI48561	Saudi Arabia	2013 Aug. 5	2014 Feb. 6	Batin_1_2013, complete genome Middle East respiratory syndrome coronavirus isolate Hafr-Al-

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TABLE 12-continued

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AHI48539	Saudi Arabia	2013 Aug. 28	2014 Feb. 6	Middle East respiratory syndrome coronavirus isolate Hafr-Al-
\IZ744 17	France	2013 Apr. 26	2015 Mar. 10	Batin_6_2013, complete genome Middle East respiratory syndrome coronavirus isolate Hu-France (UAE) - FRA1_1627- 2013_BAL_Sanger, complete
AIZ74433	France	2013 May 7	2015 Mar. 10	genome Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_IS_HTS,
AIZ74439	France	2013 May 7	2015 Mar. 10	complete genome Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_InSpu_Sanger,
AIZ7445 0	France	2013 May 7	2015 Mar. 10	complete genome Middle East respiratory syndrome coronavirus isolate Hu-France - FRA2_130569-2013_Isolate_Sanger,
KK52602	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	complete genome Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_2959_2015,
AKK52612	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	complete genome Middle East respiratory syndrome coronavirus isolate Hu/Riyadh_KSA_4050_2015,
AHN10812	Saudi Arabia	2013 Nov. 6	2014 Mar. 24	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_1_2013, complete genome
AD55071	Saudi Arabia	2014 Apr. 21	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Jeddah_C10306/KSA/2014-04-20,
AID55066	Saudi Arabia	2014	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_C7149/KSA/2014-04-05,
AID55067	Saudi Arabia	2014	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_C7569/KSA/2014-04-03,
AID55068	Saudi Arabia	2014 Apr. 7	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_C7770/KSA/2014-04-07,
AID55069	Saudi Arabia	2014 Apr. 12	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_C8826/KSA/2014-04-12,
AID55070	Saudi Arabia	2014 Apr. 14	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Jeddah_C9055/KSA/2014-04-14,
AHE78108	Saudi Arabia	2013 Nov. 5	2014 May 1	complete genome Middle East respiratory syndrome coronavirus isolate MERS-CoV-
KL59401	South Korea	2015 May 20	2015 Jun. 9	Jeddah-human-1, complete genome Middle East respiratory syndrome coronavirus isolate MERS- CoV/KOR/KNIH/002_05_2015,
LD51904	Thailand	2015 Jun. 17	2015 Jul. 7	complete genome Middle East respiratory syndrome coronavirus isolate MERS- CoV/THA/CU/17_06_2015, complete genome
AID55072	Saudi Arabia	2014 Apr. 15	2014 Nov. 12	Middle East respiratory syndrome coronavirus isolate Makkah_C9355/KSA/Makkah/2014-
AHC74088	Qatar	2013 Oct. 13	2013 Dec. 23	04-15, complete genome Middle East respiratory syndrome coronavirus isolate Qatar3, complete genome

2	8	9
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TABLE 12-continued

ccession	Country	Collection Date	Release Date	Virus Name
AHC74098	Qatar	2013 Oct. 17	2013 Dec. 23	Middle East respiratory syndrome coronavirus isolate Qatar4, complete
AHI48572	Saudi Arabia	2013 Aug. 15	2014 Feb. 6	genome Middle East respiratory syndrome coronavirus isolate
GV08379	Saudi Arabia	2012 Oct. 23	2013 Sep. 17	Riyadh_14_2013, complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_1_2012,
AID55073	Saudi Arabia	2014 Apr. 22	2014 Nov. 12	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_2014KSA_683/KSA/2014,
GV08584	Saudi Arabia	2012 Oct. 30	2013 Sep. 17	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_2_2012,
GV0839 0	Saudi Arabia	2013 Feb. 5	2013 Sep. 17	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_3_2013,
AHI48605	Saudi Arabia	2013 Mar. 1	2014 Feb. 6	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_4_2013,
AHI48583	Saudi Arabia	2013 Jul. 2	2014 Feb. 6	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_5_2013,
AHI48528	Saudi Arabia	2013 Jul. 17	2014 Feb. 6	complete genome Middle East respiratory syndrome coronavirus isolate Riyadh_9_2013,
AHI48594	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	complete genome Middle East respiratory syndrome coronavirus isolate Taif_1_2013,
AHI48550	Saudi Arabia	2013 Jun. 12	2014 Feb. 6	complete genome Middle East respiratory syndrome coronavirus isolate Wadi-Ad-
AI¥60558	United Arab Emirates	2014 Mar. 7	2014 Dec. 6	Dawasir_1_2013, complete genome Middle East respiratory syndrome coronavirus strain Abu Dhabi/Gayathi_UAE_2_2014,
AIY60538	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	complete genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_16_2014, complete genome
AIY60528	United Arab Emirates	2014 Apr. 10	2014 Dec. 6	Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_18_2014, complete
AI¥60588	United Arab Emirates	2014 Apr. 13	2014 Dec. 6	genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_26_2014, complete
AIY60548	United Arab Emirates	2014 Apr. 19	2014 Dec. 6	genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_30_2014, complete
AFY60568	United Arab Emirates	2014 Apr. 17	2014 Dec. 6	genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_33_2014, complete
AI¥60518	United Arab Emirates	2014 Apr. 7	2014 Dec. 6	genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_8_2014, complete
AIY60578	United Arab Emirates	2013 Nov. 15	2014 Dec. 6	genome Middle East respiratory syndrome coronavirus strain Abu Dhabi_UAE_9_2013, complete
KJ80137	China	2015 May 27	2015 Jun. 5	genome Middle East respiratory syndrome coronavirus strain ChinaGD01,
AHZ64057	USA	2014 May 10	2014 May 14	complete genome Middle East respiratory syndrome coronavirus strain Florida/USA- 2_Saudi Arabia_2014, complete
KM76229	Oman	2013 Oct. 28	2015 Jun. 23	genome Middle East respiratory syndrome coronavirus strain

2	Q	1
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TABLE 12-continued

GenBank Accession	Country	Collection Date	Release Date	Virus Name
AKM76239	Oman	2013 Dec. 28	2015 Jun. 23	Hu/Oman_2285_2013, complete genome Middle East respiratory syndrome coronavirus strain Hu/Oman_2874_2013, complete
AKI29284	Saudi Arabia	2015 Jan. 6	2015 May 27	genome Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA- 2049/2015, complete genome
AKI29265	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA- 2343/2015, complete genome
AKI29255	Saudi Arabia	2015 Jan. 21	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA- 2345/2015, complete genome
AKI29275	Saudi Arabia	2015 Jan. 26	2015 May 27	Middle East respiratory syndrome coronavirus strain Hu/Riyadh-KSA- 2466/2015, complete genome
AKK52582	Saudi Arabia	2015 Feb. 10	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_2959_2015, complete genome
AKK52592	Saudi Arabia	2015 Mar. 1	2015 Jun. 8	Middle East respiratory syndrome coronavirus strain Hu/Riyadh_KSA_4050_2015, complete genome
AHZ58501	USA	2014 Apr. 30	2014 May 13	Middle East respiratory syndrome coronavirus strain Indiana/USA- 1_Saudi Arabia_2014, complete genome
AGN52936	United Arab Emirates	2013	2013 Jun. 10	Middle East respiratory syndrome coronavirus, complete genome

TABLE	12
IADUG	13

-	MeV Nucleic Acid Sequences	
Description	Sequence	SEQ II NO:
GC_F_MEASLES_B3.1	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT	35
Sequence, NT (5'	CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA	
UTR, ORF, 3'	GAAATATAAGAGCCACCATGGGTCTCAAGGTGAACGTC	
UTR)	TCTGCCGTATTCATGGCAGTACTGTTAACTCTCCAAACA	
Sequence Length:	CCCGCCGGTCAAATTCATTGGGGCAATCTCTCTAAGAT	
1864	AGGGGTAGTAGGAATAGGAAGTGCAAGCTACAAAGTT	
	ATGACTCGTTCCAGCCATCAATCATTAGTCATAAAATT	
	AATGCCCAATATAACTCTCCTCAATAACTGCACGAGGG	
	TAGAGATTGCAGAATACAGGAGACTACTAAGAACAGTT	
	TTGGAACCAATTAGGGATGCACTTAATGCAATGACCCA	
	GAACATAAGGCCGGTTCAGAGCGTAGCTTCAAGTAGGA	
	GACACAAGAGATTTGCGGGAGTAGTCCTGGCAGGTGCG	
	GCCCTAGGTGTTGCCACAGCTGCTCAGATAACAGCCGG	
	CATTGCACTTCACCGGTCCATGCTGAACTCTCAGGCCAT	
	CGACAATCTGAGAGCGAGCCTGGAAACTACTAATCAGG	
	CAATTGAGGCAATCAGACAAGCAGGGCAGGAGATGAT	
	ATTGGCTGTTCAGGGTGTCCAAGACTACATCAATAATG	
	AGCTGATACCGTCTATGAACCAGCTATCTTGTGATCTA	
	ATCGGTCAGAAGCTCGGGCTCAAATTGCTTAGATACTA	
	TACAGAAATCCTGTCATTATTTGGCCCCAGCCTACGGG	
	ACCCCATATCTGCGGAGATATCTATCCAGGCTTTGAGTT	
	ATGCACTTGGAGGAGATATCAATAAGGTGTTAGAAAAG	
	CTCGGATACAGTGGAGGCGATTTACTAGGCATCTTAGA	
	GAGCAGAGGAATAAAGGCTCGGATAACTCACGTCGAC	
	ACAGAGTCCTACTTCATAGTCCTCAGTATAGCCTATCCG	
	ACGCTGTCCGAGATTAAGGGGGGTGATTGTCCACCGGCT	
	AGAGGGGGTCTCGTACAACATAGGCTCTCAAGAGTGGT	
	ATACCACTGTGCCCAAGTATGTTGCAACCCAAGGGTAC	
	CTTATCTCGAATTTTGATGAGTCATCATGTACTTTCATG	
	CCAGAGGGGGACTGTGTGCAGCCAAAATGCCTTGTACCC	
	GATGAGTCCTCTGCTCCAAGAATGCCTCCGGGGGTCCA	

TABLE 13-continued

SEQ ID			
Description	Sequence	NO:	
	CCAAGTCCTGTGCTCGTACACTCGTATCCGGGTCTTTTG GGAACCGGTTCATTTTATCACAAGGGAACCTAATAGCC AATTGTGCATCAATTCTTTGTAAGGGTACCAAACAGGT ACGATTATTAATCAAGACCCTGACAAGATCCAACACGG GCGTGGCGACCATCCAAGTCGGCGCGGGGGGGGGG		
GC_F_MEASLES_B3.1 ORF Sequence, NT	ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC ATGGGTCTCAAGGTGAACGTCTCTGCCGTATTCATGGC AGTACTGTTAACTCTCCAAAGACACCCGCCGGTCAAATTC ATTGGGGCAATCTCTCTAAGATAAGGGTAGTAGGAATA GAAGTCAACAAGTCTGCAGAGGTAGTAGGAATA GGAAGTACTACAAAGTTATGAACCGTTCCAGCCA TCAATCATTAGTCACAAAGTTATGAACCCAATAAACTCT CCTCAATAACTGCACGAGGGTAGAAGATTGCGAGAATAAC GGAGCTACTAAGAACAGTTTGGGAACCAATAAGGCCGGGTCA GAGCGTAGCTCCAGGCAGGGCACAAGAGATTGCG GGAGTAGTCCTGGCAGGTGCGGCCCTAGGTGTTGCCAC AGCTGCTCAGATAACAGCCGGCATTGCACTTCACCGGT CCATGCTGAACTACTAACAGCCGGCATTGCACTTCACCGGT CCATGCTGAACTACTAACAGCCGGCATTGCACTTCACGGGT GCCGGAAACTACTAATCAGGCAATGAGGCAATCG GCCCGGAACTACTAATCAGGCAATTGAGGCAATCG GCCCAGGCAAGCTACTAATCAGGCCATCAGAACCGG CCCAAGCTACTAATAATGAGCTGATACCGTCTATG AACCAGCTACTACTAATCAGGCCACAAATCGGAGGA TTCCAAATTGCTTAGGATCTAATCGGTCAGAAGCTGG GCTCAAATTGCTAGGTATATTGGCTCTGGCGACA TATCTATCCAGGCTTTGAGTTATGCACTGGGAGG GCTCGGATACTCACGTCTAGGACCCCATATCGGGGAGA TATCTATCCAGGCTTTGAGTTATGCACTGGGAGG GCTCGGATAACTCACGTCGACACAGGTCCTACTT ATTGGCCCCAGCTTCGAGACCCGATACGGTGG GCTCGGATAACTCACGTCGACACAGGTCCTACTTCAT AGGGGTGATTGTCCACGGGCTAGCTGGAC GCTCGGATAACTCACGTCGACACAGGTCCTACTTCAT AGGGGTGATTGTCCACGGGCTACGTGCTGGTC AACATAGGCTCTCAAGAGGGCCTACTTCAT AGGGGTGATTGTCCACGGGCACAGGGCCTCGTGC AACATAGGCTCCCAAGGGGCCCCACTACTTGA GTATGTTGCAACCTAGGCCAAGGGCCTCGTGC CAAGAATGCCTCCAGAGGGGCCCCCAATTTG ACACACGAGACCTAATTCCCGACGAGGGCCTGGTC CAAGAATGCCTCGGGGGTCCCCCAAGTCCTGGCCCA GTATGTTGCAACCTAATGCCAAGGGCCCTGGTC CAAGAATGCCTCGGGGGTCCCCCAAGTCCTGGCCGA GTCGGGAGCAAAATGCCTTATTCGCGAGGGCCTGGTC CCGGGAGCAGAGGCTACCTACTTGGCAACCAGGGCCTGGCTG CTGCGGAGCAGGAGCAACCCAATGGCCTGGCC	36	
mRNA Sequence	G*GGGAAATAAGAGAGAAAAGAAGAGGTAAGAAGAAT ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGC CGTATTCATGGGCAGTACTGTTAACTCTCCAAACACCCG CCGGTCAAATCATTGGGCCAATCTCTCTAAGATAGGG GTAGTAGGAATAGGAAGTGCAAGCTACAAAGTTATGA CTCGTTCCAGCCATCAATCATTAGTCATAAAATTAATGC CCAATATAACTCTCCTCAATAACTGCACGAGGGTAGAG ATTGCAGAATACAGGAGACTACTAAAGAACAGTTTTGGA ACCAATTAGGGAGTGCACTTAATGCACCAGAACA TAAGGCCGGTTCAGAGCGTAGCTTCAAGTAGGAGACAC AAGAGATTGCGGGAGTAGTCCTGGCAGGTCGGCCCT	37	

TABLE 13-continued

		SEQ ID
escription	Sequence	NO:
Jescription	AGGTGTTGCCACAGCTGCTCAGATAACAGCCGGCATTG CACTTCACCGGTCCATGCTGAACTCTCAGGCCATCGAC AATCTGAGAGCGAGCCTGGAACTACTAATAATGAGCA TGAGGCAATCAGACAAGCAGGCAGGAGAGAGATGATATTG GCTGTTCAGGGTGTCCAAGACTACATCAATAATGAGCT GATACCGTCATGAACCAGCTATCTTGGATCTAATG GTCAGAAGCTCGGGCTCAAATTGCTTAGATACTATACA GAAATCCTGTCATTATTTGGCCCCAGCCTACGGGACCC CATATCTGCGGAGATATCATCACGGCTTGGAGTTATGC ACTTGGAGGAGATACTATCCAGGCTTTGAGATATGC ACTTGGAGGAGATCAATAAGGTGTTAGAAAAGCCG GATACAGTGGAGCGATTACTAGGGCATCTTAGAGAGC AGAGGAATAAAGGCTCGGATAACTCACGGCGACAGG AGTCCTACTTCATAGGGGGTGATACCCACGGCTAGAG GGGGTCTGTACAACATAGGCTCTCAAGAGTGGTATAC CACTGCGCCAAGATAGGCTCTCAAGAGTGGTATAC CACTGCCCAAGATAGGCCCCCAGAGAGGGTGCACCAA GGGGGTCGTCGTACAACATAGGCCTCTCAAGAGTGGTATAC CACTGCCCAAGATATGCCACCGGGGTCCCCCAG AGGCGACTGTGCGACAACATGGCCTTGAAGTGGTCACCGAG GGGTCCTGTCGTACAACATGGCCTTCGGGGGTCCACCAA GTCCTGTGCTCGAAGAATGCCTTCGGGGGTCCACCAA GTCCTGTGCTCGAAGAATGCCTTGCGGGGTCCACCAA GTCCTGTGCTCGAAGAATGCCTTGCGGGGTCCACCAA GTCCTGTGCTCGTACACGGAAGCCTAATAGCCACTA GTGCACAATTCTTTGTAAGTGTTACCCAACAGGTAG ATTATAATCAAGACCCTGGAAGTGCACACAATG GTGCACCAAGTCGGGGCCACAAATGCCTACCGGAGCGC GTGTACTTGGCGCGGAGCAGGAGGAGTATCCGGGACGC GTGTACTCGCACGAAGATGCCTACGGGATGCCACAAT TGCGCGAATGGCTGCGGGGCCCCCCCATATCA TTGCGCGAATGGCGCGGGAGCAGAGGAGTATCCAGACGCC GTGTACTGCCCAGGAATTGGACGGCGTGTGTGCGAG CAATTGCCAAATTGGAGGACCCAACGAAATCCGGGATGCC CAAGGGCCTGGAGCTAGGGACCCACTTTCGGGAATG CAATGCCAAGCATGGCTCCCCCCCTTTCGCGAGGTGACGCC GCGGGCCTGGACGACAAACTCGGGCCTTCTGCGGAAGG CAATGCCAAGCAAGGATCCCACGACAAGTTGG CAATGCCAAATCCTAGGAACCCCACCTTTCCAGAGAA CATCAAAACCCAGGCCTAAAGGCCGACAAATTGGGGAACAGTGG TATCTACAGACCAGGCCTAAAGGCTGACGACAAGTTGG CACGAGCCTGGTGACACAAAAGGCAGAACTTACAGGAAA CATCAAAACCCATGGCACAAACGCCTGCCCCCCCCTTGCGGCCCCCCCC	NG :
C_F_MEASLES_D8 Sequence, NT (5' JTR, ORF, 3' JTR) Sequence Length: .864	CCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAA	38

TABLE 13-continued

		SEQ ID
Description	Sequence	NO :
	ACATTGCTGCCGATCACTGCCCGGTGGTCGAGGTGAAT GGCGTGACCATCCAAGTCGGGAGCAGGAGGTATCCGG	
	ACGCTGTGTACTTGCACAGGATTGACCTCGGTCCTCCC	
	ATATCTTTCGAGAGGTTGGACGTAGGGACAAATCTGGG	
	GAATGCAATTGCTAAGTTGGAGGATGCCAAGGAATTGT	
	TGGAGTCATCGGACCAGATATTGAGGAGTATGAAAGGT	
	TTATCGAGCACTAGTATAGTTTACATCCTGATTGCAGTG	
	TGTCTTGGAGGATTGATAGGGATCCCCGCTTTAATATGT	
	TGCTGCAGGGGGCGTTGTAACAAGAAGGGAGAACAAG	
	GGAACATCAAAATCCTATGTAAGGTCACTCTGATGATA ATAGGCTGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTT	
	GGGCCTCCCCCAGCCCCTCCTCCCCCTTCCTGCACCCGT	
	ACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGGC	
C F MEASLES D8	ATGGGTCTCAAGGTGAACGTCTCTGTCATATTCATGGC	39
RF Sequence, NT	AGTACTGTTAACTCTTCAAACACCCCACCGGTCAAATCC	
,	ATTEGGGCAATCTCTCTAAGATAGGGGTGGTAGGGGTA	
	GGAAGTGCAAGCTACAAAGTTATGACTCGTTCCAGCCA	
	TCAATCATTAGTCATAAAGTTAATGCCCAATATAACTCT	
	CCTCAACAATTGCACGAGGGTAGGGATTGCAGAATACA	
	GGAGACTACTGAGAACAGTTCTGGAACCAATTAGAGAT	
	GCACTTAATGCAATGACCCAGAATATAAGACCGGTTCA	
	GAGTGTAGCTTCAAGTAGGAGACACAAGAGATTTGCGG	
	GAGTTGTCCTGGCAGGTGCGGCCCTAGGCGTTGCCACA GCTGCTCAAATAACAGCCGGTATTGCACTTCACCAGTC	
	CATGCTGAACTCTCAAGCCATCGACAATCTGAGAGCGA	
	GCCTAGAAACTACTAATCAGGCAATTGAGGCAATCAGA	
	CAAGCAGGGCAGGAGATGATATTGGCTGTTCAGGGTGT	
	CCAAGACTACATCAATAATGAGCTGATACCGTCTATGA	
	ATCAACTATCTTGTGATTTAATCGGCCAGAAGCTAGGG	
	CTCAAATTGCTCAGATACTATACAGAAATCCTGTCATT	
	ATTTGGCCCCAGCTTACGGGACCCCATATCTGCGGAGA	
	TATCTATCCAGGCTTTGAGCTATGCGCTTGGAGGAGAA ATCAATAAGGTGTTGGAAAAGCTCGGATACAGTGGAG	
	GTGATCTACTGGGCATCTTAGAGAGCAGAGGAATAAAG	
	GCCCGGATAACTCACGTCGACACAGAGTCCTACTTCAT	
	TGTACTCAGTATAGCCTATCCGACGCTATCCGAGATTA	
	AGGGGGTGATTGTCCACCGGCTAGAGGGGGTCTCGTAC	
	AACATAGGCTCTCAAGAGTGGTATACCACTGTGCCCAA	
	GTATGTTGCAACCCAAGGGTACCTTATCTCGAATTTTGA	
	TGAGTCATCATGCACTTTCATGCCAGAGGGGACTGTGT	
	GCAGCCAGAATGCCTTGTACCCGATGAGTCCTCTGCTC	
	TACACTCGTATCCGGGTCTTTCGGGAACCGGTTCATTTT ATCACAGGGGAACCTAATAGCCAATTGTGCATCAATCC	
	TTTGCAAGTGTTACACAACAGGAACAATCATTAATCAA	
	GACCCTGACAAGATCCTAACATACATTGCTGCCGATCA	
	CTGCCCGGTGGTCGAGGTGAATGGCGTGACCATCCAAG	
	TCGGGAGCAGGAGGTATCCGGACGCTGTGTACTTGCAC	
	AGGATTGACCTCGGTCCTCCCATATCTTTGGAGAGGTT	
	GGACGTAGGGACAAATCTGGGGGAATGCAATTGCTAAGT	
	TGGAGGATGCCAAGGAATTGTTGGAGTCATCGGACCAG	
	ATATTGAGGAGTATGAAAGGTTTATCGAGCACTAGTAT	
	AGTTTACATCCTGATTGCAGTGTGTCTTGGAGGATTGAT AGGGATCCCCGCTTTAATATGTTGCTGCAGGGGGGGCGTT	
	GTAACAAGAAGGGAGAACAAGTTGGTATGTCAAGACC	
	AGGCCTAAAGCCTGATCTTACAGGAACATCAAAATCCT	
	ATGTAAGGTCACTCTGA	
GC F MEASLES D8	G*GCGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT	40
NRNA Sequence	ATAAGAGCCACCATGGGTCTCAAGGTGAACGTCTCTGT	
(assumes T100 tail)	CATATTCATGGCAGTACTGTTAACTCTTCAAACACCCAC	
Sequence Length:	CGGTCAAATCCATTGGGGGCAATCTCTCTAAGATAGGGG	
1925	TGGTAGGGGTAGGAAGTGCAAGCTACAAAGTTATGACT	
	CGTTCCAGCCATCAATCATTAGTCATAAAGTTAATGCC	
	TTGCAGAATACAGGAGACTACTGAGAACAGTTCTGGAA CCAATTAGAGATGCACTTAATGCAATGACCCAGAATAT	
	AAGACCGGTTCAGAGTGTAGCTTCAAGTAGGAGAGACACA	
	AGAGATTTGCGGGGAGTTGTCCTGGCAGGTGCGGCCCTA	
	GGCGTTGCCACAGCTGCTCAAATAACAGCCGGTATTGC	
	ACTTCACCAGTCCATGCTGAACTCTCAAGCCATCGACA	

ACTTCACCAGTCCATGCTGAACTCTCAAGCCATCGACA ATCTGAGAGCGAGCCTAGAAACTACTAATCAGGCAATT

TABLE 13-continued

escription	Sequence	SEQ ID NO:
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	CAGAAGCTAGGGCTCAAATTGCTCAGATACTATACAGA	
	AATCCTGTCATTATTTGGCCCCAGCTTACGGGACCCCAT ATCTGCGGAGATATCTATCCAGGCTTTGAGCTATGCGC	
	TTGGAGGAGATATCAATAAGGTGTTGGAAAAGCTCGGA	
	TACAGTGGAGGTGATCTACTGGGCATCTTAGAGAGCAG	
	AGGAATAAAGGCCCGGATAACTCACGTCGACACAGAG	
	TCCTACTTCATTGTACTCAGTATAGCCTATCCGACGCTA TCCGAGATTAAGGGGGTGATTGTCCACCGGCTAGAGGG	
	GGTCTCGTACAACATAGGCTCTCAAGAGTGGTATACCA	
	CTGTGCCCAAGTATGTTGCAACCCAAGGGTACCTTATC	
	TCGAATTTTGATGAGTCATCATGCACTTTCATGCCAGAG	
	GGGACTGTGTGCAGCCAGAATGCCTTGTACCCGATGAG	
	TCCTCTGCTCCAAGAATGCCTCCGGGGGTCCACTAAGT CCTGTGCTCGTACACTCGTATCCGGGTCTTTCGGGAACC	
	GGTTCATTTTATCACAGGGGAACCTAATAGCCAATTGT	
	GCATCAATCCTTTGCAAGTGTTACACAACAGGAACAAT	
	CATTAATCAAGACCCTGACAAGATCCTAACATACATTG	
	CTGCCGATCACTGCCCGGTGGTCGAGGTGAATGGCGTG ACCATCCAAGTCGGGAGCAGGAGGTATCCGGACGCTGT	
	GTACTTGCACAGGATTGACCTCGGTCCTCCCATATCTTT	
	GGAGAGGTTGGACGTAGGGACAAATCTGGGGAATGCA	
	ATTGCTAAGTTGGAGGATGCCAAGGAATTGTTGGAGTC	
	ATCGGACCAGATATTGAGGAGTATGAAAGGTTTATCGA	
	GCACTAGTATAGTTTACATCCTGATTGCAGTGTGTCTTG GAGGATTGATAGGGATCCCCGCTTTAATATGTTGCTGC	
	AGGGGCGTTGTAACAAGAAGGGAGAACAAGTTGGTA	
	TGTCAAGACCAGGCCTAAAGCCTGATCTTACAGGAACA	
	TCAAAATCCTATGTAAGGTCACTCTGATGATAATAGGC	
	TGGAGCCTCGGTGGCCAAGCTTCTTGCCCCTTGGGCCTC CCCCCAGCCCCTCCTCCCTGCACCCGTACCCCCG	
	TGGTCTTTGAATAAAGTCTGAGTGGGCGGCAAAAAAAA	
	ААААААААААААААААААААААААААААААААААААА	
	ААААААААААААААААААТСТАG	
H MEASLES B3	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT	41
quence, NT (5'	CACTATAGGGAAATAAGAGAGAAAAGAAGAGTAAGAA	
R, ORF, 3'	GAAATATAAGAGCCACCATGTCACCGCAACGAGACCG	
R)	GATAAATGCCTTCTACAAAGATAACCCTTATCCCAAGG GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT	
uence Length: 5	GACAGACCCTATGTTCTGCTGGCTGTCTGTTCGTCGTCATG	
2065	TTTCTGAGCTTGATCGGATTGCTGGCAATTGCAGGCATT	
	AGACTTCATCGGGCAGCCATCTACACCGCGGAGATCCA	
	TAAAAGCCTCAGTACCAATCTGGATGTGACTAACTCCA	
	TCGAGCATCAGGTCAAGGACGTGCTGACACCACTCTTT AAAATCATCGGGGGATGAAGTGGGCCTGAGAACACCTC	
	AGAGATTCACTGAGGGATGAAGTGGGCCTGAGAACACCTC AGAGATTCACTGACCTAGTGAAATTCATCTCGGACAAG	
	ATTAAATTCCTTAATCCGGATAGGGAGTACGACTTCAG	
	AGATCTCACTTGGTGCATCAACCCGCCAGAGAGGATCA	
	GAAGAGCTCATGAATGCATTGGTGAACTCAACTCTACT GGAGACCAGAACAACCACTCAGTTCCTAGCTGTCTCAA	
	AGGGAAACTGCTCAGGGCCCACTACAATCAGAGGTCA	
	ATTCTCAAACATGTCGCTGTCCTTGTTGGACTTGTACTT	
	AGGTCGAGGTTACAATGTGTCATCTATAGTCACTATGA	
	CATCCCAGGGAATGTATGGGGGGAACCTACCTAGTTGAA AAGCCTAATCTGAACAGCAAAGGGTCAGAGTTGTCACA	
	AGCCTAATCTGAACAGCAAAGGGTCAGAGTTGTCACA	
	GAAACCCGGGTTTGGGGGGCTCCGGTGTTCCATATGACA	
	AACTATTTTGAGCAACCAGTCAGTAATGGTCTCGGCAA	
	CTGTATGGTGGCTTTGGGGGGGGGCTCAAACTCGCAGCCC	
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	GATCAGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTG	
	CCCCTTATCAACGGATGATCCAGTGGTAGACAGGCTTT	
	ACCTCTCATCTCACAGAGGTGTCATCGCTGACAATCAA	
	GCAAAATGGGCTGTCCCGACAACACGAACAGATGACA	
	AGTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAA GGTAAAATCCAAGCACTCTGCGAGAATCCCGAGTGGGT	
	CONTRACTOR CONSCRETCION CONTRACTOR CONT	
	ACCATTGAAGGATAACAGGATTCCTTCATACGGGGTCC	
	ACCATTGAAGGATAACAGGATTCCTTCATACGGGGTCC TGTCTGTTGATCTGAGTCTGACGGTTGAGCTTAAAATCA	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
r	TCAGGGATGGACCTATACAAATCCAACTGCAACAATGT	
	GTATTGGCTGACTATTCCGCCAATGAGAAATCTAGCCT	
	TAGGCGTAATCAACACATTGGAGTGGATACCGAGATTC	
	AAGGTTAGTCCCAACCTCTTCACTGTCCCAATTAAGGA	
	AGCAGGCGAAGACTGCCATGCCCCAACATACCTACCTG CGGAGGTGGACGGTGATGTCAAACTCAGTTCCAACCTG	
	GTGATTCTACCTGGTCAAGATCTCCAATATGTTTTGGCA	
	ACCTACGATACCTCCAGGGTTGAGCATGCTGTGGTTTA	
	TTACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTA TCCTTTTACAGCCCCAAGCCGCTCATTTTCTTACTTTA	
	TCCTTTTAGGTTGCCTATAAAGGGGGGTCCCAATCGAAC TACAAGTGGAATGCTTCACATGGGATCAAAAACTCTGG	
	TGCCGTCACTTCTGTGTGCTTGCGGACTCAGAATCCGGT	
	GGACTTATCACTCACTCTGGGATGGTGGGCATGGGAGT	
	CAGCTGCACAGCTACCCGGGAAGATGGAACCAATCGC AGATAATGATAATAGGCTGGAGCCTCGGTGGCCAAGCT	
	TCTTGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCCCTT	
	CCTGCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTG	
	AGTCGGCGGC	
GC_H_MEASLES_B3	ATGTCACCGCAACGAGACCGGATAAATGCCTTCTACAA	42
ORF Sequence, NT	AGATAACCCTTATCCCAAGGGAAGTAGGATAGTTATTA	
	ACAGAGAACATCTTATGATTGACAGACCCTATGTTCTG CTGGCTGTTCTGTT	
	TTGCTGGCAATTGCAGGCATTAGACTTCATCGGGCAGC	
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	ATCTGGATGTGACTAACTCCATCGAGCATCAGGTCAAG GACGTGCTGACACCACTCTTTAAAATCATCGGGGATGA	
	AGTGGGCCTGAGAACACCACTCAGAGATTCACCGGGGATGA	
	TGAAATTCATCTCGGACAAGATTAAATTCCTTAATCCG	
	GATAGGGAGTACGACTTCAGAGATCTCACTTGGTGCAT	
	CAACCCGCCAGAGAGGATCAAACTAGATTATGATCAAT ACTGTGCAGATGTGGCTGCTGAAGAGCTCATGAATGCA	
	TTGGTGAACTCAACTCTACTGGAGACCAGAACAACCAC	
	TCAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGC	
	CCACTACAATCAGAGGTCAATTCTCAAACATGTCGCTG	
	TCCTTGTTGGACTTGTACTTAGGTCGAGGTTACAATGTG TCATCTATAGTCACTATGACATCCCAGGGAATGTATGG	
	GGGAACCTACCTAGTTGAAAAGCCTAATCTGAACAGCA	
	AAGGGTCAGAGTTGTCACAACTGAGCATGTACCGAGTG	
	TTTGAAGTAGGTGTGATCAGAAACCCGGGTTTGGGGGC TCCGGTGTTCCATATGACAAACTATTTTGAGCAACCAG	
	TCAGTAATGGTCTCCGGCAACTGTATGGTGGCTTTGGGG	
	GAGCTCAAACTCGCAGCCCTTTGTCACGGGGACGATTC	
	TATCATAATTCCCTATCAGGGATCAGGGAAAGGTGTCA	
	GCTTCCAGCTCGTCAAGCTGGGTGTCTGGAAATCCCCA ACCGACATGCAATCCTGGGTCCCCTTATCAACGGATGA	
	TCCAGTGGTAGACAGGCTTTACCTCTCATCTCACAGAG	
	GTGTCATCGCTGACAATCAAGCAAAATGGGCTGTCCCG	
	ACAACACGAACAGATGACAAGTTGCGAATGGAGACAT	
	GCTTCCAGCAGGCGTGTAAAAGGTAAAATCCAAGCACTC TGCGAGAATCCCCGAGTGGGTACCATTGAAGGATAACAG	
	GATTCCTTCATACGGGGTCCTGTCTGTTGATCTGAGTCT	
	GACGGTTGAGCTTAAAATCAAAATTGCTTCGGGATTCG	
	GGCCATTGATCACACACGGCTCAGGGATGGACCTATAC AAATCCAACTGCAACAATGTGTATTGGCTGACTATTCC	
	GCCAATGAGAAAATCTAGCCTTAGGCGTAATCAACACAT	
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	TTCACTGTCCCAATTAAGGAAGCAGGCGAAGACTGCCA	
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	GATCTCCAATATGTTTTGGCAACCTACGATACCTCCAG	
	GGTTGAGCATGCTGTGGTTTATTACGTTTACAGCCCAA	
	GCCGCTCATTTTCTTACTTTTATCCTTTTAGGTTGCCTAT	
	AAAGGGGGTCCCAATCGAACTACAAGTGGAATGCTTCA CATGGGATCAAAAACTCTGGTGCCGTCACTTCTGTGTG	
	CTTGCGGACTCAGAATCCGGTGGACTTATCACTCACTCT	
	GGGATGGTGGGCATGGGAGTCAGCTGCACAGCTACCCG GGAAGATGGAACCAATCGCAGATAA	
GC_H_MEASLES_B3 mRNA Sequence	G*GGGAAATAAGAGAGAAAAGAGAGAGAAGAAGAAAAT ATAAGAGCCACCATGTCACCGCAACGAGACCGGATAA	43
•	ATGCCTTCTACAAAGATAACCCTTATCCCAAGGGAAGT	
Sequence Length:	AGGATAGTTATTAACAGAGAACATCTTATGATTGACAG	
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TABLE 13-continued

MeV Nucleic Acid Sequences		
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	ATTCACTGACCTAGTGAAATTCATCTCGGACAAGATTA	
	AATTCCTTAATCCGGATAGGGAGTACGACTTCAGAGAT	
	CTCACTTGGTGCATCAACCCGCCAGAGAGGATCAAACT AGATTATGATCAATACTGTGCAGATGTGGCTGCTGAAG	
	AGATTATGATGAATACTGIGCAGATGIGGCIGCIGAAG	
	ACCAGAACAACCACTCAGTTCCTAGCTGTCTCAAAGGG	
	AAACTGCTCAGGGCCCACTACAATCAGAGGTCAATTCT	
	CAAACATGTCGCTGTCCTTGTTGGACTTGTACTTAGGTC GAGGTTACAATGTGTCATCTATAGTCACTATGACATCC	
	CAGGGAATGTATGGGGGGAACCTACCTAGTTGAAAAGCC	
	TAATCTGAACAGCAAAGGGTCAGAGTTGTCACAACTGA	
	GCATGTACCGAGTGTTTGAAGTAGGTGTGATCAGAAAC	
	CCGGGTTTGGGGGGCTCCGGTGTTCCATATGACAAACTA TTTTGAGCAACCAGTCAGTAATGGTCTCGGCAACTGTA	
	TGGTGGCTTTGGGGGGGGGGGGGGGGGGGGGGGGGGGCCCTTTGT	
	CACGGGGACGATTCTATCATAATTCCCTATCAGGGATC	
	AGGGAAAGGTGTCAGCTTCCAGCTCGTCAAGCTGGGTG	
	TCTGGAAATCCCCAACCGACATGCAATCCTGGGTCCCC TTATCAACGGATGATCCAGTGGTAGACAGGCTTTACCT	
	CTCATCTCACAGAGGTGTCATCGCTGACAGGCTTTACCT	
	AATGGGCTGTCCCGACAACACGAACAGATGACAAGTTG	
	CGAATGGAGACATGCTTCCAGCAGGCGTGTAAAGGTAA	
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	GTTGATCTGAGTCTGACGGTTGAGCTTAAAATCAAAAT	
	TGCTTCGGGATTCGGGCCATTGATCACACGCGCTCAG	
	GGATGGACCTATACAAATCCAACTGCAACAATGTGTAT	
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	TTAGTCCCAACCTCTTCACTGTCCCAATTAAGGAAGCA	
	GGCGAAGACTGCCATGCCCCAACATACCTACCTGCGGA	
	GGTGGACGGTGATGTCAAACTCAGTTCCAACCTGGTGA	
	TTCTACCTGGTCAAGATCTCCAATATGTTTTGGCAACCT ACGATACCTCCAGGGTTGAGCATGCTGTGGTTTATTAC	
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	AGTGGAATGCTTCACATGGGATCAAAAACTCTGGTGCC	
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	CTTATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG	
	AATGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCTT	
	GCCCCTTGGGCCTCCCCCAGCCCCTCCTCCCCTG	
	CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTG	
	GGCGGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
	АЛЛООЧИЛЛИЧТООЧИЛЛИТОООТЛИЧТООЧИЛ АААААААААААААААААААААААААААААААААААА	
	TAG	
C H MEASLES D8	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACT	44
equence, NT (5'	CACTATAGGGAAATAAGAGAGAAAAGAGAGAGAAGAA	
R, ORF, 3'	GAAATATAAGAGCCACCATGTCACCACAACGAGACCG	
IR)	GATAAATGCCTTCTACAAAGACAACCCCCCATCCTAAGG GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT	
equence Length: 065	GAAGTAGGATAGTTATTAACAGAGAACATCTTATGATT GATAGACCTTATGTTTTGCTGGCTGTTCTATTCGTCATG	
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	AGACTTCATCGGGCAGCCATCTACACCGCAGAGATCCA	
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	GAGATTCACTGACCTAGTGAAGTTCATCTCTGACAAGA	
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	GAGACCCAGGGCAACCAATGCATGGGGGAACTCAACTCTACTG	
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	GTCGAGGTTACAATGTGTCATCTATAGTCACTATGACA	
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	GCCTAATCTGAGCAGCAAAGGGTCAGAGTTGTCACAAC	

TABLE 13-continued

Description	Sequence	SEQ ID NO:
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	ATCAGGGAAAGGTGTCAGCTTCCAGCTTGTCAAGCTAG	
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	CCTCTCATCTCACAGAGGGCGTTATCGCTGACAATCAAG	
	CAAAATGGGCTGTCCCGACAACACGGACAGATGACAA	
	GTTGCGAATGGAGACATGCTTCCAGCAGGCGTGTAAGG	
	GTAAAATCCAAGCACTTTGCGAGAATCCCGAGTGGACA	
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	AAATTGTTTCAGGATTCGGGCCATTGATCACACACGGT	
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	TAGGTGTAATCAACACATTGGAGTGGATACCGAGATTC	
	AAGGTTAGTCCCAACCTCTTCACTGTTCCAATTAAGGA AGCAGGCGAGGACTGCCCATGCCCCAACATACCTACCTG	
	CGGAGGTGGATGGTGATGTCAAACTCAGTTCCAATCTG	
	GTGATTCTACCTGGTCAAGATCTCCAATATGTTCTGGCA	
	ACCTACGATACTTCCAGAGTTGAACATGCTGTAGTTTAT	
	TACGTTTACAGCCCAAGCCGCTCATTTTCTTACTTTAT	
	CCTTTTAGGTTGCCTGTAAGGGGGGTCCCCATTGAATTA CAAGTGGAATGCTTCACATGGGACCAAAAACTCTGGTG	
	CCGTCACTTCTGTGTGTGCTTGCGGACTCAGAATCTGGTGG	
	ACATATCACTCACTCTGGGATGGTGGGCATGGGAGTCA	
	GCTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAG	
	ATAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTC	
	TTGCCCCTTGGGCCTCCCCCAGCCCCTCCTCCCCTTCC TGCACCCGTACCCCGTGGTCTTTGAATAAAGTCTGAG	
	TGGGCGGC	
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	GTGGGCTTGAGGACACCTCAGAGATTCACTGACCTAGT	
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	CTGTGCAGATGTGGCTGCTGAAGAACTCATGAATGCAT	
	TGGTGAACTCAACTCTACTGGAGACCAGGGCAACCAAT	
	CAGTTCCTAGCTGTCTCAAAGGGAAACTGCTCAGGGCC	
	CACTACAATCAGAGGCCAATTCTCAAACATGTCGCTGT CCCTGTTGGACTTGTATTTAAGTCGAGGTTACAATGTGT	
	CATCTATAGTCACTATGACATCCCAGGGAATGTACGGG	
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	TTGAAGTAGGTGTTATCAGAAATCCGGGTTTGGGGGGCT	
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	GACAGTTGAGCTTAAAATCAAAATTGTTTCAGGATTCG	
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	AAATCCAACCACAACAATATGTATTGGCTGACTATCCC	
	GCCAATGAAGAACCTGGCCTTAGGTGTAATCAACACAT TGGAGTGGATACCGAGATTCAAGGTTAGTCCCAACCTC	
	TTCACTGTTCCAATTAAGGAAGCAGGCGAGGACTGCCA	
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Description	Sequence	SEQ ID
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	GATGGTGGGCATGGGAGTCAGCTGCACAGCCACTCGGG	
	AAGATGGAACCAGCCGCAGATAG	
GC_H_MEASLES_D8 mRNA Sequence	G*GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAAT ATAAGAGCCACCATGTCACCACAACGAGACCGGATAA	46
	ATGCCTTCTACAAAGACAACCCCCATCCTAAGGGAAGT	
Sequence Length: 2126	AGGATAGTTATTAACAGAGAACATCTTATGATTGATAG ACCTTATGTTTGCTGGCTGTTCTATTCGTCATGTTTCTG	
	AGCTTGATCGGGTTGCTAGCCATTGCAGGCATTAGACT	
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	AATCTGAGCAGCAAAGGGTCAGAGTTGTCACAACTGAG CATGCACCGAGTGTTTGAAGTAGGTGTTATCAGAAATC	
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	GTTGATCTGAGTCTGACAGTTGAGCTTAAAATCAAAAT	
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	GGATGGACCTATACAAATCCAACCACAACAATATGTAT TGGCTGACTATCCCGCCAATGAAGAACCTGGCCTTAGG	
	TGTAATCAACACATTGGAGTGGATACCGAGATTCAAGG	
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	GGCGAGGACTGCCATGCCCCAACATACCTACCTGCGGA GGTGGATGGTGATGTCAAACTCAGTTCCAATCTGGTGA	
	TTCTACCTGGTCAAGATCTCCAATATGTTCTGGCAACCT	
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	TTTAGGTTGCCTGTAAGCCGCTCATTTTCTTACTTTTATCCT	
	AGTGGAATGCTTCACATGGGACCAAAAACTCTGGTGCC	
	GTCACTTCTGTGTGCGTCGGACTCAGAATCTGGTGGA	
	CATATCACTCACTCTGGGATGGTGGGCATGGGAGTCAG CTGCACAGCCACTCGGGAAGATGGAACCAGCCGCAGA	
	TAGTGATAATAGGCTGGAGCCTCGGTGGCCAAGCTTCT	
	TGCCCCTTGGGCCTCCCCCCAGCCCCTCCTCCCTCCT GCACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGT	
	GCACCCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGT GGGCGCCAAAAAAAAAA	
	АААААААААААААААААААААААААААААААААААА	
	ААААААААААААААААААААААААААААААААААААА	
	MeV mRNA Sequences	

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TABLE 13-continued

	MeV Nucleic Acid Sequences	
escription	Sequence	SEQ I NO:
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	AAUGCAAUGACCCAGAACAUAAGGCCGGUUCAGAGCG UAGCUUCAAGUAGGAGACACAAGAGAUUUGCCGGGAG	
	UAGUCCUGGCAGGUGCGGCCCUAGGUGUUGCCACAGC	
	UGCUCAGAUAACAGCCGGCAUUGCACUUCACCGGUCC	
	AUGCUGAACUCUCAGGCCAUCGACAAUCUGAGAGCGA	
	GCCUGGAAACUACUAAUCAGGCAAUUGAGGCAAUCAG ACAAGCAGGGCAGG	
	UGUCCAAGACUACAUCAAUAAUGAGCUGAUACCGUCU	
	AUGAACCAGCUAUCUUGUGAUCUAAUCGGUCAGAAGC	
	UCGGGCUCAAAUUGCUUAGAUACUAUACAGAAAUCCU	
	GUCAUUAUUUGGCCCCAGCCUACGGGACCCCAUAUCU	
	GCGGAGAUAUCUAUCCAGGCUUUGAGUUAUGCACUU GGACGAGAUAUCAAUAAGGUGUUAGAAAAGCUCGGA	
	UACAGUGGAGGCGAUUUACUAGGCAUCUUAGAGAGGC	
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	AGUCCUACUUCAUAGUCCUCAGUAUAGCCUAUCCGAC	
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	GAGGGGGUCUCGUACAACAUAGGCUCUCAAGAGUGG	
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	GUACCCGAUGAGUCCUCUGCUCCAAGAAUGCCUCCGG	
	GGGUCCACCAAGUCCUGUGCUCGUACACUCGUAUCCG	
	GGUCUUUUGGGAACCGGUUCAUUUUAUCACAAGGGA	
	ACCUAAUAGCCAAUUGUGCAUCAAUUCUUUGUAAGU GUUACACAACAGGUACGAUUAUUAAUCAAGACCCUGA	
	CAAGAUCCUAACAUACAUUGCUGCCGAUCGCUGCCCG	
	GUAGUCGAGGUGAACGGCGUGACCAUCCAAGUCGGGA	
	GCAGGAGGUAUCCAGACGCUGUGUACUUGCACAGAAU	
	UGACCUCGGUCCUCCCAUAUCAUUGGAGAGGUUGGAC	
	GUAGGGACAAAUCUGGGGAAUGCAAUUGCCAAAUUG GAGGAUGCCAAGGAAUUGUUGGAAUCAUCGGACCAG	
	AUAUUGAGAAGUAUGAAAGGUUUAUCGAGCACUAGC	
	AUAGUCUACAUCCUGAUUGCAGUGUGUCUUGGAGGG	
	UUGAUAGGGAUCCCCACUUUAAUAUGUUGCUGCAGG	
	GGGCGUUGUAACAAAAGGGAGAACAAGUUGGUAUG	
	UCAAGACCAGGCCUAAAGCCUGACCUUACAGGAACAU CAAAAUCCUAUGUAAGAUCGCUUUGAUGAUAAUAGG	
	CUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUUGGGC	
	CUCCCCCCAGCCCUCCUCCCCUUCCUGCACCCGUACC	
	CCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGGC	
C_F_MEASLES_B3.1	AUGGGUCUCAAGGUGAACGUCUCUGCCGUAUUCAUGG	70
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	UCAUUGGGGCAAUCUCUCUAAGAUAGGGGUAGUAGG	
	AAUAGGAAGUGCAAGCUACAAAGUUAUGACUCGUUC CAGCCAUCAAUCAUUAGUCAUAAAAUUAAUGCCCAAU	
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	CAGAAUACAGGAGACUACUAAGAACAGUUUUGGAAC	
	CAAUUAGGGAUGCACUUAAUGCAAUGACCCAGAACAU	
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	UGCACUUCACCGGUCCAUGCUGAACUCUCAGGCCAUC	
	GACAAUCUGAGAGCGAGCCUGGAAACUACUAAUCAGG	
	CAAUUGAGGCAAUCAGACAAGCAGGGCAGGAGAUGA	
	UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA	
	UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA AUGAGCUGAUACCGUCUAUGAACCAGCUAUCUUGUGA	
	UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA AUGAGCUGAUACCGUCUAUGAACCAGCUAUCUUGUGA UCUAAUCGGUCAGAAGCUCGGGCUCAAAUUGCUUAGA	
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	UAUUGGCUGUUCAGGGUGUCCAAGACUACAUCAAUA AUGAGCUGAUACCGUCUAUGAACCAGCUAUCUUGUGA UCUAAUCGGUCAGAAGCUCGGGCUCAAAUUGCUUAGA UACUAUACAGAAAUCCUGUCAUUAUUUGGCCCCAGCC UACGGGACCCCAUAUCUGCGGGGAGAUAUCCAUGCC UUUGAGUUAUGCACUUGGAGGGAAUAUCAAUAAGGU GUUAGAAAAGCUCGGAUACAGUGGAGGCGAUUUACU AGGCAUCUUAGAGAGCAGAGGAAUAAAGGCUCGGAU	
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	AGCAGGCGAAGACUGCCAUGCCCCAACAUACCUACCU	
	GCGGAGGUGGACGGUGAUGUCAAACUCAGUUCCAACC	
	UGGUGAUUCUACCUGGUCAAGAUCUCCAAUAUGUUU	
	UGGCAACCUACGAUACCUCCAGGGUUGAGCAUGCUGU	
	GGUUUAUUACGUUUACAGCCCAAGCCGCUCAUUUUCU	
	UACUUUUAUCCUUUUAGGUUGCCUAUAAAGGGGGUC	
	CCAAUCGAACUACAAGUGGAAUGCUUCACAUGGGAUC AAAAACUCUGGUGCCGUCACUUCUGUGUGCCUUGCGGA	
	CUCAGAAUCCGGUGGACUUAUCACUCACUCUGGGAUG	
	GUGGGCAUGGGAGUCAGCUGCACAGCUACCCGGGAAG	
	AUGGAACCAAUCGCAGAUAA	
GC H MEASLES B3	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAA	77
mRNA Sequence	UAUAAGAGCCACCAUGUCACCGCAACGAGACCGGAUA	
(assumes T100	AAUGCCUUCUACAAAGAUAACCCUUAUCCCAAGGGAA	
Tail)	GUAGGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG	
Sequence Length:	ACAGACCCUAUGUUCUGCUGGCUGUUCUGUUCGUCAU	
2126	GUUUCUGAGCUUGAUCGGAUUGCUGGCAAUUGCAGG	
	CAUUAGACUUCAUCGGGCAGCCAUCUACACCGCGGAG AUCCAUAAAAGCCUCAGUACCAAUCUGGAUGUGACUA	
	ACUCCAUCGAGCAUCAGGUCAAGGACGUGCUGACACC	
	ACUCUUUAAAAUCAUCGGGGAUGAAGUGGGCCUGAG	
	AACACCUCAGAGAUUCACUGACCUAGUGAAAUUCAUC	
	UCGGACAAGAUUAAAUUCCUUAAUCCGGAUAGGGAG	
	UACGACUUCAGAGAUCUCACUUGGUGCAUCAACCCGC	
	CAGAGAGGAUCAAACUAGAUUAUGAUCAAUACUGUG	
	UGAACUCAACUCUACUGGAGACCAGAACAACCACUCA GUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGGGCCC	
	ACUACAAUCAGAGGUCAAUUCUCAAACUGCUCAGGGCCC	
	CCUUGUUGGACUUGUACUUAGGUCGAGGUUACAAUG	
	UGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAUGUA	
	UGGGGGAACCUACCUAGUUGAAAAGCCUAAUCUGAAC	
	AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGUACC	
	GAGUGUUUGAAGUAGGUGUGAUCAGAAACCCGGGUU	
	UGGGGGCUCCGGUGUUCCAUAUGACAAACUAUUUUG	
	AGCAACCAGUCAGUAAUGGUCUCGGCAACUGUAUGGU	
	GGCUUUGGGGGAGCUCAAACUCGCAGCCCUUUGUCAC GGGGACGAUUCUAUCAUAAUUCCCUAUCAGGGAUCAG	
	GGGAAGGUGUCAGCUUCCAGCUCGUCAAGCUGGGUGU	
	CUGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCC	
	UUAUCAACGGAUGAUCCAGUGGUAGACAGGCUUUACC	
	UCUCAUCUCACAGAGGUGUCAUCGCUGACAAUCAAGC	
	AAAAUGGGCUGUCCCGACAACACGAACAGAUGACAAG	
	UUGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAA	
	GGUAAAAUCCAAGCACUCUGCGAGAAUCCCGAGUGGG	
	UACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGG	
	UCCUGUCUGUUGAUCUGAGUCUGACGGUUGAGCUUA	

	MeV Nucleic Acid Sequences	
Description	Sequence	SEQ ID NO:
	AAUCUAGCCUUAGGCGUAAUCAACACAUUGGAGUGG	
	AUACCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUG	
	UCCCAAUUAAGGAAGCAGGCGAAGACUGCCAUGCCCC	
	AACAUACCUACCUGCGGAGGUGGACGGUGAUGUCAAA CUCAGUUCCAACCUGGUGAUUCUACCUGGUCAAGAUC	
	UCCAAUAUGUUUUGGCAACCUACGAUACCUCCAGGU	
	UGAGCAUGCUGUGGUUUAUUACGUUUACAGCCCAAGC	
	CGCUCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUA	
	UAAAGGGGGUCCCAAUCGAACUACAAGUGGAAUGCU	
	UCACAUGGGAUCAAAAACUCUGGUGCCGUCACUUCUG UGUGCUUGCGGACUCAGAAUCCGGUGGACUUAUCACU	
	CACUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAG	
	CUACCCGGGAAGAUGGAACCAAUCGCAGAUAAUGAUA	
	AUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCU	
	UGGGCCUCCCCCAGCCCCUCCUCCCCUUCCUGCACCC	
	GUACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCG	
	ССААААААААААААААААААААААААААААААААААА	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	
C_H_MEASLES_D8	UCAAGCUUUUGGACCCUCGUACAGAAGCUAAUACGAC	78
Sequence, NT (5' JTR, ORF, 3'	UCACUAUAGGGAAAUAAGAGAGAAAAGAAGAGUAAG AAGAAAUAUAAGAGCCACCAUGUCACCACAACGAGAC	
JTR, ORF, 3	CGGAUAAAUGCCUUCUACAAAGACAACCCCCAUCCUA	
Sequence Length:	AGGGAAGUAGGAUAGUUAUUAACAGAGAACAUCUUA	
2065	UGAUUGAUAGACCUUAUGUUUUGCUGGCUGUUCUAU	
	UCGUCAUGUUUCUGAGCUUGAUCGGGUUGCUAGCCAU	
	UGCAGGCAUUAGACUUCAUCGGGCAGCCAUCUACACC	
	GCAGAGAUCCAUAAAAGCCUCAGCACCAAUCUGGAUG UAACUAACUCAAUCGAGCAUCAGGUUAAGGACGUGCU	
	GACACCACUCAAUCGAGCAUCAGGUUAAGGACGUGCU GACACCACUCUUCAAGAUCAUCGGUGAUGAAGUGGGC	
	UUGAGGACACCUCAGAGAUUCACUGACCUAGUGAAGU	
	UCAUCUCUGACAAGAUUAAAUUCCUUAAUCCGGACAG	
	GGAAUACGACUUCAGAGAUCUCACUUGGUGUAUCAAC	
	CCGCCAGAGAGAAUCAAAUUGGAUUAUGAUCAAUAC	
	UGUGCAGAUGUGGCUGCUGAAGAACUCAUGAAUGCA	
	UUGGUGAACUCAACUCUACUGGAGACCAGGGCAACCA	
	AUCAGUUCCUAGCUGUCUCAAAGGGAAACUGCUCAGG GCCCACUACAAUCAGAGGCCAAUUCUCAAACAUGUCG	
	CUGUCCCUGUUGGACUUGUAUUUAAGUCGAGGUUAC	
	AAUGUGUCAUCUAUAGUCACUAUGACAUCCCAGGGAA	
	UGUACGGGGGAACUUACCUAGUGGAAAAGCCUAAUC	
	UGAGCAGCAAAGGGUCAGAGUUGUCACAACUGAGCA	
	UGCACCGAGUGUUUGAAGUAGGUGUUAUCAGAAAUC CGGGUUUGGGGGCUCCGGUAUUCCAUAUGACAAACUA	
	UCUUGAGCAACCAGUCAGUAAUGAUUUCAGCAACUAC	
	AUGGUGGCUUUGGGGGAGCUCAAGUUCGCAGCCCUCU	
	GUCACAGGGAAGAUUCUAUCACAAUUCCCUAUCAGGG	
	AUCAGGGAAAGGUGUCAGCUUCCAGCUUGUCAAGCUA	
	GGUGUCUGGAAAUCCCCAACCGACAUGCAAUCCUGGG	
	UCCCCCUAUCAACGGAUGAUCCAGUGAUAGACAGGCU UUACCUCUCAUCUCA	
	CAAGCAAAAUGGGCUGUCCCGACAACACGGACAAU	
	ACAAGUUGCGAAUGGAGACAUGCUUCCAGCAGGCGUG	
	UAAGGGUAAAAUCCAAGCACUUUGCGAGAAUCCCGAG	
	UGGACACCAUUGAAGGAUAACAGGAUUCCUUCAUACG	
	GGGUCUUGUCUGUUGAUCUGAGUCUGACAGUUGAGC	
	UUAAAAUCAAAAUUGUUUCAGGAUUCGGGCCAUUGA	
	UCACACACGGUUCAGGGAUGGACCUAUACAAAUCCAA	
	CCACAACAAUAUGUAUUGGCUGACUAUCCCGCCAAUG AAGAACCUGGCCUUAGGUGUAAUCAACACAUUGGAG	
	UGGAUACCGAGAUUCAAGGUUAGUCCCAACCUCUUCA	
	CUGUUCCAAUUAAGGAAGCAGGCGAGGACUGCCAUGC	
	CCCAACAUACCUACCUGCGGAGGUGGAUGGUGAUGUC	
	AAACUCAGUUCCAAUCUGGUGAUUCUACCUGGUCAAG	
	AUCUCCAAUAUGUUCUGGCAACCUACGAUACUUCCAG	
	AGUUGAACAUGCUGUAGUUUAUUACGUUUACAGCCC	
	AAGCCGCUCAUUUUCUUACUUUUAUCCUUUUAGGUUG CCUGUAAGGGGGGGUCCCCAUUGAAUUACAAGUGGAA	
	UGCUUCACAUGGGACCAAAAACUCUGGUGCCGUCACU	
	UCUGUGUGCUUGCGGACUCAGAAUCUGGUGGACAUA	
	UCACUCACUCUGGGAUGGUGGGCAUGGGAGUCAGCUG	
	CACAGCCACUCGGGAAGAUGGAACCAGCCGCAGAUAG	
	UGAUAAUAGGCUGGAGCCUCGGUGGCCAAGCUUCUUG	
	CCCCUUGGGCCUCCCCCAGCCCCUCCUCCCUCCUG	

	MeV Nucleic Acid Sequences	
Description	Sequence	SEQ II NO:
	CACCCGUACCCCGUGGUCUUUGAAUAAAGUCUGAGU GGGCGGC	
GC_H_MEASLES_D8 ORF Sequence, NT	AUGUCACCACAACGAGACCGGAUAAAUGCCUUCUACA AAGACAACCCCCCAUCCUAAGGGAAGUAGGAUAGUUAU UAACAGAGAACAUCUUAUGAUUGAUAGACCUUAUGU UUGCUGGCUGUUCUAUUCGAGGCAUUAGACUUCAU GAUCGGGUUCCAAUCGACGCAUUAGACUUCUGACAGC UCAGCACCAAUCUGGAUGAACUAACUCAUUCAAUCGAGCA UCAGGUUAAGACGGCGUGACGACACCACUCUUCAAAAUC AUCGGUGAUGAAGUGGGCUUGAGGACACCUCAGAGA UUCACUUAAUCCGGACAGGAAUACGACUUCAAGAGA UUCACUUAGUGUAUCAACCGCCCAGAGAUUCA AAUUCCUUAAUCCGGACAGGAAUACGACUUCAAGAGA UUCACUUAGUGAUGAAGUUGAGGACACCUCAGAGA UUCACUUAGUGAUCAAUACUGUGCAGAGUUGGC GAAGAACUCAUGAUCAAUCGGUGUCCU GAAGAACUCAUGAUCAAUCGUUGCCAGAUGUGUCUC AAAGGGAACUGCUCAGGGCCCACUACAAUCAG UUGACUUCAAAACAUGUCGCUGUCCUAGAGAGUUAC UUGAGAUCAGGGUUACAAUCGUGUCCUAGUGUCUC AAAGGGAAACUGCUCAGGGCCCACUACAAUCAGUGC CAAUUCUCAAAACAUGUCGCUGUCCUAGUGUCUC AAGGGAAACUGCUCAGGGCCCACUACAAUCAGUGC CUUAGACAUCCAGGGAUCUGGCGGGAACUUACCU AUUUAAGUCCAGGGUUACAGGGGCAACUUACCU AUUUAAGUCCAGGGAUGCCGGGUAUUGAAGU AGUGUUAUCAGAAAUCUGGGGGCACCUAUGAGG CUCAAGUUCGCAGACAAUCGGGUUUGGGGAACUUACCU AUGAGAUUCCAGAAAUCUGGGGCACCAGUCAGG AUUGCCACAACUGACAGGGAUGUUGGAGGU CUCAGGUUUCAGCAACUGCCUGUUGGGGAACUCCGGU AUUCCAUAUGACAAACUAUCUUGAGCAACCAGUCAGG AUGCUUUCAGCAACUGCAUGGUGUGGGAAAUUCUA UCACAAUUUCAGCAACUGCAUGGGGAAGUUCUA CUCCAGUUGUCAAGGAUGCCGGUUUGGGGAAGUUCAA CUCCAGUUGCCAGCACUGGGUCUGGGAAAUCCCCA ACCGACUCGCUGGCAAUGAGGGUGUUGAAGGAG AUCCAUUCAGCAACUGCGUUAGGGAAAUCCCCA ACCGACUGCAUCCAGGGUUUAGGGAAAUCCCCA ACCGACAUCCAACUGGGUUUACCUCUCAUCUCA	79
GC_H_MEASLES_D8 mRNA Sequence (assumes T100 tail) Sequence Length: 2126	G*GGGAAUAAGAGAGAAAAGAAGAUAAGAAGAA UAUAAGAGCCACCAUGUCACCACACGAGACCGGAUA AAUGCCUUCUACAAAGACAACCCCCAUCCUAAGGGAA GUAGAUAGUUAUUAACAGAGAACAUCUUAUGAUUG AUAGACCUUAUUGUCUGCUGCUUCUAUUCGUCA UGUUUCUGAGCUUGAUCGGCUGCUUCUAUUCGAG GAUUCUGAGCUUGAUCGGGCAGCCAUCUACACCGCAGA GAUCCAUAAAAGCCUCAGCACCAAUCUGGAUGUAACU AACUCAAUCGAGCAUCAGGUUAAGGACGUGCUGACAC CACUCUUCAAGAUCAUCGGUGAUGAAGUUGCAU GGACACCUCAGAGAUUCACUGACCUAGUGAAGUUCAU CUCUGACAAGAUAAUCCCUUAGUGUAAGUUCAU UACGACUUCAAGAGUCACUUGACCUAGUGAAGUUCAU	80
	CAGAGAGAAUCAAUUGGAUUAUGAUCAAUACUGUG CAGAUGUGGCUGCUGAAGAACUCAUGAAUGCAUGG UGAACUCAACUC	

CCCUGUUGGACUUGUAUUUAAGUCGAGGUUACAAUG UGUCAUCUAUAGUCACUAUGACAUCCCAGGGAAUGUA

TABLE 13-continued

Description	Sequence	SEQ ID NO:
	CGGGGGAACUUACCUAGUGGAAAAGCCUAAUCUGAGC	
	AGCAAAGGGUCAGAGUUGUCACAACUGAGCAUGCACC	
	GAGUGUUUGAAGUAGGUGUUAUCAGAAAUCCGGGUU	
	UGGGGGCUCCGGUAUUCCAUAUGACAAACUAUCUUGA	
	GCAACCAGUCAGUAAUGAUUUCAGCAACUGCAUGGUG	
	GCUUUGGGGGAGCUCAAGUUCGCAGCCCUCUGUCACA	
	GGGAAGAUUCUAUCACAAUUCCCUAUCAGGGAUCAGG	
	GAAAGGUGUCAGCUUCCAGCUUGUCAAGCUAGGUGUC	
	UGGAAAUCCCCAACCGACAUGCAAUCCUGGGUCCCCC	
	UAUCAACGGAUGAUCCAGUGAUAGACAGGCUUUACCU	
	CUCAUCUCACAGAGGCGUUAUCGCUGACAAUCAAGCA	
	AAAUGGGCUGUCCCGACAACACGGACAGAUGACAAGU	
	UGCGAAUGGAGACAUGCUUCCAGCAGGCGUGUAAGG	
	GUAAAAUCCAAGCACUUUGCGAGAAUCCCGAGUGGAC	
	ACCAUUGAAGGAUAACAGGAUUCCUUCAUACGGGGUC	
	UUGUCUGUUGAUCUGAGUCUGACAGUUGAGCUUAAA	
	AUCAAAAUUGUUUCAGGAUUCGGGCCAUUGAUCACAC	
	ACGGUUCAGGGAUGGACCUAUACAAAUCCAACCACAA	
	CAAUAUGUAUUGGCUGACUAUCCCGCCAAUGAAGAAC	
	CUGGCCUUAGGUGUAAUCAACACAUUGGAGUGGAUA	
	CCGAGAUUCAAGGUUAGUCCCAACCUCUUCACUGUUC	
	CAAUUAAGGAAGCAGGCGAGGACUGCCAUGCCCCAAC	
	AUACCUACCUGCGGAGGUGGAUGGUGAUGUCAAACUC	
	AGUUCCAAUCUGGUGAUUCUACCUGGUCAAGAUCUCC	
	AAUAUGUUCUGGCAACCUACGAUACUUCCAGAGUUGA	
	ACAUGCUGUAGUUUAUUACGUUUACAGCCCAAGCCGC	
	UCAUUUUCUUACUUUUAUCCUUUUAGGUUGCCUGUA	
	AGGGGGGUCCCCAUUGAAUUACAAGUGGAAUGCUUC	
	ACAUGGGACCAAAAACUCUGGUGCCGUCACUUCUGUG	
	UGCUUGCGGACUCAGAAUCUGGUGGACAUAUCACUCA	
	CUCUGGGAUGGUGGGCAUGGGAGUCAGCUGCACAGCC	
	ACUCGGGAAGAUGGAACCAGCCGCAGAUAGUGAUAA	
	UAGGCUGGAGCCUCGGUGGCCAAGCUUCUUGCCCCUU	
	GGGCCUCCCCCAGCCCUCCUCCCCUUCCUGCACCCG	
	UACCCCCGUGGUCUUUGAAUAAAGUCUGAGUGGGCGG	
	Саадаалаалаалаалаалаалаалаалаалаалаалаа	
	<u>AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA</u>	
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	

TABLE 14

MeV Amino Acid Sequences		
Description	Sequence	SEQ ID NO:
GC_F_MEASLES_B3.1 ORF Sequence, AA	MGLKVNVSAVFMAVLLTLQTPAGQIHWGNLSKIGVV GIGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVEIA EYRRLRTVLEPIRDALNAMTQNIRPVQSVASSRHK RPAGVVLAGAALGVATAAQITAGIALHRSMLNSQAID NLRASLETTNQAIEAIRQAGQEMILAVQGVQVINNE LIPSMNQLSCDLIGQKLGLKLRYYTEILSLFGPSLRDP ISAEISIQALSYALGGDINKVLEKLGYSGGDLLGILESR GIKARITHVDTESYFIVLSIAYPTLSEIKGVIVHRLEGVS YNIGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEG TVCSQNALYPMSPLLQECLRGSTKSCARTLVSGSFGN RFILSQGNLIANCASILCKCYTTGTINQDPDKILTYIAA DRCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGPPISLE RLDVGTNLGNAIAKLEDAKELLESSDQILRSMKGLSST SIVYILIAVCLGGLIGIPTLICCCRGRCNKKGEQVGMSR PGLKPDLTGTSKSYVRSL*	47
GC_F_MEASLES_D8 ORF Sequence, AA	MGLKVNVSVIFMAVLLTLQTPTGQIHWGNLSKIGVVG VGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVGIAE YRRLLRTVLEPIRDALNAMTQNIRPVQSVASSRRHKR FAGVVLAGAALGVATAAQITAGIALHQSMLNSQAIDN LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNELI PSMNQLSCDLIGQKLGLKLRYYTEILSLFGPSLRDPIS AEISIQALSYALGGDINKVLEKLGYSGGDLLGILESRGI KARITHVDTESYFIVLSIAYPTLSEIKGVIVHRLEGVSY NIGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEGT VCSQNALYPMSPLLQECLRGSTKSCARTLVSGSFGNR	48

	MeV Amino Acid Sequences	CEO ID
Description	Sequence	SEQ ID NO:
	FILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAAD HCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGPPISLER LDVGTNLGNAIAKLEDAKELLESSDQILRSMKGLSSTS IVYILIAVCLGGLIGIPALICCCRGRCNKKGEQVGMSRP GLKPDLTGTSKSYVRSL*	
GC_H_MEASLES_B3 ORF Sequence, AA	MSPQRDRINAFYKDNPYPKGSRIVINREHLMIDRPYVL LAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLSTN LDVTNSIEHQVKDVLTPLPKIIGDEVGLRTPQRFTDLV KFISDKIKFLNPDREYDRRDLTWCINPPERIKLDYDQY CADVAAEELMNALVNSTLLETRTTTQFLAVSKGNCS GPTTIRGQFSNMSLSLLDLYLGRGYNVSSIVTMTSQG MYGGTYLVEKPNLNSKGSELSQLSMYRVPEVGVIRNP GLGAPVFHMTNYFBQPVSNGLGNCMVALGELKLAAL CHGDDSIIPYQGSGKGVSFQLVKLGVKSPTDMQSW VPLSTDDPVVDRLVLSSHEVIADNQAKWAVPTTRT DDKLRMETCFQQACKGKIQALCENPEWVPLKDNRIPS YGVLSVDLSLTVELKIKIASGFGPLITHGSGMDLYKSN CNNVYWLTIPPMRNLALGVINTLEWIPRKVSPNLFTV PIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILPGQDL QYVLATYDTSRVEHAVVYVYSPSRSFSVPYPFLPIK GVPIELQVECFTWDQKLWCRHFCVLADSESGGLITHS GMVGMGVSCTATREDGTNRR*	49
GC_H_MEASLES_D8 ORF Sequence, AA	MSPQRDRINAFYKDNPHPKGSRIVINREHLMIDRPYVL LAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLSTN LDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRFTDLV KFISDKIKFLNPDREYDFRDLTWCINPPERIKLDYDQY CADVAAEELMNALVNSTLLETRATNQFLAVSKGNCS GPTTIRGQFSNMSLSLLDLYLSRGYNVSSIVTMTSQGM YGGTYLVEKPNLSSKGSELSQLSMHRVFEVGVIRNPG LGAPVFHMTNYLEQPVSNDFSNCMVALGELKFAALC HREDSITIPYQGSCKGVSFQLVKLGVMKSPTDMQSW VPLSTDDPVIDRLYLSSHRGVIADNQAKWAVPTTRTD DKLRMETCFQQACKGKIQALCENFEWTPLKDNRIFSY GVLSVDLSLTVELKIKIVSGFGPLITHGSGMDLYKSNH NNMYWLTIPPMKNLALGVINTLEWIPRFKVSPNLFTV PIKEAGEDCHAPTYLPAEVDGDVKLSSNLVILPGQDL QVVLATYDTSRVEHAVVYVYSPSRSFSYPYPRLPV RGVPIELQVECFTWDQKLWCRHFCVLADSESGGHITH SGWCMGVSCTATREDGTSRR*	50

TABLE 15

Туре	Virus Name	GenBank Accession
hemagglutinin	hemagglutinin [Measles virus strain Moraten]	AAF85673.1
hemagglutinin	hemagglutinin [Measles virus strain Rubeovax]	AAF85689.1
hemagglutinin	hemagglutinin [Measles virus]	AAF89824.1
hemagglutinin	hemagglutinin protein [Measles virus]	CAA91369.1
hemagglutinin	hemagglutinin [Measles virus]	BAJ23068.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39848.1
hemagglutinin	hemagglutinin [Measles virus]	AAA50551.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P08362.1
hemagglutinin	hemagglutinin [Measles virus]	AAB63802.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56650.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56642.1
hemagglutinin	hemagglutinin [Measles virus]	AAA74936.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAH56665.1
hemagglutinin	hemagglutinin [Measles virus]	ACC86105.1
hemagglutinin	hemagglutinin [Measles virus strain Edmonston-Zagreb]	AAF85697.1
hemagglutinin	hemagglutinin [Measles virus]	AAR89413.1
hemagglutinin	hemagglutinin [Measles virus]	AAA56653.1
hemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P35971.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94916.1
hemagglutinin	hemagglutinin [Measles virus]	AAC03036.1
hemagglutinin	hemagglutinin [Measles virus]	AAF85681.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94927.1
hemagglutinin	Hemagglutinin [Measles virus]	CAB94925.1
hemagglutinin	hemagglutinin protein [Measles virus]	BAB39835.1

TABLE 15-continued

Гуре	Virus Name	GenBank Accession
hemagglutinin	Hemagglutinin [Measles virus]	CAB94931.1
hemagglutinin	hemagglutinin [Measles virus genotype A]	AFO84712.1
nemagglutinin	hemagglutinin [Measles virus]	AAA56639.1
nemagglutinin	Hemagglutinin [Measles virus]	CAB94926.1
nemagglutinin	hemagglutinin protein [Measles virus]	BAB39836.1
nemagglutinin	Hemagglutinin [Measles virus]	CAB94929.1
nemagglutinin	RecName: Full = Hemagglutinin glycoprotein	P06830.1
nemagglutinin	Hemagglutinin [Measles virus]	CAB94928.1
nemagglutinin	hemagglutinin protein [Measles virus]	BAB39837.1 AAA74935.1
nemagglutinin nemagglutinin	hemagglutinin [Measles virus] hemagglutinin protein [Measles virus]	CAB43780.1
iemagglutinin	hemagglutinin [Measles virus]	BAA09952.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43815.1
emagglutinin	hemagglutinin [Measles virus]	AAF28390.1
emagglutinin	Hemagglutinin [Measles virus]	CAB94923.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43785.1
emagglutinin	hemagglutinin [Measles virus]	ABD34001.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43782.1
nemagglutinin	hemagglutinin protein [Measles virus]	CAB43781.1
emagglutinin	hemagglutinin [Measles virus]	BAH22353.1
emagglutinin	hemagglutinin [Measles virus]	AAC35878.2
emagglutinin	hemagglutinin protein [Measles virus]	AAL86996.1
emagglutinin	hemagglutinin [Measles virus]	CAA76066.2
nemagglutinin	hemagglutinin [Measles virus]	AAA46428.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43803.1
emagglutinin	Hemagglutinin [Measles virus]	CAB94918.1 AAF72162.1
nemagglutinin nemagglutinin	hemagglutinin [Measles virus] hemagglutinin [Measles virus]	AAF72162.1 AAM70154.1
nemagglutinin	hemagglutinin protein [Measles virus]	CAB43776.1
iemagglutinin	hemagglutinin [Measles virus genotype D4]	ACT78395.1
emagglutinin	hemagglutinin [Measles virus genotype D7]	AAL02030.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43789.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43774.1
emagglutinin	Hemagglutinin [Measles virus]	CAB94920.1
emagglutinin	Hemagglutinin [Measles virus]	CAB94922.1
nemagglutinin	hemagglutinin [Measles virus]	ABB59491.1
nemagglutinin	hemagglutinin protein [Measles virus]	BAB39843.1
nemagglutinin	hemagglutinin protein [Measles virus]	CAB43804.1
remagglutinin	hemagglutinin [Measles virus]	AAX52048.1
nemagglutinin	Hemagglutinin [Measles virus]	CAB94930.1
nemagglutinin	hemagglutinin [Measles virus]	AAA74526.1
nemagglutinin	hemagglutinin protein [Measles virus]	CAB43814.1 ABB59493.1
nemagglutinin nemagglutinin	hemagglutinin [Measles virus] hemagglutinin [Measles virus genotype D4]	AAL02019.1
nemagglutinin	Hemagglutinin [Measles virus]	CAB94919.1
emagglutinin	hemagglutinin protein [Measles virus]	AAL86997.1
emagglutinin	hemagglutinin [Measles virus genotype C2]	AAL02017.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43769.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43808.1
emagglutinin	hemagglutinin [Measles virus]	BAO97032.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43805.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43777.1
emagglutinin	hemagglutinin [Measles virus]	AAL67793.1
emagglutinin	hemagglutinin [Measles virus]	AAF89816.1
emagglutinin	hemagglutinin [Measles virus genotype D4]	AAL02020.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43786.1
emagglutinin	hemagglutinin protein [Measles virus strain	AEP40452.1
	MVi/New Jersey.USA/45.05]	
emagglutinin	hemagglutinin [Measles virus]	AAA74531.1
emagglutinin	hemagglutinin [Measles virus]	AAB63800.1
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iemagglutinin	hemagglutinin protein [Measles virus]	CAB43810.1
iemagglutinin	hemagglutinin [Measles virus]	AAF89817.1
emagglutinin	hemagglutinin [Measles virus] hemagglutinin [Measles virus genotype D6]	AAL02022.1
emagglutinin	hemagglutinin protein [Measles virus]	CAB43800.1
emagglutinin	hemagglutinin protein [Measles virus]	AGA17219.1
nemagglutinin	hemagglutinin protein [Measles virus]	CAB43770.1
emagglutinin	hemagglutinin protein [Measles virus strain	AEP40444.1
	MVI/Texas.USA/4.07]	
nemagglutinin	hemagglutinin [Measles virus]	AAX52047.1
emagglutinin	hemagglutinin [Measles virus]	AAB63794.1
nemagglutinin	hemagglutinin [Measles virus]	AAB63796.1
nemagglutinin	hemagglutinin [Measles virus]	AAA74528.1
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emagglutinin	hemagglutinin [Measles virus]	AAB63795.1

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	iusion protein	iusion protein [measies virus genotype H1]	AIU00714.1

TABLE 15-continued

Туре	Virus Name	GenBank Accessio
fusion protein	fusion protein [Measles virus genotype H1]	AIG53694.1
fusion protein	fusion protein [Measles virus genotype 111]	AIG53668.1
fusion protein	fusion protein [Measles virus]	ACC86094.1
iusion protein	fusion protein [Measles virus]	AIG53670.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53070.1
fusion protein	fusion protein [Measles virus genotype B3]	AGA17216.1
fusion protein	fusion protein [Measles virus genotype B3]	AIG53671.1
fusion protein	fusion protein [Measles virus strain	AEP40451.1
usion protein	MVi/New Jersey.USA/45.05]	AEI 40451.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53684.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53688.1
usion protein	fusion protein [Measles virus genotype B3]	AGA17214.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53683.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53667.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53686.1
lusion protein	fusion protein [Measles virus genotype H1]	AIG53685.1
lusion protein	fusion protein [Measles virus genotype H1]	AIG53681.1
•	unnamed protein product [Measles virus]	CAA34589.1
lusion protein	fusion protein [Measles virus genotype H1]	AIG53678.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53710.1
iusion protein	fusion protein [Measles virus genotype H1]	AIG53669.1
iusion protein	fusion protein [Measles virus genotype H1]	AIG53664.1
fusion protein	fusion protein [Measles virus]	AAA50547.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53679.1
fusion protein	fusion protein [Measles virus genotype 111]	AIG53709.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53672.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53697.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53689.1
•	fusion protein [Measles virus genotype H1]	AIG53676.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53675.1
fusion protein		
fusion protein	fusion protein [Measles virus genotype H1]	AIG53663.1
usion protein	fusion protein [Measles virus]	BAA19841.1
fusion protein	fusion protein [Measles virus]	AAF02701.1
usion protein	fusion protein [Measles virus genotype H1]	AIG53680.1
fusion protein	fusion protein [Measles virus genotype H1]	AIG53674.1
c protein	C protein [Measles virus strain Moraten]	AAF85670.1
C protein	RecName: Full = Protein C	P03424.1
C protein	C protein [Measles virus]	ACN54404.1
C protein	C protein [Measles virus]	ACN54412.1
C protein	RecName: Full = Protein C	P35977.1
C protein	C protein [Measles virus]	AAF85678.1
C protein	C protein [Measles virus]	ABD33998.1
C protein	unnamed protein product [Measles virus]	CAA34586.1
C protein	C protein [Measles virus]	BAJ51786.1
C protein	C protein [Measles virus]	BAA33869.1
C protein	virulence factor [Measles virus]	ABO69700.1
C protein	C protein [Measles virus]	NP_056920.1
C protein	C protein [Measles virus]	ADO17333.1
C protein	C protein [Measles virus]	ACC86082.1
C protein	C protein [Measles virus]	BAA33875.1
C protein	C protein [Measles virus]	ABY21189.1
C protein	C protein [Measles virus]	BAE98296.1
C protein	C protein [Measles virus]	ADU17782.1
C protein	C protein [Measles virus strain	AEP40417.1
-	MVi/Virginia.USA/15.09]	
C protein	C protein [Measles virus]	ADU17814.1
C protein	C protein [Measles virus]	ADU17798.1
C protein	C protein [Measles virus genotype D4]	AFY12700.1
C protein	C protein [Measles virus]	ADU17784.1
C protein	C protein [Measles virus strain	AEP40465.1
	MVi/California.USA/16.03]	
C protein	C protein [Measles virus]	ABB71643.1
C protein	C protein [Measles virus]	AEI91027.1
C protein	C protein [Measles virus]	ADU17874.1
C protein	C protein [Measles virus]	ADU17903.1
C protein	C protein [Measles virus]	CAA34579.1
C protein	C protein [Measles virus]	ADU17790.1
	C protein [Measles virus]	ADU17790.1 ADU17800.1
C protein	C protein [Measles virus]	
C protein	C protein [Measles virus]	ABB71667.1
C protein	unnamed protein product [Measles virus]	CAA34572.1
] protein	C protein [Measles virus strain	AEP40433.1
-	MVi/Arizona.USA/11.08/2]	
protein [C protein [Measles virus]	ADU17830.1
C protein	C protein [Measles virus]	ADU17947.1
C protein	C protein [Measles virus]	ADU17818.1
c protein	1 L J	

TABLE 15-continued

Туре	Virus Name	GenBank Accessio
туре	vitus ivalle	Gendank Accessio
a . :	MVi/New Jersey,USA/45.05]	
C protein	C protein [Measles virus strain MV//Terres LISA/4.07]	AEP40441.1
C protein	MVi/Texas.USA/4.07] C protein [Measles virus]	ADU17864.1
C protein	C protein [Measles virus]	ADU17838.1
C protein	C protein [Measles virus]	ADU17881.1
C protein	C protein [Measles virus strain	AEP40425.1
	MVi/Washington.USA/18.08/1]	
C protein	C protein [Measles virus]	ADU17927.1
C protein	C protein [Measles virus]	ADU17953.1
C protein	C protein [Measles virus]	ADU17889.1
C protein	C protein [Measles virus]	ADU17963.1
C protein	C protein [Measles virus]	ADU17893.1
C protein	C protein [Measles virus]	ADU17820.1
C protein	C protein [Measles virus]	ABB71651.1
C protein	C protein [Measles virus]	ADU17786.1
C protein	C protein [Measles virus] C protein [Measles virus]	ADU17862.1 ADU17923.1
C protein C protein	C protein [Measles virus] C protein [Measles virus]	ADU17923.1 ADU17959.1
C protein	C protein [Measles virus]	ADU17959.1 ADU17951.1
C protein	C protein [Measles virus]	ADU179916.1
C protein	C protein [Measles virus]	ADU17957.1
C protein	C protein [Measles virus]	ADU17925.1
C protein	C protein [Measles virus]	ADU17901.1
C protein	C protein [Measles virus]	ADU17887.1
C protein	C protein [Measles virus]	ADU17832.1
C protein	C protein [Measles virus]	ADU17891.1
C protein	C protein [Measles virus]	ADU17961.1
C protein	C protein [Measles virus]	ADU17872.1
C protein	C protein [Measles virus]	ADU17929.1
C protein	C protein [Measles virus]	ADU17908.1
C protein	C protein [Measles virus]	ADU17910.1
C protein	C protein [Measles virus]	ADU17921.1
C protein	C protein [Measles virus]	ADU17824.1
C protein	C protein [Measles virus strain MVi/Pennsylvania.USA/20.09]	AEP40473.1
C protein	C protein [Measles virus]	ADU17828.1
C protein	C protein [Measles virus]	ADU17812.1
C protein	C protein [Measles virus genotype D8]	AFY12692.1
C protein	nonstructural C protein [Measles virus]	ABA59559.1
C protein	RecName: Full = Protein C	Q00794.1
C protein	nonstructural C protein [Measles virus]	ADO17934.1
C protein	nonstructural C protein [Measles virus]	ACJ66773.1
C protein	C protein [Measles virus genotype G3]	AFY12708.1
C protein	RecName: Full = Protein C	P26035.1
C protein	C protein [Measles virus]	BAA84128.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName:	Q77M43.1
	Full = Nucleocapsid protein;	
	Short = NP; Short = Protein N	
nucleoprotein	nucleocapsid protein [Measles virus strain Rubeovax]	AAF85683.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName:	Q89933.1
	Full = Nucleocapsid protein; Short = NP; Short = Protein N	
nucleoprotein	short = NP; Short = Protein N mucleocapsid protein [Measles virus strain AIK-C]	AAF85659.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54102.1
nucleoprotein	nucleoprotein [Measles virus]	AAA56643.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03050.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18990.1
nucleoprotein	nucleoprotein [Measles virus]	AAA56640.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName:	P35972.1
	Full = Nucleocapsid protein;	
	Short = NP; Short = Protein N	
nucleoprotein	RecName: Full=Nucleoprotein; AltName:	P10050.1
	Full = Nucleocapsid protein;	
	Short = NP; Short = Protein N	
nucleoprotein	N protein [Measles virus]	BAB60956.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName:	BIAAA7.1
	Full = Nucleocapsid protein;	
	Short = NP; Short = Protein N	
nucleoprotein	nucleoprotein [Measles virus]	AAA18991.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46894.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46871.1
	pucieoprotein (Menciec surgia)	CAB46872.1
nucleoprotein	nucleoprotein [Measles virus]	
nucleoprotein nucleoprotein	nucleoprotein [Measles virus]	ABU49606.1
nucleoprotein nucleoprotein nucleoprotein nucleoprotein		

MeV NCBI Accession Numbers (Amino Acid Sequences)		
Туре	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	CAB46892.1
nucleoprotein	unnamed protein product [Measles virus]	CAA34584.1
nucleoprotein	nucleoprotein [Measles virus]	AAA18997.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46863.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30352.1
nucleoprotein nucleoprotein	nucleoprotein [Measles virus] nucleocapsid protein [Measles virus]	ABI54103.1 AAA46433.1
nucleoprotein	mucleoprotein [Measles virus]	CAB46902.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46873.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46906.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74547.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74537.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46862.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09961.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15875.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15871.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46882.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60124.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54104.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46869.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46880.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74541.1
nucleoprotein	nucleocapsid protein [Measles virus strain	AEP40446.1
	MVi/New Jersey.USA/45.05]	ADIE 4110.1
nucleoprotein	nucleoprotein [Measles virus] nucleoprotein [Measles virus]	ABI54110.1 CAB46903.1
nucleoprotein nucleoprotein	nucleoprotein [Measles virus]	CAB46899.1
nucleoprotein	mucleoprotein [Measles virus]	CAB46901.1
nucleoprotein	mucleocapsid protein [Measles virus]	ABB71640.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60113.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60114.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60116.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46895.1
nucleoprotein	nucleoprotein Measles virus	CAB60121.1
nucleoprotein	nucleoprotein [Measles virus]	ABI54111.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46889.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46898.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	ALE27083.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60118.1
nucleoprotein	nucleocapsid protein [Measles virus]	CAA34570.1
nucleoprotein	nucleoprotein [Measles virus]	AAC29443.1
nucleoprotein	nucleocapsid protein [Measles virus strain MVi/Washington.USA/18.08/1]	AEP40422.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15872.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46874.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74550.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71648.1
nucleoprotein nucleoprotein	nucleoprotein [Measles virus] nucleoprotein [Measles virus]	CAB46900.1 BAH22440.1
nucleoprotein	nucleocapsid protein [Measles virus]	AAA46432.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA33867.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74539.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60115.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60123.1
nucleoprotein	nucleocapsid protein [Measles virus]	ABB71664.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60125.1
nucleoprotein	nucleoprotein Measles virus	AAA74546.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46886.1
nucleoprotein	nucleoprotein [Measles virus]	BAH22350.1
nucleoprotein	nucleoprotein [Measles virus]	CAB46867.1
nucleoprotein	nucleocapsid protein [Measles virus]	BAA09954.1
nucleoprotein	nucleoprotein [Measles virus]	AAO15873.1
nucleoprotein	nucleocapsid protein [Measles virus]	AEP95735.1
nucleoprotein	nucleoprotein [Measles virus]	AAL37726.1
nucleoprotein	nucleoprotein [Measles virus]	AAA74549.1
nucleoprotein	RecName: Full = Nucleoprotein; AltName: Full = Nucleocapsid protein;	P26030.1
	Short = NP; Short = Protein N	
nucleoprotein	nucleoprotein [Measles virus ETH55/99]	AAK07777.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17238.1
nucleoprotein	nucleoprotein [Measles virus]	AEF30351.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17242.1
	nucleoprotein [Measles virus ETH54/98]	AAK07776.1
nucleoprotein		
nucleoprotein	nucleoprotein [Measles virus]	AAA74548.1
nucleoprotein nucleoprotein nucleoprotein nucleoprotein		

TABLE 15-continued

Туре	Virus Name	GenBank Accession
nucleoprotein	nucleoprotein [Measles virus]	AAA19223.1
nucleoprotein	nucleoprotein [Measles virus genotype B3]	AGA17241.1
nucleoprotein	nucleoprotein [Measles virus]	CAB60122.1
nucleoprotein	nucleoprotein [Measles virus]	CAC34599.1
nucleoprotein	nucleoprotein [Measles virus]	AAC03042.1
nucleoprotein	mucleoprotein [Measles virus]	CAC34604.1
nucleoprotein	mucleoprotein [Measles virus]	AAA74544.1
nucleoprotein	mucleocapsid protein [Measles virus]	NP 056918.1
V Protein	RecName: Full = Non-structural protein V	Q9IC37.1
V Protein	RecName: Full = Non-structural protein V	Q9EMA9.1
V Protein	V protein [Measles virus]	ACN54411.1
V Protein	V protein [Measles virus]	ACN54403.1
V Protein	V protein [Measles virus]	AEP95742.1
V Protein	V protein [Measles virus strain	AEP40416.1
v 110tem	MVi/Virginia.USA/15.09]	ALA 40410.1
V Protein	V protein [Measles virus]	ADU17801.1
V Protein	V protein [Measles virus]	ADU17801.1 ADU17849.1
V Protein V Protein	V protein [Measles virus]	ABB71642.1
V Protein		
V Protein	V protein [Measles virus genotype D8]	AFY12693.1
V Protein	V protein [Measles virus]	YP_003873249.2 AEP40432.1
v Protein	V protein [Measles virus strain	AEP40432.1
IZ Durata las	MVi/Arizona.USA/11.08/2]	D2 (0)(1)
V Protein	RecName: Full = Non-structural protein V	P26036.1
V Protein	V protein [Measles virus strain	AEP40464.1
VD 4 1	MVi/California.USA/16.03]	
V Protein	V protein [Measles virus strain	AEP40456.1
	MVi/California.USA/8.04]	
V Protein	V protein [Measles virus]	ABY21188.1
V Protein	V protein [Measles virus strain	AEP40424.1
	MVi/Washington.USA/18.08/1]	
V Protein	V protein [Measles virus]	BAH96581.1
V Protein	V protein [Measles virus]	ABB71666.1
V Protein	RecName: Full = Non-structural protein V	P60168.1
V Protein	V protein [Measles virus]	BAH96589.1
V Protein	V protein [Measles virus]	ADU17954.1
V Protein	V protein [Measles virus strain	AEP40400.1
	MVi/New York.USA/26.09/3]	
V Protein	V protein [Measles virus]	ABY21196.1
V Protein	virulence factor [Measles virus]	ABO69701.1
V Protein	V protein [Measles virus]	ABB71650.1
V Protein	V protein [Measles virus]	ACC86086.1
V Protein	V protein [Measles virus genotype D4]	AFY12702.1
V Protein	V protein [Measles virus strain	AEP40448.1
	MVi/New Jersey.USA/45.05]	
V Protein	V protein [Measles virus]	BAE98295.1
V Protein	V protein [Measles virus]	ACC86083.1
V Protein	V protein [Measles virus]	ACU5139.1
V Protein	V protein [Measles virus]	ADO17334.1
V Protein	V protein [Measles virus]	ADU17930.1
V Protein	V protein [Measles virus genotype G3]	AFY12710.1
V Protein	V protein [Measles virus genotype 05]	AEP40472.1
, Hotelli		ALI 40472.1
17 D 4 1	MVi/Pennsylvania.USA/20.09]	A DI 11 2000 1
V Protein	phosphoprotein [Measles virus]	ADU17839.1
V Protein	V protein [Measles virus]	ADU17894.1
V Protein	V protein [Measles virus]	ACN50010.1
V Protein	V protein [Measles virus]	ADU17892.1
	unnamed protein product [Measles virus]	CAA34585.1
V Protein	V protein [Measles virus]	ABD33997.1

TABLE 16

Name	Sequence	SEQ ID NO:
	Flagellin Nucleic Acid Sequences	
NT (5' UTR, ORF, 3' UTR)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTAT AGGGAAATAAGAGAGAAAAGAAGAGAGTAAGAAGAAATATAAG AGCCACCATGGCACAAGTCATTAATACAAACAGCCTGTCGCTG TTGACCCAGAATAACCTGAACAAATCCCAGTCCGCACTGGGGCA CTGCTATCGAGGCGTTGGCTCTCCGGTATCCAACAGCGG AAAGACGATGCGGCAGGCCAGGC	51

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TABLE 16-continued

Name	Sequence	SEQ ID NO:
	Sequence	
ORF Sequence, NT	CTTCTTGCCCCTGGGCCTCCCCCCAGCCCCTCCTCCCCCCTCCTG CACCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAGTGGGGGGGC ATGGCACAAGTCATTAATACAAACAGCCTGTCGCTGTTGACCC AGAATAACCTGAACAAATCCCAGTCCGCACTGGGCACTGCTAT CGACGGTTGTCTTCCGGTCTGCGTATCAACGGCGACTGCTAT CGACGGCAGGACAGCAGGCGTTGCAACCGTTTACCGCGAACA TCAAAGGTCTGACTCAGGCTTCCCGTAACGCATTACCGCGAACA ACGACCTGCAGCCGTGGCGTGAACGAACACAC AACAACCTGCAGGCCGTGAACGACTCCAGCCTGAACGACAT CTCAATGCCAGCCTGTGCCTGAACCGCGTCAGCTGCGGA ATGGTACTAACTCCAGTCTGACCTCGACTCCAGGCTGAA ATCACCCAGCGCCTGAACGAAATCCAACCTGGCAGGA CTCAGTTCAACGGCGGTGAAAGTCCTGGCGCGGAGACAACACCCT GACCATCCAGGTGGTGCAACGACGGTGAAACTACCGGCAGA CTCAGTTCAACGGCGTGAAAGTCCTGGCGCGGGAGAACACCCCT GACCATCCAGGTGGTGCCAACGACGGGAGAACACCCCT GACCATCCAGGTGGTGCCAACGACGGGAGAACACCCCT GACCATCCAGGTGGTGCCAACGCCGGAAAGAACTGCTGTAAC CGTTGATAAAGAATCAGCTCTAAAACACTGGGACTGGTAAAC CGTTGATAAAGAATCACCTATAAAAATGGTACAGATCGCTGTAAC GCCCAGAGCATACTGGGCTGATATCAAATTGATACA GCCCAGAGCATACTGGGGCTGATACCAAGGACGTGGTGTCA ATACTTATTAGATGTATAAACTACCAAGAGAGTTAATATTGATAC GACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACAGCTAT CGGGGAACGGCCCATATAACCACACGTGCGGAAGCTACAGCTAT CGGGGAACGGCCCATATAACCCACAACTACGACAACTACGCTTAT CGGGGAACGGCCCATATAACCCACAACTACGGCTGAACTAC CAAAGAGGGGTGTTACTGGCGCCGATAAGGCTAATTGCGGCTACA CAAAGAGGGGCTTACTGGCGCCGATAAGGACAATACTAGCCTT GTAAAACTATCGTTGGAGGATAAAACGGTAAGGTAA	52
mRNA Sequence (assumes T100 tail)	TACTGCGT G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAUAUAA GAGCCACCAUGGCACAAGUCAUUAAUACAAACAGCCUGUCGC UGUUGACCCAGAAUAACCUGAACAAAUCCCAGUCCGCACUGG GCACUGCUAUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACA	53

GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG

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TABLE 16-continued

SEQ ID NO:
81

Name	Sequence	SEQ ID NO:
	CGCAAAACGUCCUCUCUUUACUGCGUUGAUAAUAGGCUGGAG CCUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCAGC CCCUCCUCCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAA UAAAGUCUGAGUGGGCGGC	
ORF Sequence, NT	AUGGCACAAGUCAUUAAUACAAACAGCCUGUCGCUGUUGACC CAGAAUAACCUGAACAAAUCCCAGUCCGCACUGGCACUGCU AUCGAGCGUUUGUCUUCCGGUCUGCGUAUCAACAGCGCGAAA GACGAUGCGCCAGGACAGGCGUUCCCGUAACGCUAACGAC GGUAUCUCCAUUGCGCAGACCACUGAAGGCCGCCUGAACGAC GGUAUCUCCAUUGCGCAGACCACUGAAGGCCGCCUGAACGAA AUCAAAAGACACACCACUGAAGCUCCCGUGAACGCUAACGAC GGUAUCUCCAUUGCGCAGACCCAUGAAGCCGCUCAACGAC CAGGCUGAAUGCACACCCAGGCGUGAACUGGCGGUUCAG UCUGCGAAUGGUACUAACGCCUGAACUCGACCUCCACUCCAUC CAGGCUGAAUCACCCAGGCCUGAACGAAAUCGACCGUGAA AUCACACACCCUGACCAUCCAGGUUGAGCUCAACGCCGUGAA ACUAUCGAUAUGACUAACGGCCUGAAAGUCCUGGCGCAG GACAACACCCUGACCAUCCAGGUUGAUGACGCUCUAAAAACCU CGGACUUGAUAAGCUUAAUGUCCAAGAUGCCUACACCCCGGA AGAACUGCUGUAACGCUUGAUAAAAUCAGCUCUUAAAAAGG GUACAGAUCCUUUUACAGCCCAGGGGUUACUGGGCUGAU AUCAAAUUUAAAGAUGUCCAAGAUGCUAUAUAAAAGG CUGCAAUUGGCGGUGGUGCAACGGGGUUACUGGGGCUGAU AUCAAAUUUAAAGAUGGUCAUAUUUUGAUGAGAUGUUAAAAGG CGGGCCUUCUGCUGGUGUUAUUAUAUCGACUGUUAUAAAGG CUGCAACUGCGGAAGCUACAGCUAUUUUGAUGAAACUCCG UUGGCAACUGCGGAAGCUACAGCUAUUUUGAUGAAACUCCG UUGGCAACUGCGGAAGCUACAGCUAUUUGAGGAACGGCCACU AUAACAAUGGGGUUACUAGGCCUAUUUGAGGAACGGCCACU AUAACCACCACAACUAGCUAUUUGAUGAGAACGGCUAU GGUGCUUCUGCUGGGUACAACUACUUGUGCACAGGGGU UUGGCAACUGCGGAAGCUACAGCUUUGUGAGCAGGGGU UUGGCAACUGCGGUAACAGCUAUUGCUGAGCAGGGGU UUGGCAACUGCGGAAUUACUGAACUACUACUACUAACUACU GUUUGAGGAUAAAACCGGUAAGGUUAUUGAGGUGGCUAUG CAGGAAAAGGGCGAAUUACUGCAACUACUUAUAAA GAUGGUCUCCGCUUAAAACCGUUAUGAGAACUACUUAUACA GAAAACAGGGGGACGAAUUACUGCAACUACUUAUACA GAACAGCGGUGAAAUUACUGCAACUGCUAAACCACUAUUACA GAACAGGGGGUAAAAUCUGAAACUGGAACCACUUAAACA GAACAGGGGUGAAAUUCUGAAGCUUUGUAACACUACUUAUACA GAACACGCGUUAAAAGCGUUAAAGACUUGCUACGAUAACAUUACA GAACAGCGGUGAACUUAAAGGGUUAAUACAGAUAACAUAACUUCA GAACACCACUUCCAACUGGGCACUUAGCACAGAUAACCUGAAACUUCA GAACAGCGGUGAACUUAAAGGUUAAUACGGUUAAAACCUG UCUUCUGCCCGUAGCCGUAUCGAACCGGUUCGAAACCGUUUCA AACUCCACCAUUCGACCGGCAAUACCGUAAAUACCGGAAUCCGGAAACCUGCACAGCUUC GAAGCCUCCAUCAGACGUAUCGGCGAAUACCGUAAAUACCUG GAACCUCCACAUUCUGGCGCGCAGAUUCCGCACAGGUUCGCAAACCUGGCC GAAGUCUCCACACAUUCUGCGCGCACAGCUUCGCACAGGUUCGCAAACCUGCACAGCUUCGACCGAGAUUCCGCCGAAAACCUACGUAAACCUGAAACCUGAAACCUGAACCUGCCCUUACGACAACCUGAAAC	82
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAA GAGCCACCAUGGCACAGUCAUUAAUACAAACAGCCUGUCGC UGUUGACCCAGGAUAACCUGAACAAAUCCCAGUCCGCACUGG GCACUGCUAUCGAGCGUUUGCUCCGUUCGCGUAUCGAACA GCGCGAAAGAUCAAAGGUCUGACUCAGGCUUCCCGUAUCAACA GCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAUCAACG CUAACGACGUUAUCUCCAUUGGCAGACACUGAAGGGCGC UGAACGAAUCAACAACACCUGCAGCGUGUGCGUGACUGG CUCAUCCAGUCUGCAUUGCAACUCAGGCUGACUCAG ACUCCAUCCAGGCUGAAUCAACUCCCAGGUUGCGUGAACUGG ACCGUUCAGUCUGCGAAUGGUACUAACUCCCAGGUUGACUGA ACCGUGUAUCCGGCCAGACUCAGUUCAACGGCCGUGAAAGUCC UGGCGCAGGACUUCGAUUCAACGGCCUGAAAGUCC UGGCGCAGGACUACGUUCAACGGCGUGAACGACC ACGGUGAAACUAUCGAUUGAUUUAAUGUCAACGGCGUGAAAGUCC UGCCGUCAGUCUGCGUAUGAUUGAUUUAAUGUCAACGGCCUAC AACACUGGGACUUCGUUGAUCAACGGCCAAGAAUACUGU AAAACUGGACUUGGGUUGAUCAACGGCGGGUUACUGG GCCGGUGUAUCCGAUUCGGUGGUGCAACGGGGGUUACUGG GGCGGAUAUCCAAUUUGACUUAAUGACAACUACUUAU AUAAAGCUGCAAUUGGCGGUGGUCCAACGGGGGUUACUGG GGCCGAUAUCCAAUUUGGCGUGGUCAACGGGGGUUACUGG GGCCGAUAUCAAAUUUAAAGAGGUCAAUACUAUUUAAAGAG UUAAAGCCGGUGCUUCUGCGGGGGUCAACGCGGUGAAA AACUCCGUUGGCAACUGCGGAAGCUACAGCUAUAU AACCAACUGCCAACGCGGGCCAAGACCUUGUAA AACUCCGUUGGCAACUGCGGAAGCUACAGCUUGUAA AACUCCGUUGGCACCGCGAACACGCUGUGAAA AACUCCGUUGGCACCGCCCAAAUACUUGGGGAAC GGCCACUAUAACCCACAACUGCGGGCCCAAGACUGCUGGUA AACUUCGGUGCGCCCAAACGGUCAACUUGCUGGAGA AACUUCGUUGGAAAAACGGUAAACUAGCUUGUAA AACUUCGGUGACGGUUCAAACGGUUAAUUCGGGCGCUACA UAUAAGGGUGAUAAAACGGUAAACUAGCUUGUGA AACUUCAGAAACAGGGCGAUAACGGACCAUUGCUGGAA AACUUCAGAAACAGGGGUUAAAACGGUUAAUUGAGAGUUGAU AACUUCAGAACAGGGGUUCAAACUGAGCUUGGA AACUUCAGAACAGGGGUUAAAACGGUAACUAGCUUGUGA AACUUCAGAACAGGCGUUGAAAAUUGAUGCUGCUGACAACACU AACUUCAGAACAGGCGUUGAAAAUUGAUGCUGCUGGC ACAGGUUGAUAACCCCUGGCAGAAAAUUGAUGCUGCCU ACCGUUGAAAACCCACUGCGUUAAAACGGUUAAUACAGA UAAGACUGAAAACCGGCUGAAAAUUGAUGCUGCCUGGC ACAGGUUAACCCACUGGCCUGGC	83

Name	Sequence	SEQ ID NO:
	UAACCUGUCUUCUGCCCGUAGCCGUAUCGAAGAUUCCGACUA	
	CGCAACCGAAGUCUCCAACAUGUCUCGCGCGCAGAUUCUGCA	
	GCAGGCCGGUACCUCCGUUCUGGCGCAGGCGAACCAGGUUCC	
	GCAAAACGUCCUCUUUUACUGCGUUGAUAAUAGGCUGGAGC	
	CUCGGUGGCCAUGCUUCUUGCCCCUUGGGCCUCCCCCAGCC	
	CCUCCUCCCUUCCUGCACCCGUACCCCCGUGGUCUUUGAAU	
	AAAGUCUGAGUGGGCGGCAAAAAAAAAAAAAAAAAAAAA	
	ААААААААААААААААААААААААААААААААААААААА	
	ААААААААААААААААААААААААААААААААААААААА	

TABLE 17

	Flagellin Amino Acid Sequences	
Name	Sequence	SEQ ID NO:
ORF	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA	54
Sequence,	GQAIANRFTANIKGLTQASRNANDGISIAQTTEGALNEINNNLQRV	
AA	${\tt RELAVQSANGTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL}$	
	AQDNTLTIQVGANDGETIDIDLKEISSKTLGLDKLNVQDAYTPKET	
	AVTVDKTTYKNGTDPITAQSNTDIQTAIGGGATGVTGADIKFKDG	
	QYYLDVKGGASAGVYKATYDETTKKVNIDTTDKTPLATAEATAI RGTATITHNQIAEVTKEGVDTTTVAAQLAAAGVTGADKDNTSLV	
	KLSFEDKNGKVIDGGYAVKMGDDFYAATYDEKTGAITAKTTTYT	
	DGTGVAQTGAVKFGGANGKSEVVTATDGKTYLASDLDKHNFRT	
	GGELKEVNTDKTENPLOKIDAALAOVDTLRSDLGAVONRFNSAIT	
	NLGNTVNNLSSARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQA	
	NQVPQNVLSLLR	
Flagellin-	MAQVINTNSLSLLTQNNLNKSQSALGTAIERLSSGLRINSAKDDAA	55
GS linker-	GQAIANRFTANI KGLTQASRNANDGISIAQTTEGALNEINNNLQRV	
circumsporozoite	RELAVQSANSTNSQSDLDSIQAEITQRLNEIDRVSGQTQFNGVKVL	
protein	AQDNTLTIQVGANDGETIDIDLKQINSQTLGLDTLNVQQKYKVSD	
(CSP)	${\tt TAATVTGYADTTIALDNSTFKASATGLGGTDQKIDGDLKFDDTTG$	
	KYYAKVTVTGGTGKDGYYEVSVDKTNGEVTLAGGATSPLTGGLP	
	ATATEDVKNVQVANADLTEAKAALTAAGVTGTASVVKMSYTDN	
	${\tt NGKTIDGGLAVKVGDDYYSATQNKDGSISINTTKYTADDGTSKTA}$	
	LNKLGGADGKTEVVSIGGKTYAASKAEGHNFKAQPDLAEAAATT	
	TENPLQKIDAALAQVDTLRSDLGAVQNRFNSAITNLGNTVNNLTS	
	ARSRIEDSDYATEVSNMSRAQILQQAGTSVLAQANQVPQNVLSLL	
	RGGGGSGGGGSMMAPDPNANPNANPNANPNANPNANPNANPNA	
	NPNANPNANPNANPNANPNANPNANPNANPNANPNANPN	
	ANPNANPNKNNQGNGQGHNMPNDPNRNVDENANANNAVKNNN	
	NEEPSDKHIEQYLKKIKNSISTEWSPCSVTCGNGIQVRIKPGSANKP KDELDYENDIEKKICKMEKCSSVFNVVNS	
		56
Flagellin- RPVT	MMAP DP NANPNANP NANPNANPNANPNANP NANPNANPNANP	20
linker-	QCNGQGHNMPNDPNRNVDENANANANANANANANANANANANANANANANANANANA	
	QUAGQUARIANI ND FININY DEMANANINY KAMINI EFSDART EQT LKKIKNSISTEWSPCSVTCGNGIQVRIKPGSANKPKDELDYENDIEK	
protein	KICKMEKCSSVFNVVNSRPVT <u>MAQVINTNSLSLLTQNNLNKSQSA</u>	
(CSP)	LGTAIERLSSGLRINSAKDDAAGQAIANRFTANIKGLTQASRNAND	
(002)	GISIAQTTEGALNEINNNLQRVRELAVQSANSTNSQSDLDSIQAEIT	
	QRLNEIDRVSGQTQFNGVKVLAQDNTLTIQVGANDGETIDIDLKQI	
	NSQTLGLDTLNVQQKYKVSDTAATVTGYADTTIALDNSTFKASAT	
	GLGGTDQKIDGDLKFDDTTGKYYAKVTVTGGTGKDGYYEVSVD	
	KTNGEVTLAGGATSPLTGGLPATATEDVKNVQVANADLTEAKAA	
	LTAAGVTGTASVVKMSYTDNNGKTIDGGLAVKVGDDYYSATQN	
	KDGSISINTTKYTADDGTSKTALNKLGGADGKTEVVSIGGKTYAA	
	SKAEGHNFKAQPDLAEAAATTTENPLQKIDAALAQVDTLRSDLG	
	$\underline{AVQNRFNSAITNLGNTVNNLTSARSRIEDSDYATEVSNMSRAQILQ}$	
	QAGTSVLAQANQVPQNVLSLLR	

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TABLE 18

Human Metaphe	umovirus Mutant Amino Acid Sequences	
Strain	Sequence	SEQ ID NO:
HMPV_SC_DSCAV1_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGFSLIKTELDLTKSALRELKTVSADQLAREEQIEDPGSGSFVLG AIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LAFAVRELKDFVSKNLTRALNKNKCDIDDLKMAVSFSOFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGIL CGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWY CQNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYFC KVSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQ DADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFNVALDQVFE NIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKK PTGAPPELSGVTNNGFIPHN	85
HMPV_SC_DSTRIC_4MMV	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAICKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRKKGFGIL CGVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWY CQNAGSTVYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPC KVSTGRHPISNVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQ DADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPE <u>HQMH</u> VALDQVFE NIENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKK	86
HMPV_SC_DM_Krarup_T74LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIPDLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	87
HMPV_SC_TM_Krarup_T74LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVRQFS DNAGITPAISLDMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNVACLLREDQGMVC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHFISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPENQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIKKTKKP TGAPPELSGVTNNGFIPHN	88
HMPV_SC_4M_Krarup_T74LS170LD185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIEN <u>PGSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTINEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDFIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIKKTKKP TGAPPELSGVTNNGFIPHN	89
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIPDLKMAVSFSOFNRRFLNVVROFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDFIKFPENOFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	90
HMPV_SC_DM_Krarup_E51PT74L	MSWKVVIIFSLLITPOHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTL <u>P</u> VG DVENLTCSDGPSLIKTELDL <u>L</u> KSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG	91

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TABLE 18-continued

Human Metapneum	ovirus Mutant Amino Acid Sequences	
Strain	Sequence	SEQ ID NO:
	AI AGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVPCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_SC_TM_Krarup_E51PT74LD454N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLPVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDIKFPENJGPQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	92
HMPV_SC_StabilizeAlpha_T74L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSPSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	93
HMPV_SC_StabilizeAlpha_V55L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DLENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLMVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNEVGIIKQLNKGCSVITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVITLIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	94
HMPV_SC_StabilizeAlpha_S170L	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLTRAINKNKCDIDDLKMAVSFSQFNRFFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVVQLSKVEGEQHVIKGRPVSSSFDFIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	95
HMPV_SC_StabilizeAlpha_T174W	MSWKVVIIFSLLITPOHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	96
HMPV_SC_4M_StabilizeAlpha_V55LT74LS170LT174	MSWKVVIIFSLLITPOHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DLENLTCSDGPSLIKTELDLLKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVLKNLWRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS	97

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TABLE 18-continued

Human M	Metapneumovirus Mutant Amino Acid Sequences	
Strain	Sequence	SEQ ID NO:
	DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_ProlineStab_E51P	MSWKVVIIPSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLPVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP	98
HMPV_ProlineStab_D185P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDI <u>P</u> DLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSPDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP	99
HMPV_ProlineStab_D183P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKC <u>P</u> IDDLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	100
HMPV_ProlineStab_E131P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPEQQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	101
HMPV_ProlineStab_D447P	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPG <u>SGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFPPIKF <u>P</u> EDQPQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	102
HMPV_TrimerRepulsionD454N	MSWKVVIIFSLLITPOHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC	103

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TABLE 18-continued

Human M	Metapneumovirus Mutant Amino Acid Sequences	
Strain	Sequence	SEQ ID NO:
	QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMYALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSFDPIKFPE <u>NO</u> FQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP TGAPPELSGVTNNGFIPHN	
HMPV_TrimerRepulsionE453N	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENP <u>GSGS</u> FVLG AIALGVAAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQFNRFLNVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSKVEGEQHVIKGRPVSSSPDPIKFPQDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP	104
HMPV_StabilizeAlphaF196W	MSWKVVIIPSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVG DVENLTCSDGPSLIKTELDLTKSALRELKTVSADQLAREEQIENPGSGSFVLG AIALGVAAAAVTAGVAIAKTIRLESEVTAINNALKKTNEAVSTLGNGVRV LATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVSFSQMRRFLMVVRQFS DNAGITPAISLDLMTDAELARAVPNMPTSAGQIKLMLENRAMVRRKGFGILI GVYGSSVIYMVQLPIFGVIDTPCWIVKAAPSCSEKKGNYACLLREDQGWYC QNAGSTVYYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYPCK VSTGRHPISMVALSPLGALVACYKGVSCSIGSNRVGIIKQLNKGCSYITNQD ADTVTIDNTVYQLSXVEGEQHVIKGRPVSSSFDPIKPPEDQFQVALDQVFENI ENSQALVDQSNRILSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKP	105

TABLE 19

Strain	Nucleic Acid Sequence	SEQ II NO:
	Human Metapneumovirus Mutant Nucleic Acid Sequences	
HMPV SC DSCAV1 4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAG	GCCTGCTGATCA 106
	CACCTCAGCACGGCCTGAAAGAGAGCTAC	CCTGGAAGAGT
	CCTGCAGCACCATCACAGAGGGCTACCTC	STCTGTGCTGAG
	AACCGGCTGGTACACCAACGTGTTCACAC	CTGGAAGTGGGC
	GACGTCGAGAATCTGACATGCTCTGATGC	GCCCTAGCCTGA
	TCAAGACCGAGCTGGATCTGACCAAGAG	CGCCCTGAGAG
	AACTCAAGACCGTGTCTGCCGATCAGCTC	GGCCAGAGAGGA
	ACAGATCGAGAATCCTGGCAGCGGCAGC	ITTGTGCTGGGA
	GCCATTGCTCTTGGAGTGGCTGCTGCTGC	CAGCTGTTACAG
	CAGGCGTGGCCATCTGCAAGACCATCAGA	ACTGGAAAGCG
	AAGTGACCGCCATCAACAACGCCCTGAAC	GAAGACAAACG
	AGGCCGTCAGCACTCGGCAATGGCGT	TAGAGTGCTGGC
	CTTTGCCGTGCGCGAGCTGAAGGACTTCC	GTGTCCAAGAAC
	CTGACACGGGCCCTGAACAAGAACAAGTC	GCGACATCGAC
	GACCTGAAGATGGCCGTGTCCTTTAGCC	AGTTCAACCGGC
	GGTTTCTGAACGTCGTGCGGCAGTTTAGC	CGACAACGCCGG
	AATCACACCAGCCATCAGCCTGGACCTGA	ATGACAGATGCT
	GAGCTGGCTAGAGCCGTGCCTAACATGCC	CTACATCTGCCG
	GCCAGATCAAGCTGATGCTCGAGAATAGA	AGCCATGGTCCG
	ACGGAAAGGCTTCGGCATTCTGTGTGGCC	GTGTACGGCAGC
	AGCGTGATCTATATGGTGCAGCTGCCTAT	TCTTCGGCGTGA
	TCGACACCCCTGCTGGATTGTGAAGGCC	CGCTCCTAGCTG
	TAGCGAGAAGAAGGGCAATTACGCCTGCC	CTGCTGAGAGA
	GGACCAAGGCTGGTATTGTCAGAACGCCC	GCAGCACCGTG
	TACTACCCTAACGAGAAGGACTGCGAGAG	CAAGAGGCGAC
	CACGTGTTCTGTGATACCGCCGCTGGAA	TCAATGTGGCCG
	AGCAGAGCAAAGAGTGCAACATCAACATC	CAGCACCACCA
	ACTATCCCTGCAAGGTGTCCACCGGCAG	GCACCCTATTTC
	TATGGTGGCTCTGTCTCCTCTGGGAGCCC	CTGGTGGCTTGTT
	ATAAGGGCGTGTCCTGTAGCATCGGCAG	CAACAGAGTGG
	GCATCATCAAGCAGCTGAACAAGGGCTG	CAGCTACATCAC
	CAACCAGGACGCCGATACCGTGACCATCC	GACAACACCGTG
	TATCAGCTGAGCAAGGTGGAAGGCGAACA	AGCACGTGATC
	AAGGGCAGACCTGTGTCCAGCAGCTTCGA	ACCCTATCAAGT

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TABLE 19-continued

train	Nucleic Acid Sequence	SEQ ID NO:
	TCCCTGAGGATCAGTTCAACGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
MPV_SC_DSTRIC_4MMV	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	107
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCTGCAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGTGTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGCACCAGTGGCATGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
MPV_SC_DM_Krarup_T74LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	108
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	GACGTCGAGAATCTGACATGCTCTGATGGCUCTAGUCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAG CAGATCGAGAATCCTGGCAGCGGCGGCGGCTGTGTGCTGGGAG CCATTGCTCTTGGAGTGGCGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGGG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTGGGATGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCAACGGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCATGGCCGTTAGAGTGCTGGCC ACAGCCGTGCGCGGAGCTGAAGGACTTCGTGTCCAAGAAACC	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTGTGCTGGAGAG CCATTGCTCTTGGAGTGGCTGCTGCAGCGCGTGTACAGC AGCGTGGCCATCGCTAAGACCATCAGACTGGAAGACGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCATGGCGTTAGAGTGCTGGC ACAGCCGTCGGCGAGCTGAAGAGACTTCGTGTCCAAGAACC TGACACGGCCCATTAACAAGAACAAGTGCGACACCCCTGA CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG TTTCTGAAGATGGCCGTGTCCTTTAGCCAGCTCAACCGGCG TTTCTGAAGATGGCCGTGCCTTAAGCAGCACCGCGGA TTCCTGAACGTCGTGCCGGCCTGATGGCGCAGAGATGCTGA GCTGGCTAGAGCCGTGCCTGATGCCTACGCGCGGC CAGATCAAGCCGTGCCTGACATCGCCTGACCCAGGCCGGC	
	TCAAGACCGAGCTGGATCTGCTCAAGAGGCGCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGGCGCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGGGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTGTGCGGAGAG CCATTGCTCTTGGAGTGGCTGCTGCGCAGCTGTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAACGA GGCCGTCAGCACACTCGGCATGGCGTTAGAGTGGCGC ACAGCCGTCGGCGAGCTGAAGAGACTTCGTGTCCAAGAACC TGACACGGCCATTAACAACGACGCCGTTAAGAGCGCAGC CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG TTTCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG TTTCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG CCTGAAGATGGCCGTGCCTTAACAAGGCCGCAGA TTCCGACCAGCATCAGCCTGGACCTGATGCCAAGATGCTGA GCTGGCTAAGCCGTGCCTGACAGCCTGACGCCGGC CAGATCAAGCTGATGCTGAGAATAGAGCCATGGTCCGAC GGAAAGGCTCGGCATCTGCAGTGACGGCGGCGCGCG ACCACCCTGCTGGATTGTGAAGGCCGTCTCAGGCGGCAGCA CGTGATCTATATGGTGCAGCTGCCTGCTGCTGAGAGAGGGCA	

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TABLE 19-continued

	TABLE 19-continued	
Strain	Nucleic Acid Sequence	SEQ ID NO:
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAAGAGGGGCAT CATCAAGCAGCTGTAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGATCA AGCTGAGCAAGGTGGAAGCGAACACACCGTGATCAAGG GCAGACCTGTGTCCAGGCGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGTGGCCCTGGACCAGGTCTCGAC GAATCCTGTCTAGCCCGGCTCGGGCACCAGGCTTCAAC GAATCCTGTCAGCCGACCAGGGAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCGCGCGCCCTGG ATCCTGGTGCCATCTTCATCATGAGAAGACACCCGAC	
	AGCCCACCGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	
HMPV_SC_TM_Krarup_T74LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCTGCTGCTATCA CACCTCAGCACGGCCGAAAGAGAGGCACCTGGTGTGGAAGAGT CCTGCAGGACACATCACAGAGGGCTACCTGGTGTGGAGAGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTGGAGGC GACGTCGAGAATCTGGCATGCTCTGATGGCCCTGGAGAGAGA	109
HMPV_SC_4M_Krarup_T74LS170LD185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGAGACTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGGTGGTGGGG AACCGGCTGGACATCTGACACGGCTCTGGAAGAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCAGG TCAAGACCGAGCTGGCATCTGCTCAAGAGCGCCCTGAGAGAGA	110

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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ ID NO:
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_SC_5M_Krarup_T74LS170LD185PD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	111
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA	
	ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA	
	CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG	
	CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC	
	AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA	
	GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGCTTAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTGA	
	CCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCGG	
	TTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGAA	
	TCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTGA	
	GCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGGC	
	CAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGAC	
	GGAAAGGCTTCCGCATTCTGATTGGCGTGTACGGCAGCAG	
	CGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATCG	
	ACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTAG	
	CGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGGA	
	CCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTAC	
	TACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCAC	
	GTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAGC	
	AGAGCAAAGAGTGCAACATCAACATCAGCACCACCAACT	
	ATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	

HMPV_SC_DM_Krarup_E51PT74L

ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG ${\tt CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC}$ AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA ${\tt GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC}$ ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC

CAATGGCTTCATCCCTCACAAC

GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA

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Strain

TABLE 19-continued

SEO ID Nucleic Acid Sequence NO: TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC HMPV_SC_TM_Krarup_E51PT74LD454N ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA 113 CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGCCTGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA ${\tt CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG}$ CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA 114

HMPV_SC_StabilizeAlpha_T74L

CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGCTCAAGAGCGCCCTGAGAGA

Nucleic Acid Sequence

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Strain

TABLE 19-continued

ACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGAA CAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGAG CCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAGC AGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCGA AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA AGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC HMPV_SC_StabilizeAlpha_V55L ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA 115 CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACCTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACCCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG ACCAACAATGGCTTCATCCCTCACAAC

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SEO ID

NO:

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TABLE 19-continued

	TABLE 19-continued	
Strain	Nucleic Acid Sequence	SEQ I NO:
HMPV_SC_StabilizeAlpha_S170L	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGGTGGCTGAG AACCGGCTGTACACCAACAGGTCTCACACTGGAAGTGGC GACGTCGAGAATCTGACAAGGCCCCTGAGCCAGCCGGG CACGTCGAGACTGGACTG	116
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG ACCAACAATGGCTTCATCCCTCACAAC	
HMPV_SC_StabilizeAlpha_T174W	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGGTGGGAGGG GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCGG GACGTCGAGAATCTGGCCAGCGGCAGCTGGGAGGGA AACTCAAGACCGTGTCTGGCGAGCGGCGCGCGAGAGGA ACTCAAGACCGTGTCTGGCGAGCGGCGCGCGGAGGGA GCCATTGCTCTGGAGTGGCGCGCGCGCGCGGCGGCTGTACAG GCCATGGCCCTCGGCAAGGAGCATTGGGCTGGCG AAGTGACCGCCATCACAACGACCCTGAAGAAGCAAACG AAGTGACCGCCATCACAACGACCCTGAAGAAGCAAACG CACGCCGTGGCCATCGGCAACGACGTGAAGACCAACG CACGCCGTGGCCGCGCGCGCGCTGTGCGCACGCGC CACAGCCGTGGCGCGGCGGCGGCTGTAGAGGCGTCCGGC GGTTTCTGAACGTCGTGCGCGCGCGGCAGTTAGCGGCACATCGGC GACCTGAAGATGGCCGTGCCTGAACAACGCCGGG GGTTCTGAACGTCGTGCGCGCGGCAGTTAGCGCACACGGC GACCTGGACGGCCATCAGCCTGGAACGACACGCGG GGTTCCGAACGTCGTGGCGCGGCCGTTAGCCGACACGCGG CCCAGATCAAGCTGGGCGCGCTGCTAACATGCCTGCACGCGG GCCAGATCAAGCTGGGCGCGCTGCTAACATGCCTGCGCGCG ACCGGAAAGGCTTCGGCAGCTGGACCATGGTCCG ACGGGAACGCCTGGCAGCTGGACCTGGTCCGGCAGCTGGCACGCGG CCCAGATCAGCCTGGCAGCTGCTACATCGCCGG CGCGGAACGGCTGGCGACTTGGCGTGCCTACCTGCCG ACGGGAACGCCTGGCAGCTGCCTATCTTCGGCGGCG CCCCAGCCCGCGCGGCGCCCTCCTGGCGGCGCGCCCCTACCTGCCG ACGGAAAGGCTTGGGCAGCTGCCTACCTTCGGCGGCGCCC ACGGAAAGGCTGGGAATTGCGCAGCCGCGCCCCCAGCTG TACGACACCCCGCGCGGCGCG	117

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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ II NO:
	TCCCTGAGGATCAGTTCCAGGTGGCCTGGACCAGGTGT CGAGAACATCGAGAATCCCAGGCCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGGTCATCCTGATCGCCGTGCTGGGCAGCTC CATGATCCTGGTGTCCATCTTCATCATGAAGAAGAC AAGAACCCCACCGGCGCTCCTCCAGAACTGACGGAGTG ACCAACAATGGCTTCATCCTCACAAC	
HMPV_SC_4M_StabilizeAlpha_V55LT74LS170LT174W	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGGCTGAG AACCGGCTGGTACACCACGGGCTGCACAGGGGG CACCTCCGAGAATCTGACAGCGGCCCTGAGAGA ACTCAAGACCGTGTCTGCCGCAAGAGGGGGG CATGCTCTTGGAGTGGCTGCTGCGCGCAGAGAGAGA CAGATCCTGGCAGGGGCGCGGGCGGGGGGGGGG	118
HMPV_ProlineStab_E51P	CAATGGCTTCATCCTCACAAC ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGTGGTGAG AACCGGCTGGTACACCAGAGGGCTACCTGTCTGGGCTGAG GACGTCGAGAATCTGACAGAGGGCTACCTGTCTGGGCG GACGTCGAGATCTGACAGACGTCTGATGGCCCTGAGAG AACTCAAGACCGAGCTGGTCTGACCAAGAGCGCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCGCAGCGCTGGGCCAGAGAGGA ACAGATCGAGAATCCTGGCGCAGCGCTGGAGCGTTAGACTGGCA GCCATTGCTCTGGAGTGCTGCTGCTGCCGGCAGTACAG CAGGCGTCGCCATCACACAGCGCTCGAGACGTACAG CAGGCGTCGCCATCACACAGCGCTTGGTGCCAGCG AGTGACCGCCATCACACAGCGCTGAGAGAGCAAACG AGGCCGTCGGCCAGCTGAAGGACTTCGTGCTGGC CACAGCCGTCGCCAGCTGAAGGACTTCGTGCCAGAAC CTGACAGCGGCCAGCTGAAGGACTTCGTGCCAGAAC GACCTGAAGATGGCCGTGTCCTTTAGCAGGTCAACGGC GACTTGGACACCTCGGCGACGTTGACGCCGCAGACGGC GACTGGCTAGGCCGTGCCCTACACTGGCCGGC CCAGACCGCGCCGCGCGCCCCTACACGCCG GGCTACGACCAGCCGTGCCCTACACTGGCCG CCCGGAACGCGTCGGCAGTTCAGGCCGCCGC AGGGGGAACATCAGCCGGCAGTTGGAAGGCCGCG AGCGGAAAGACTGCGGCATTGTGAAGGCCACCTACGCCG AGGCGGAACATCAGCCGGCAGTTGGAAGGCCGCCTAGCTGGC AGGCGGAACACTGGCAGTTGGCAGCCCCTACCTGCGGGAAC AGGCCAAGGCGGCAGTTGGAAGGCCGCCCTACCTGGCGGC AGCCTGAAGACTGGGCATTGGCAGCCGCCTACCTCGGCGGC AGCCGGAAAGACGCGGCAGTTGGAAGGCCGCCTCACGCG AGCCAGACAAGAAGGCAATTGCCCGCCGCGCAGACCGGC AGCCAGACCAAGGCGGCATTGCGAGACAAAGGCGACC CACGGCAAAGAAGAGGCATTCGCGGCGCAGACACAAGGCGAC CACGGCAACGCTGGGAATTGCCCGCGCGCAGACCGGC CACGGCAACGCGGCGAGATTGCGAGACCAAAGGCGCACCGTG TACCACCCTGGGAATGGCAGCTGCCGCGCAGACCGGC CACGGCAACGACGGCATTGCCGCGCGCGCAGACCGGC CACGGCAAGGCAATACACCGCGCGCAGCACCGGC CACGGCAACGAGCGCAATCAACCACAAGGCGCACCGCG CACGGCAAAGAGCCGCCGCGCGCGCAGACCGGC CACGGCAACAAGAGCCGCCGCGCGCGCAGACCGGC CACGGCAACAAGAGCCGCCGCGCGCGCAGACCGGC CACGGCAACAAGAGCCGCCGCGCGCGCGCACCGCG CACGGCAACAAGAGCCGCCGCGCGCGCGCACCGCG CACGGCAACAAGAGCCGCCGCGCGCGCGCCGCCGCCGCCG	119

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TABLE 19-continued

	 19-continued	
Strain	Nucleic Acid Sequence	SEQ I NO:
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
IMPV ProlineStab D185P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	120
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCCCTG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA	
	CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA	
	CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT	
	GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC	
	AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D183P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	121
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCCCTATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG	
	CTTTCTC3 ACCTCCTCCCCC3 CTTTTACCC3 C3 ACCCCCC3	
	GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	

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	TABLE 19-continued	CDO 11
Strain	Nucleic Acid Sequence	SEQ II NO:
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA GCGAGAAGAAGGGCCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCIGGTATIGTCAGAACGCCGGCAGCACCGIGTA CTACCCTAACGAGAGGACIGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCACCAAC	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA	
	GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA	
	CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_E131P		122
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCAGCTGTTACAG	
	AGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACGA GGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGCC	
	ACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAACC	
	TGACACGGGCCATTAACAAGAACAAGTGCGACATCGACG	
	ACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGCG GTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGGA	
	ATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCTG	
	AGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCGG	
	CCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCGA CGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGCA	
	GCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGATC	
	GACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTGTA	
	GCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGAGG	
	ACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTGTA CTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGACCA	
	CGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCGAG	
	CAGAGCAAAGAGTGCAACATCAACATCAGCACCAACA	
	TATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTCTAT GGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTTATA	
	AGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGGGCAT	
	CATCAAGCAGCTGAACAAGGGCTGCAGCTACATCACCAAC	
	CAGGACGCCGATACCGTGACCATCGACAACACCGTGTATC AGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATCAAGG	
	GCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGTTCCCC	
	TGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTTCGAG	
	AACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCCAACA GAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGCTTCAT	
	CATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTCCATG	
	ATCCTGGTGTCCATCTTCATCATTATCAAGAAGACCAAGA	
	AGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTGACCAA CAATGGCTTCATCCCTCACAAC	
HMPV_ProlineStab_D447P	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	123
-		
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGA	
	ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	

AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC

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TABLE 19-continued

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	TABLE 19-continued	
Strain	Nucleic Acid Sequence	SEQ ID NO:
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACCGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA	
	TCGACACCCCTGCTGGATTGTGAAGGCCGCCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCCCCACCTATCAAGT	
	TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
MPV_TrimerRepulsionD454N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA	124
	CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG	
	AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC	
	GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA	
	AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA	
	GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCGCAGCTGTTACAG	
	CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG	
	AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG	
	AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC	
	CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC	
	CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC	
	GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC	
	GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG	
	AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT	
	GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG	
	GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG	
	ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC	
	AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG	
	TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA	
	GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG	
	TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGGCGAC	
	CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG	
	AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA	
	ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC	
	TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT	
	ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG	
	GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC	
	CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG	
	TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC	
	AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT	
	TCCCTGAGAACCAGTTCCAGGTGGCCCTGGACCAGGTGTT CCACAACCAGTGCACAGTTCCCAGGTGGCCCTGGACCAGGTGTT	
	CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC	
	AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC	
	CATGATCCTGGTGTCCATCTTCATCATCATCAGAAGAAGACC	
	AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG	
	ACCAACAATGGCTTCATCCCTCACAAC	
MDV TrimerPepulcionE452N	RTCR COTCCR R COTCCT CR TCR TCTTCR COCTCCTCR TCR	195
MPV_TrimerRepulsionE453N	ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT	125
	CCTGCAGCACCATCACAGAGGGCTACCTGTCTGGCAGAGG	

CCTGCAGCACCATCACAGAGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG

Nucleic Acid Sequence

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SEO ID

NO:

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Strain

TABLE 19-continued

AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTTCAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACACCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT TCCCTCAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT CGAGAACATCGAGAATTCCCCAGGCTCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG ACCAACAATGGCTTCATCCCTCACAAC HMPV_StabilizeAlphaF196W ATGAGCTGGAAGGTGGTCATCATCTTCAGCCTGCTGATCA 126 CACCTCAGCACGGCCTGAAAGAGAGCTACCTGGAAGAGT CCTGCAGCACCATCACAGAGGGGCTACCTGTCTGTGCTGAG AACCGGCTGGTACACCAACGTGTTCACACTGGAAGTGGGC GACGTCGAGAATCTGACATGCTCTGATGGCCCTAGCCTGA TCAAGACCGAGCTGGATCTGACCAAGAGCGCCCTGAGAG AACTCAAGACCGTGTCTGCCGATCAGCTGGCCAGAGAGGA ACAGATCGAGAATCCTGGCAGCGGCAGCTTTGTGCTGGGA GCCATTGCTCTTGGAGTGGCTGCTGCTGCAGCTGTTACAG CAGGCGTGGCCATCGCTAAGACCATCAGACTGGAAAGCG AAGTGACCGCCATCAACAACGCCCTGAAGAAGACAAACG AGGCCGTCAGCACACTCGGCAATGGCGTTAGAGTGCTGGC CACAGCCGTGCGCGAGCTGAAGGACTTCGTGTCCAAGAAC CTGACACGGGCCATTAACAAGAACAAGTGCGACATCGAC GACCTGAAGATGGCCGTGTCCTTTAGCCAGTGGAACCGGC GGTTTCTGAACGTCGTGCGGCAGTTTAGCGACAACGCCGG AATCACACCAGCCATCAGCCTGGACCTGATGACAGATGCT GAGCTGGCTAGAGCCGTGCCTAACATGCCTACATCTGCCG GCCAGATCAAGCTGATGCTCGAGAATAGAGCCATGGTCCG ACGGAAAGGCTTCGGCATTCTGATTGGCGTGTACGGCAGC AGCGTGATCTATATGGTGCAGCTGCCTATCTTCGGCGTGA TCGACACCCCTGCTGGATTGTGAAGGCCGCTCCTAGCTG TAGCGAGAAGAAGGGCAATTACGCCTGCCTGCTGAGAGA GGACCAAGGCTGGTATTGTCAGAACGCCGGCAGCACCGTG TACTACCCTAACGAGAAGGACTGCGAGACAAGAGGCGAC CACGTGTTCTGTGATACCGCCGCTGGAATCAATGTGGCCG AGCAGAGCAAAGAGTGCAACATCAACATCAGCACCACCA ACTATCCCTGCAAGGTGTCCACCGGCAGGCACCCTATTTC TATGGTGGCTCTGTCTCCTCTGGGAGCCCTGGTGGCTTGTT ATAAGGGCGTGTCCTGTAGCATCGGCAGCAACAGAGTGG GCATCATCAAGCAGCTGAACAAGGGCTGCAGCTACATCAC CAACCAGGACGCCGATACCGTGACCATCGACAACACCGTG TATCAGCTGAGCAAGGTGGAAGGCGAACAGCACGTGATC AAGGGCAGACCTGTGTCCAGCAGCTTCGACCCTATCAAGT TCCCTGAGGATCAGTTCCAGGTGGCCCTGGACCAGGTGTT CGAGAACATCGAGAATTCCCAGGCTCTGGTGGACCAGTCC AACAGAATCCTGTCTAGCGCCGAGAAGGGAAACACCGGC TTCATCATCGTGATCATCCTGATCGCCGTGCTGGGCAGCTC CATGATCCTGGTGTCCATCTTCATCATTATCAAGAAGACC AAGAAGCCCACCGGCGCTCCTCCAGAACTGAGCGGAGTG ACCAACAATGGCTTCATCCCTCACAAC

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TABLE 19-continued

11101	LE 19-continued	
Strain	Nucleic Acid Sequence	SEQ II NO:
Human Metap	neumovirus mRNA Sequences	
Muman Metap	neumovirus mRNA Sequences AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAAGAGGUCUCUGGUGCU GAGAACCGGCUGGUACACCAAGAGGUUCACACUGGAAGA GUCCUGCAGCACCAUCACAAGGUUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGUCUGGUGCUGCUG GAGAACCGGCUGGAUCUGACACUGGAUCAGCUGCCAG GAGAGAUCAAGACCGUGUCUGCCGAUCAGCUGCCAG AGAGGAACUCAAGACCGUGUCUGCCGAUCAGCUGCUGCA GCUGUUACAAGACCGUGUCUUGGAAGACCAUUCAGA GCUGUUACAGCAGGCGUGGCCUUCUGCAAGACCAUUCAGA GUGUGGAAGUGAAGU	127
IMPV_SC_DSURIC_4MMV	CCAUGAUCCUGGUGUCCAUCUUCAUCAUCAUGAUGAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCUCACAAC AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAUA GUCCUCCAGCACGACGCUGAAAGAGGCUACCUGUGGAGA GUCCUGCAGCACCAUCACAAGAGGGCUACCUGUGUGGUG GAGAACCGGCUGGUACACAAGAGGGCUCUGAUGGCCUG GAGAACCGGCUGGUACACCACGUGUUCACACUGGAAGA GUCCUGAGACACAUCACAAGAGGGCUACUGAUGACCACUGGAGAA GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCAG GAGAACAGAUCAAGACCGUGUCUGCCAGUCGCUGCUGCUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUCUGCUGCUGCUG UGCUGGGAGCCAUUGCUCUUGGAAGACCAUCAGA GCUGUUACAGCAGGCGUGGCCAUCUGCAAGACCAUCAGA GCUGUUACAGCAGGCGUGGCCAUCUGCAAGACCAUCAGA GCUGUUACAGCAGGCGUCAGCACCAUCGGCAAGCCUUG UGCUGGAGCAAUGCCGUCAGCAGCGCCAUUG AGAGUACUGGCCACAGCCGUCGCGCAUCUGCUAAC GUGUCCAAGAACCUGACAGCCGUCAGCAAGACCAUCAGA AUGCCAACAACGGCGUCAGCACACUCGGCAAUGAGCUU GUGUCCAAGAACCUGACACGCGGCAGCUUAACAAGAACAAG UGCGACAACGGCCGUUCAGAACGUGUGGGGCAUUUC GUGUCCAAGAACCUGACCAGCCGUGCCGU	128

Strain	Nucleic Acid Sequence	SEQ ID NO:
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGCACCAGUGGCAUGUGGCCCUGGACCAGGUGUUCGA GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA CAGAAUCCUGUCUACCCGAGAAAGGGAAACACCGGCUU CAUCAUCGUGAUCAUCCUGAUCAUCAUCAUCAUCAUCAGAGAA CAGAACCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU GACCAACAAUGGCUUCAUCCUCACAAC	
HMPV_SC_DM_Krarup_U74LD185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAAGA GUCCUGCAGCACCGCCUGAAAGAGAGCUACCUGGUGGAAGA GUCCUGCAGCACCAUCACAAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUCUCACACUGGAAGU GGGCGACGUCGAGAAUCUGCUCAACGUGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAACAUCGCCCAG GAGAGAACAGAUCGAGAUCUGCCGAUCACCUGCCAG GCUGUUACAGACGGUGGCCAUCGCUAAGACCAUCAGA CUGGUACAGAGCGUGGCCAUCGCUAAGACCAUCAGA CUGGUACAGAGCGUGGCCAUCGCUAAGACCCUGGAA GCUGUUACAGCAGCGUCAGCACCCUGGAAGACCAUCAGA CUGGAAAGCUGACCGCCAUCACACACCCCUGAAG AAGACAAACGAGGCCGUCAGCACAUCAACAACGCCUUGAA GCUGUCCAGAAACCUGACACGCGCGAGCUGAAGACCUUC GUGUCCAAGAACCUGACACGCGCGAGCUGAAGACCUC GUGUCCAAGAACCUGACACCACCAGCCGUGACCAUCAACAAG UGCGACAUCCCUGACACACCAGCCGUGACGCUGCUGUUA AGCGUACAUCCUGACCUGA	129
HMPV_SC_UM_Krarup_U74LD185PD454N	UGACCAACAAUGGCUUCAUCCCUCACAAC AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAAGAGGCUACCUGGUGGU GAGAACCGGCUGGACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUG GAGAACCGACCAUCGCUGGAUCUGCUCAGAGGCCCUG GAGAGACUCAAGACCGAGCUGGCUCAGAGCGCGGCGU GAGAGAACCAAAUCCGAGCUGGCUCAGAGCGCGGCGU UGCUGGGAGCCAUUGCUCUUGGAUCUGCUCAGGCAGCUGCCAG AGAGAACCAAAUCGAGAAUCCUGGCAGCGGCGCUGCUGCAG CUGUUACAGCAGGCGUGGCCAUCGACAACAGCCCUCGGCAGCUGCUGCUGCUGCUGCGGGAGCCUCGCCAGGCAGCUGGCAUCAACAACAACCACCUCGGCAAUCGCUAGAAAGCAUCAGA CUGGAAAGCGAAGUGACCGCCCUCGCUAAGACACCCUCGGA AGACAAACGAGGCGUCGCCAUCAACAACGACCUCGUG UGCUGGCGCCCGCCGCAGCUGGCAAUGGCGUU AGAGCAAACCGAGCCUCAGCACACUCGGCAAUGGCGUU GUGUCCAAGAACCUGACAGGGCCAUUAACAACAACGACCUUC GUGUCCAAGAACCUGACCGGCCAUUAACAAGAACAAG CUGGACAUCCCUGACCUGA	130

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TABLE 19-continued

TABLI	E 19-continued	
Strain	Nucleic Acid Sequence	SEQ NO:
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGACCAAGGUGGAAGGCGAACAGCACGUGUUCAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU GACCAACAAUGGCUUCAUCCCUCACAAC	
	GALLAACAOGEOULAULEULALAAL	
MPV_SC_4M_Krarup_U74LS170LD185P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	131
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA	
	GUGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGCAGCACCGUGUACUACCCUAACGA	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGGGGGGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
MPV_SC_5M_Krarup_U74LS170LD185PD454N		13
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	

AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG ${\tt AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU}$ AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA

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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ I NO:
	GUGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG	
	CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
		100
MPV_SC_DM_Krarup_E51PU74L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	133
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AUGCCUACAUCUGCCGGCCAGAUCUAGCUGGCGUCCGAG	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCCCCAGGCUCUGGUGGACCAGUCCA	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
MPV SC UM Krarup E51PU74LD454N	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	134

HMPV_SC_UM_Krarup_E51PU74LD454N

AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG

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TABLE 19-continued

SEO ID Strain Nucleic Acid Sequence NO: CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU GACCAACAAUGGCUUCAUCCCUCACAAC HMPV_SC_SUabilizeAlpha_U74L AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU 135 CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGCUCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU

Strain	Nucleic Acid Sequence	SEQ I NO:
	±	
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	UGACCAACAAUGGCUUCAUCCCUCACAAC	
HMPV_SC_SUabilizeAlpha_V55L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	136
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACCUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCA	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
IMPV_SC_SUabilizeAlpha_S170L	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	137
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGCUUAAGAACCUGACACGGGCCAUUAACAAGAACAA GUGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAG	
	CCAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUU	
	UAGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGA	
	CCUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAA	
	CAUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGA	
	GAAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUC	
	UGAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUG	
	AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG CAAUUACGCCUGCCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGAGAGCACCAAGGCUGGUA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	

TABLE	19-continued

	.9-continued	
Strain	Nucleic Acid Sequence	SEQ ID NO:
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCG UGAGGAUCAGUUCCAGGUGGACCUGGUCGACCAGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA ACAGAUCCUGUCUAGCCGAGAAGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCUGGGCAGCU UCAUCAUCGUGAUCAUCCUGAUCAUCAUCAUCAAGAAGA CCAAGAAUCCCGCGCCUCUCAUCAUUAUCAAGAAGA CCAAGAACCCCGCCGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCUCACAAC	
HMPV_SC_SUabilizeAlpha_U174W	AUGAGCUGGAAGGUGGUCAUCAUCAUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGUGUGU GAGAACCGGCUGGIACACCACGUGUUCACACUGGUGU GGGCACCGUCGAGAUCUGACAUGUCUGAUGGCCUAG CCUGAUCAAGACCGAGCUGACUGACCUGAUCUGAU	138
HMPV_SC_4M_SUabilizeAlpha_V55LU74LS170LU174W		139

Nucleic Acid Sequence

CAGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGG AUUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGG CAAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA

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NO:

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Strain

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TABLE 19-continued

UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU 140 CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGCCUGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU

HMPV_ProlineSUab_D185P

CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU

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TABLE	19-continued
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Strain	Nucleic Acid Sequence	SEQ II NO:
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCCCUGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC	
MDV BrolinsClab D192D	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	142
MPV_ProlineSUab_D183P	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGCAGAAGA	142
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCCCUAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	AGAACAUCGAGAAUUCCCCAGGCUCUGGUGGACCAGUCCA	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG	
	UGACCAACAAUGGCUUCAUCCCUCACAAC	
MPV_ProlineSUab_E131P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	143

AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU CACACCUCAGCACGGCCUGAAAGAAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU

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TABLE 19-continued

TZ	ABLE 19-continued	
Strain	Nucleic Acid Sequence	SEQ I NO:
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGCCUAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG	
	AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGCGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UGAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCG	
	AGAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCA	
	ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU	
	UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU	
	CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA	
	CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC	
MPV_ProlineSUab_D447P	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	144
MPV_PIOTINESGAD_D447P	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	144
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
	GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG	
	CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU	
	GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG	
	AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG	
	UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCA	
	GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA	
	CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU	
	AGAGUGCUGGCCACAGCCGUGCGCGGGCUGAAGGACUUC	
	GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG	
	UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC	
	CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU	
	AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC	
	CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC	
	AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG	
	AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC	
	GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA	
	UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGGC	
	AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA	
	UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA	
	GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG	
	AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG	
	AGUGCAACAUCAACAUCAGCACCACCAACUAUCCCUGCA	
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACAACCAA GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	

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TABLE 19-continued

SEO ID Nucleic Acid Sequence Strain NO: ACAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCU UCAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCU CCAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGA CCAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAG UGACCAACAAUGGCUUCAUCCCUCACAAC HMPV_UrimerRepulsionD454N AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU 145 CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCAACUAUCCCUGCA AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC UGAGAACCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU GACCAACAAUGGCUUCAUCCCUCACAAC HMPV UrimerRepulsionE453N AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU 146 CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU GGGCGACGUCGAGAAUCUGACAUGCUCUGAUGGCCCUAG CCUGAUCAAGACCGAGCUGGAUCUGACCAAGAGCGCCCU GAGAGAACUCAAGACCGUGUCUGCCGAUCAGCUGGCCAG AGAGGAACAGAUCGAGAAUCCUGGCAGCGGCAGCUUUG UGCUGGGAGCCAUUGCUCUUGGAGUGGCUGCUGCUGCA GCUGUUACAGCAGGCGUGGCCAUCGCUAAGACCAUCAGA CUGGAAAGCGAAGUGACCGCCAUCAACAACGCCCUGAAG AAGACAAACGAGGCCGUCAGCACACUCGGCAAUGGCGUU AGAGUGCUGGCCACAGCCGUGCGCGAGCUGAAGGACUUC GUGUCCAAGAACCUGACACGGGCCAUUAACAAGAACAAG UGCGACAUCGACGACCUGAAGAUGGCCGUGUCCUUUAGC CAGUUCAACCGGCGGUUUCUGAACGUCGUGCGGCAGUUU AGCGACAACGCCGGAAUCACACCAGCCAUCAGCCUGGAC CUGAUGACAGAUGCUGAGCUGGCUAGAGCCGUGCCUAAC AUGCCUACAUCUGCCGGCCAGAUCAAGCUGAUGCUCGAG AAUAGAGCCAUGGUCCGACGGAAAGGCUUCGGCAUUCU GAUUGGCGUGUACGGCAGCAGCGUGAUCUAUAUGGUGC AGCUGCCUAUCUUCGGCGUGAUCGACACACCCUGCUGGA UUGUGAAGGCCGCUCCUAGCUGUAGCGAGAAGAAGGGC AAUUACGCCUGCCUGCUGAGAGAGGACCAAGGCUGGUA UUGUCAGAACGCCGGCAGCACCGUGUACUACCCUAACGA GAAGGACUGCGAGACAAGAGGCGACCACGUGUUCUGUG AUACCGCCGCUGGAAUCAAUGUGGCCGAGCAGAGCAAAG AGUGCAACAUCAACAUCAGCACCAACUAUCCCUGCA

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TABLE 19-continued

Strain	Nucleic Acid Sequence	SEQ II NO:
	AGGUGUCCACCGGCAGGCACCCUAUUUCUAUGGUGGCUC	
	UGUCUCCUCUGGGAGCCCUGGUGGCUUGUUAUAAGGGC	
	GUGUCCUGUAGCAUCGGCAGCAACAGAGUGGGCAUCAUC	
	AAGCAGCUGAACAAGGGCUGCAGCUACAUCACCAACCAG	
	GACGCCGAUACCGUGACCAUCGACAACACCGUGUAUCAG	
	CUGAGCAAGGUGGAAGGCGAACAGCACGUGAUCAAGGG	
	CAGACCUGUGUCCAGCAGCUUCGACCCUAUCAAGUUCCC	
	UCAGGAUCAGUUCCAGGUGGCCCUGGACCAGGUGUUCGA	
	GAACAUCGAGAAUUCCCAGGCUCUGGUGGACCAGUCCAA	
	CAGAAUCCUGUCUAGCGCCGAGAAGGGAAACACCGGCUU	
	CAUCAUCGUGAUCAUCCUGAUCGCCGUGCUGGGCAGCUC	
	CAUGAUCCUGGUGUCCAUCUUCAUCAUUAUCAAGAAGAC	
	CAAGAAGCCCACCGGCGCUCCUCCAGAACUGAGCGGAGU	
	GACCAACAAUGGCUUCAUCCCUCACAAC	
IMPV SUabilizeAlphaF196W	AUGAGCUGGAAGGUGGUCAUCAUCUUCAGCCUGCUGAU	147
	CACACCUCAGCACGGCCUGAAAGAGAGCUACCUGGAAGA	
	GUCCUGCAGCACCAUCACAGAGGGCUACCUGUCUGUGCU	
	GAGAACCGGCUGGUACACCAACGUGUUCACACUGGAAGU	
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	UGACCAACAAUGGCUUCAUCCCUCACAAC	

EQUIVALENTS

Those skilled in the art will recognize, or be able to ⁵⁵ ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure

described herein. Such equivalents are intended to be encompassed by the following claims.

All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

<160> NUMBER OF SEQ ID NOS: 147

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SEQUENCE LISTING

403

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408

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Ser Leu Ile Lys Thr Glu Leu Asp Leu T 65 70	hr Lys Ser Ala Leu Arg Glu 75 80	
Leu Lys Thr Val Ser Ala Asp Gln Leu A 85 9	-	
Asn Pro Arg Gln Ser Arg Phe Val Leu G 100 105	ly Ala Ile Ala Leu Gly Val 110	
Ala Ala Ala Ala Val Thr Ala Gly V. 115 120	al Ala Ile Ala Lys Thr Ile 125	
Arg Leu Glu Ser Glu Val Thr Ala Ile A 130 135	sn Asn Ala Leu Lys Lys Thr 140	
Asn Glu Ala Val Ser Thr Leu Gly Asn G 145 150	ly Val Arg Val Leu Ala Thr 155 160	
Ala Val Arg Glu Leu Lys Asp Phe Val S 165 1	er Lys Asn Leu Thr Arg Ala 70 175	
Ile Asn Lys Asn Lys Cys Asp Ile Asp A 180 185	sp Leu Lys Met Ala Val Ser 190	
Phe Ser Gln Phe Asn Arg Arg Phe Leu A 195 200	sn Val Val Arg Gln Phe Ser 205	
Asp Asn Ala Gly Ile Thr Pro Ala Ile S 210 215	er Leu Asp Leu Met Thr Asp 220	
Ala Glu Leu Ala Arg Ala Val Pro Asn M 225 230	et Pro Thr Ser Ala Gly Gln 235 240	
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Leu	Lys	Thr	Val	Ser 85	Ala	Asp	Gln	Leu	Ala 90	Arg	Glu	Glu	Gln	Ile 95	Glu
Asn	Pro	Arg	Gln 100	Ser	Arg	Phe	Val	Leu 105	Gly	Ala	Ile	Ala	Leu 110	Gly	Val
Ala	Thr	Ala 115	Ala	Ala	Val	Thr	Ala 120	Gly	Ile	Ala	Ile	Ala 125	Гуз	Thr	Ile
Arg	Leu 130	Glu	Ser	Glu	Val	Asn 135	Ala	Ile	Lys	Gly	Ala 140	Leu	Lys	Thr	Thr
Asn 145	Glu	Ala	Val	Ser	Thr 150	Leu	Gly	Asn	Gly	Val 155	Arg	Val	Leu	Ala	Thr 160
Ala	Val	Arg	Glu	Leu 165	Гла	Glu	Phe	Val	Ser 170	Lys	Asn	Leu	Thr	Ser 175	Ala
Ile	Asn	Гуз	Asn 180	ГЛа	Cys	Aab	Ile	Ala 185	Asp	Leu	ГАз	Met	Ala 190	Val	Ser
Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Asn	Asp
Ala 225	Glu	Leu	Ala	Arg	Ala 230	Val	Ser	Tyr	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
Ile	Lys	Leu	Met	Leu 245	Glu	Asn	Arg	Ala	Met 250	Val	Arg	Arg	Lys	G1y 255	Phe
Gly	Ile	Leu	11e 260	Gly	Val	Tyr	Gly	Ser 265	Ser	Val	Ile	Tyr	Met 270	Val	Gln
Leu	Pro	Ile 275	Phe	Gly	Val	Ile	Asn 280	Thr	Pro	Суя	Trp	Ile 285	Ile	Lys	Ala
Ala	Pro 290	Ser	Сүз	Ser	Glu	Lys 295	Asp	Gly	Asn	Tyr	Ala 300	Сув	Leu	Leu	Arg
Glu 305	Asp	Gln	Gly	Trp	Tyr 310	Сув	гла	Asn	Ala	Gly 315	Ser	Thr	Val	Tyr	Tyr 320
Pro	Asn	Glu	Lys	Asp 325	Суз	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сув 335	Asp
Thr	Ala	Ala	Gly 340	Ile	Asn	Val	Ala	Glu 345	Gln	Ser	Arg	Glu	Сув 350	Asn	Ile
Asn	Ile	Ser 355	Thr	Thr	Asn	Tyr	Pro 360	Сув	Lys	Val	Ser	Thr 365	Gly	Arg	His
Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Суз
Tyr 385	Lys	Gly	Val	Ser	Суз 390	Ser	Thr	Gly	Ser	Asn 395	Gln	Val	Gly	Ile	Ile 400
Lys	Gln	Leu	Pro	Lys 405	Gly	Cys	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp

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Thr	Val	Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
Ile	Arg 450	Phe	Pro	Glu	Asp	Gln 455	Phe	Asn	Val	Ala	Leu 460	Asp	Gln	Val	Phe
Glu 465	Ser	Ile	Glu	Asn	Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Lys	Ile 480
Leu	Asn	Ser	Ala	Glu 485	Lys	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
Leu	Ile	Ala	Val 500	Leu	Gly	Leu	Thr	Met 505	Ile	Ser	Val	Ser	Ile 510	Ile	Ile
Ile	Ile	Lys 515	Гла	Thr	Arg	Lys	Pro 520	Thr	Gly	Ala	Pro	Pro 525	Glu	Leu	Asn
Gly	Val 530	Thr	Asn	Gly	Gly	Phe 535	Ile	Pro	His	Ser					
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Ala	Val	Thr	Leu 20	Сүз	Phe	Ala	Ser	Ser 25	Gln	Asn	Ile	Thr	Glu 30	Glu	Phe
Tyr	Gln	Ser 35	Thr	Суз	Ser	Ala	Val 40	Ser	Lys	Gly	Tyr	Leu 45	Ser	Ala	Leu
Arg	Thr 50	Gly	Trp	Tyr	Thr	Ser 55	Val	Ile	Thr	Ile	Glu 60	Leu	Ser	Asn	Ile
Lys 65	Glu	Asn	ГЛа	Сүз	Asn 70	Gly	Thr	Asp	Ala	Lys 75	Val	Гуа	Leu	Ile	Lys 80
Gln	Glu	Leu	Aab	Lys 85	Tyr	Гла	Asn	Ala	Val 90	Thr	Glu	Leu	Gln	Leu 95	Leu
Met	Gln	Ser	Thr 100	Pro	Ala	Ala	Asn	Asn 105	Arg	Ala	Arg	Arg	Glu 110	Leu	Pro
Arg	Phe	Met 115	Asn	Tyr	Thr	Leu	Asn 120	Asn	Thr	Lys	Asn	Thr 125	Asn	Val	Thr
Leu	Ser 130	Гуз	Гүз	Arg	Гуз	Arg 135	Arg	Phe	Leu	Gly	Phe 140	Leu	Leu	Gly	Val
Gly 145	Ser	Ala	Ile	Ala	Ser 150	Gly	Ile	Ala	Val	Ser 155	ГЛа	Val	Leu	His	Leu 160
Glu	Gly	Glu	Val	Asn 165	-	Ile	Lys	Ser	Ala 170	Leu	Leu	Ser	Thr	Asn 175	Lys
Ala	Val	Val	Ser 180	Leu	Ser	Asn	Gly	Val 185	Ser	Val	Leu	Thr	Ser 190	Lys	Val
Leu	Asp	Leu 195	Гүз	Asn	Tyr	Ile	Asp 200	Гуа	Gln	Leu	Leu	Pro 205	Ile	Val	Asn
ГЛа	Gln 210	Ser	СЛа	Ser	Ile	Ser 215	Asn	Ile	Glu	Thr	Val 220	Ile	Glu	Phe	Gln
Gln 225	Lys	Asn	Asn	Arg	Leu 230	Leu	Glu	Ile	Thr	Arg 235	Glu	Phe	Ser	Val	Asn 240
Ala	Gly	Val	Thr	Thr 245	Pro	Val	Ser	Thr	Tyr 250	Met	Leu	Thr	Asn	Ser 255	Glu

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Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys 260 265 270

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Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile 275 280 295
Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro 290 295 300
Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro 305 310 315 320
Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg 325 330 335
Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe 340 345 350
Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp 355 360 365
Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Ile 370 375 380
Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr 385 390 395 400
Asp Val Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys 405 410 415
Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile 420 425 430
Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp 435 440 445
Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly 450 455 460
Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro 465 470 475 480
Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn 485 490 495
Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu 500 505 510
Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr 515 520 525
Thr Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val 530 535 540
Gly Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser 545 550 555 560
Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn 565 570
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tcacaaaact tcgaaacaag atatctaatc ctgagtctca taccaaaaat agaagattct 180
aactettgtg gtgaccaaca gatcaagcaa tacaagaggt tattggatag actgatcatt 240
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agatcagaca ttgaaaaact caaggaagca atcagggaca caaataaagc agtgcagtca	480
gttcagaget etgtaggaaa tttgatagta geaattaaat eagteeagga ttatgteaae	540
aaagaaateg tgecategat tgegagaeta ggttgtgaag cageaggaet teagttaggg	600
attgcattaa cacagcatta ctcagaatta acaaatatat ttggtgataa cataggatcg	660
ttacaagaaa aaggaataaa attacaaggt atagcatcat tataccgtac aaatatcaca	720
gaaatattca caacatcaac agttgacaaa tatgatattt atgatctatt atttacagaa	780
tcaataaagg tgagagttat agatgttgat ttgaatgatt actcaataac cctccaagtc	840
agacteeett tattgaceag actgetgaae acteaaatet acaaagtaga tteeatatea	900
tacaatatee aaaatagaga atggtatate eetetteeea geeatateat gaegaaaggg	960
gcatttetag gtggageaga tgteaaagaa tgeatagaag eatteageag ttatatatge	1020
cettetgate caggatttgt actaaaceat gaaatggaga getgtetate aggaaacata	1080
teecaatgte caagaaceae agteacatea gaeatagtte etaggtatge atttgteaat	1140
ggaggagtgg ttgcgaattg tataacaact acatgtacat gcaatggtat cggtaataga	1200
atcaaccaac cacctgatca aggagtcaaa attataacac ataaagaatg taatacaata	1260
ggtatcaacg gaatgetatt caacacaaac aaagaaggaa etettgeatt etacacacea	1320
gacgacataa cattaaacaa ttetgttgea ettgateega ttgacatate aategagete	1380
aacaaggcca aatcagatct tgaggaatca aaagaatgga taagaaggtc aaatcaaaag	1440
ctagatteta ttggaagttg geateaatet ageaetaeaa teatagttat tttgataatg	1500
atgattatat tgtttataat taatataaca ataattacaa ttgcaattaa gtattacaga	1560
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ctggtgttat tatcaatagt cttcatcata gtgctaacta attccatcaa aagtgaaaag	180
gcccgcgaat cattgctaca agacataaat aatgagttta tggaagttac agaaaagatc	240
caagtggcat cggataatac taatgatcta atacagtcag gagtgaatac aaggettett	300
acaatteaga gteatgteea gaattatata eeaatateat tgacacaaca aatateggat	360
cttaggaaat tcattagtga aattacaatt agaaatgata atcaagaagt gccaccacaa	420
agaataacac atgatgtggg tataaaacct ttaaatccag atgatttetg gagatgeaeg	480
tetggtette catetttgat gaaaacteea aaaataagat taatgeeggg accaggatta	540
ttagetatge caacgactgt tgatggetgt gteagaacee egteettagt gataaatgat	600
ctgatttatg cttacacctc aaatctaatt actcgaggtt gccaggatat agggaaatca	660
etgatttatg ettacaeete aaatetaatt aetegaggtt geeaggatat agggaaatea tateaagtat taeagatagg gataataaet gtaaaeteag aettggtaee tgaettaaat	
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tatcaagtat tacagatagg gataataact gtaaactcag acttggtacc tgacttaaat	660 720

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gcatcatcag gcatagaaga tattgtactt gatattgtca attatgatgg ctcaatctcg 900 acaacaagat ttaagaataa taatataagt tttgatcaac catatgoggo attataccoa 960 tetgttggae cagggatata etacaaagge aaaataatat ttetegggta tggaggtett 1020 gaacateeaa taaatgagaa tgeaatetge aacacaaetg ggtgteetgg gaaaacaeag 1080 agagactgta atcaagcatc tcatagtcca tggttttcag atagaaggat ggtcaactct 1140 1200 ataattgttg ttgacaaggg cttgaactca gttccaaaat tgaaggtatg gacgatatct atgagacaaa attactgggg gtcagaagga agattacttc tactaggtaa caagatctac 1260 atatacacaa gatetacaag tiggcacage aagttacaat taggaataat igacattact 1320 gactacagtg atataaggat aaaatggaca tggcataatg tgctatcaag accaggaaac 1380 aatqaatqte catqqqqaca tteatqteeq qatqqatqta taacqqqaqt atataceqat 1440 gcatateeac teaateeeac aggaageatt gtateatetg teatattgga eteacaaaaa 1500 togagagtea acceagteat aacttactea acageaaceg aaagggtaaa egagetgget 1560 atoogaaaca aaacactoto agotgggtao acaacaacaa gotgoattao acactataac 1620 1680 aaaqqqtatt qttttcatat aqtaqaaata aatcataaaa qcttaaacac atttcaaccc

aaagggtatt gttttcatat agtagaaata aatcataaaa gcttaaacac atttcaacce 1680 atgttgttca aaacagagat tccaaaaagc tgcagt 1716

<210> SEQ ID NO 11 <211> LENGTH: 1716 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 11

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gactacageg acateeggat caagtggaee tggeacaaeg tgetgageag aceeggeaae	1380
aatgagtgee ettggggeea cagetgeeee gatggatgta teaceggegt gtacacegae	1440
geetaceeee tgaateetae eggeteeate gtgteeageg tgateetgga cageeagaaa	1500
agcagagtga accocgtgat cacatacagc accgccaccg agagagtgaa cgaactggcc	1560
atcagaaaca agaccetgag egeeggetae accaecaeaa getgeateae acaetaeaae	1620
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atgetgttea agaeegagat eeccaagage tgetee	1716
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aacagetgeg gegaceagea gateaageag taeaagegge tgetggaeag aetgateate	240
cccctgtacg acggcctgcg gctgcagaaa gacgtgatcg tgaccaacca ggaaagcaac	300
gagaacaccg acccccggac cgagagatto ttoggoggog tgatoggcac aatogoootg	360
ggagtggeca caagegeeca gattacagee getgtggeee tggtggaage caageaggee	420
agaagegaca tegagaaget gaaagaggee ateegggaca eeaacaagge egtgeagage	480
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aaagaaateg tgeeetetat egeeeggetg ggetgtgaag etgeeggaet geagetggge	600
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gagatettea ceaccageae egtggataag taegaeatet aegaeetget gtteaeegag	780
agcatcaaag tgegegtgat egaegtggae etgaaegaet aeageateae eetgeaagtg	840
cggctgcccc tgctgaccag actgctgaac acccagatet acaaggtgga cagcatetee	900
tacaacatoo agaacegega gtggtacato estetgecea gecacattat gaceaaggge	960
gcetttetgg geggageega egtgaaagag tgeategagg eetteageag etacatetge	1020
cccagegaee etggettegt getgaaceae gagatggaaa getgeetgag eggeaacate	1080
agecagtgee ceagaaeeae egtgaeetee gaeategtge ceagataege ettegtgaat	1140
ggeggegtgg tggecaactg catcaccacc acctgtacct gcaacggeat eggeaacegg	1200
atcaaccage etcoegatea gggegtgaag attateacee acaaagagtg taacaceate	1260
ggcatcaacg gcatgctgtt caataccaac aaagagggca cootggcott ctacaccooc	1320
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aacaaggeea agagegaeet ggaagagtee aaagagtgga teeggeggag caaccagaag	1440
ctggacteta teggeagetg geaceagage ageaceacea teategtgat eetgattatg	1500

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atgattatcc tgttcatca	at caacattacc atcatcacta	tegecattaa gtactacegg	1560
atccagaaac ggaaccgg	gt ggaccagaat gacaagcoot	acgtgctgac aaacaag	1617
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<400> SEQUENCE: 13			
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His Cys Gln Ile Asp	Ile Thr Lys Leu Gln His	Val Gly Val Leu Val	
20	25	30	
Asn Ser Pro Lys Gly	Met Lys Ile Ser Gln Asn	Phe Glu Thr Arg Tyr	
35	40	45	
Leu Ile Leu Ser Leu	Ile Pro Lys Ile Glu Asp	Ser Asn Ser Cys Gly	
50	55	60	
Asp Gln Gln Ile Lys	Gln Tyr Lys Arg Leu Leu	Asp Arg Leu Ile Ile	
65	70	80	
Pro Leu Tyr Asp Gly	Leu Arg Leu Gln Lys Asp	Val Ile Val Thr Asn	
85	90	95	
Gln Glu Ser Asn Glu	Asn Thr Asp Pro Arg Thr	Glu Arg Phe Phe Gly	
100	105	110	
Gly Val Ile Gly Thr	Ile Ala Leu Gly Val Ala	Thr Ser Ala Gln Ile	
115	120	125	
Thr Ala Ala Val Ala	Leu Val Glu Ala Lys Gln	Ala Arg Ser Asp Ile	
130	135	140	
Glu Lys Leu Lys Glu 145	Ala Ile Arg Asp Thr Asn 150 155		
Val Gln Ser Ser Val	Gly Asn Leu Ile Val Ala	Ile Lys Ser Val Gln	
165	170	175	
Asp Tyr Val Asn Lys	Glu Ile Val Pro Ser Ile	Ala Arg Leu Gly Cys	
180	185	190	
Glu Ala Ala Gly Leu	Gln Leu Gly Ile Ala Leu	Thr Gln His Tyr Ser	
195	200	205	
Glu Leu Thr Asn Ile	Phe Gly Asp Asn Ile Gly	Ser Leu Gln Glu Lys	
210	215	220	
Gly Ile Lys Leu Gln	Gly Ile Ala Ser Leu Tyr	Arg Thr Asn Ile Thr	
225	230 235	240	
Glu Ile Phe Thr Thr	Ser Thr Val Asp Lys Tyr	Asp Ile Tyr Asp Leu	
245	250	255	
Leu Phe Thr Glu Ser	Ile Lys Val Arg Val Ile	Asp Val Asp Leu Asn	
260	265	270	
Asp Tyr Ser Ile Thr	Leu Gln Val Arg Leu Pro	Leu Leu Thr Arg Leu	
275	280	285	
Leu Asn Thr Gln Ile	Tyr Lys Val Asp Ser Ile	Ser Tyr Asn Ile Gln	
290	295	300	
Asn Arg Glu Trp Tyr	Ile Pro Leu Pro Ser His	Ile Met Thr Lys Gly	
305	310 315	320	
Ala Phe Leu Gly Gly	Ala Asp Val Lys Glu Cys	Ile Glu Ala Phe Ser	
325	330	335	
Ser Tyr Ile Cys Pro	Ser Asp Pro Gly Phe Val	Leu Asn His Glu Met	
340	345	350	

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Glu	Ser	Cys 355	Leu	Ser	Gly	Asn	Ile 360	Ser	GIn	-	PIO	Arg 365	Thr	Thr	Val	
Thr	Ser 370	Asp	Ile	Val	Pro	Arg 375		Ala	Phe	Val	Asn 380	Gly	Gly	Val	Val	
Ala 385	Asn	Cys	Ile	Thr	Thr 390	Thr	Сув	Thr	Cys	Asn 395	Gly	Ile	Gly	Asn	Arg 400	
Ile	Asn	Gln	Pro	Pro 405	Asp	Gln	Gly	Val	Lys 410	Ile	Ile	Thr	His	Lys 415	Glu	
СЛа	Asn	Thr	Ile 420	Gly	Ile	Asn	Gly	Met 425	Leu	Phe	Asn	Thr	Asn 430	ГÀа	Glu	
Gly	Thr	Leu 435	Ala	Phe	Tyr	Thr	Pro 440	Asp	Asp	Ile	Thr	Leu 445	Asn	Asn	Ser	
Val	Ala 450	Leu	Asp	Pro	Ile	Asp 455	Ile	Ser	Ile	Glu	Leu 460	Asn	Lys	Ala	Lys	
Ser 465	Asp	Leu	Glu	Glu	Ser 470	Lys	Glu	Trp	Ile	Arg 475	Arg	Ser	Asn	Gln	Lys 480	
Leu	Asp	Ser	Ile	Gly 485	Ser	Trp	His	Gln	Ser 490	Ser	Thr	Thr	Ile	Ile 495	Val	
		Ile	500					505					510			
Thr	Ile	Ala 515	Ile	Lys	Tyr	Tyr	Arg 520	Ile	Gln	Lys	Arg	Asn 525	Arg	Val	Asp	
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444

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Gln	Ala	Leu 835	His	Gly	Ala	Asn	Leu 840	Arg	Gln	Asp	Asp	Ser 845	Val	Arg	Asn		
Leu	Phe 850	Ala	Ser	Val	Гуз	Ser 855	Ser	Gln	Ser	Ser	Pro 860	Ile	Ile	Pro	Gly		
Phe 865	Gly	Gly	Asp	Phe	Asn 870	Leu	Thr	Leu	Leu	Glu 875	Pro	Val	Ser	Ile	Ser 880		
Thr	Gly	Ser	Arg	Ser 885	Ala	Arg	Ser	Ala	Ile 890	Glu	Asp	Leu	Leu	Phe 895	-		
Lys	Val	Thr	Ile 900	Ala	Asp	Pro	Gly	Tyr 905	Met	Gln	Gly	Tyr	Asp 910	Aap	Сув		
Met	Gln	Gln 915	Gly	Pro	Ala	Ser	Ala 920	Arg	Asp	Leu	Ile	Cys 925	Ala	Gln	Tyr		
Val	Ala 930	Gly	Tyr	Гла	Val	Leu 935	Pro	Pro	Leu	Met	Asp 940	Val	Asn	Met	Glu		
Ala 945	Ala	Tyr	Thr	Ser	Ser 950	Leu	Leu	Gly	Ser	Ile 955	Ala	Gly	Val	Gly	Trp 960		
Thr	Ala	Gly	Leu	Ser 965	Ser	Phe	Ala	Ala	Ile 970	Pro	Phe	Ala	Gln	Ser 975	Ile		
Phe	Tyr	Arg	Leu 980	Asn	Gly	Val	Gly	Ile 985	Thr	Gln	Gln	Val	Leu 990	Ser	Glu		
Asn	Gln	Lys 995	Leu	Ile	Ala	Asn	Lys 100		e Ası	n Glı	n Al	a Le 10		ly A	la Met		
Gln	Thr 1010		Phe	e Thi	r Thi	Th: 10:		an G	lu A	la Pl		rg 020	Lys '	Val	Gln		
Asp	Ala 1025		. Asr	1 Ası	n Asr	n Ala 103		ln A	la L	eu So		ув 035	Leu J	Ala	Ser		
Glu	Leu 1040		Asr	n Thi	r Phe	e Gly 104		La I	le S	er A		er 050	Ile	Gly .	Asp		
Ile	Ile 1059		ı Arg	g Lei	ı Asp	Va. 10		eu Gi	lu G	ln A	-	la 065	Gln	Ile .	Asp		
Arg	Leu 1070		e Asr	ı Gly	/ Arç	g Lev 10'		ır Tl	nr L	eu Ai		la 080	Phe '	Val .	Ala		
Gln	Gln	Leu	. Val	. Arg	g Sei	c Glu	ı Se	er A	la A	la L	eu S	er .	Ala (Gln	Leu		

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													-	con	ntir	nueo	1	
	1085						109	0					1	095				
Ala	Lys 1100		ь Га	s Va	ıl A	sn	Glu 110		s V	/al	Lys	Al		ln 110	Ser	Lys	Arg	ł
Ser	Gly 1115		е Су	s Gl	y G	ln	Gly 112		rΗ	lis	Ile	Va		er 125	Phe	Val	Val	L
Asn	Ala 1130		Asi	n Gl	y L	eu	Tyr 113!		.e №	let	His	Va		ly 140	Tyr	Tyr	Pro	>
Ser	Asn 1145		; Il	e Gl	u V	al	Val 115		r A	la	Tyr	Gl	-	eu 155	Сув	Asp	Ala	à
Ala	Asn 1160		Th:	r As	n C	уз	Ile 1169		аF	ro	Val	As		ly 170	Tyr	Phe	Ile	3
ГЛа	Thr 1175		n Asi	n Tr	ir A	rg	Ile 118		1 A	/ab	Glu	Tr		er 185	Tyr	Thr	Gly	7
Ser	Ser 1190		ту	r Al	a F	ro	Glu 119		οI	le	Thr	Se		eu 200	Asn	Thr	Гуз	3
Tyr	Val 1205		ı Pro	5 G]	.n V	al	Thr 1210	-	rθ	ln	Asn	11		er 215	Thr	Asn	Leu	1
Pro	Pro 1220) Le	u Le	eu G	ly	Asn 122!		rI	'hr	Gly	11		.sp 230	Phe	Gln	Asp	ç
Glu	Leu 1235	-	Gl	u Pr	le F	he	Lys 124		n V	7al	Ser	Th		er 245	Ile	Pro	Asn	ı
Phe	Gly 1250		Le	u Th	nr G	ln	Ile 125!		n I	hr	Thr	Le		eu 260	Asp	Leu	Thr	r
Tyr	Glu 1265		Le	u Se	er I	eu	Gln 127		n V	Val	Val	Ьу		la 275	Leu	Asn	Glu	1
Ser	Tyr 1280		e Asj	p Le	eu L	уs	Glu 128		u G	ly	Asn	ту		'hr 290	Tyr	Tyr	Asn	ı
Lys	Trp 1295		Trj	р Ту	'r I	le	Trp 130		u G	Чy	Phe	11		la 305	Gly	Leu	Val	L
Ala	Leu 1310		ı Le	u Cy	′s V	7al	Phe 131!		e I.	le	Leu	су		уя 320	Thr	Gly	Сув	3
Gly	Thr 1325		n Cy	s Me	et G	ly	Lys 133		u I	Ъз	Суз	As		rg 335	Сув	Суз	Asp	Ş
Arg	Tyr 1340		ı Gl	u Ty	'r A	ap	Leu 134!		u F	ro	His	Ly		al 350	His	Val	His	3
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Met	Ile			Val	. Ph	ie I	Leu 1	Leu	Met			eu	Leu	Thr	Pro		r Glu	Lu
1	m -		-	5				-	-	10			-			15		
Ser	Tyr	Val	Азр 20	Va]	. G1	y F	Pro I	-	Ser 25	: Va	1 L	уs	Ser	Ala	1 Cys 30	3 I l	e Glu	LU
Val	Asp	Ile 35	Gln	Glr	1 Th	ır E		Phe 40	Asp	ь Гу	s T	hr	Trp	Pro 45	Arg	g Pro	o Ile	le
Asp	Val 50	Ser	Lys	Ala	a As	-	31y 3 55	Ile	Ile	а Ту	ΥP		G1n 60	Gly	' Arg	g Thi	r Ty:	ŗr
Ser 65	Asn	Ile	Thr	Ilε	• Th 70		Fyr (Gln	Gly	∕Le	u P 7		Pro	Tyr	Glr	ı Gl	y Asj 80	_
His	Gly	Asp	Met	Tyr	: Va	11	fyr :	Ser	Ala	ı Gl	уН	is	Ala	Thr	Gl	7 Th:	r Th:	ır

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COL		T 11	ue	u

						400	,											50
											-	con	tin	ued		 		
				85					90					95				
Pro	Gln	Lys	Leu 100	Phe	Val	Ala	Asn	Tyr 105	Ser	Gln	Asp	Val	Lys 110	Gln	Phe			
Ala	Asn	Gly 115	Phe	Val	Val	Arg	Ile 120	Gly	Ala	Ala	Ala	Asn 125	Ser	Thr	Gly			
Thr	Val 130	Ile	Ile	Ser	Pro	Ser 135	Thr	Ser	Ala	Thr	Ile 140	Arg	Гуз	Ile	Tyr			
Pro 145	Ala	Phe	Met	Leu	Gly 150	Ser	Ser	Val	Gly	Asn 155	Phe	Ser	Asp	Gly	Lys 160			
Met	Gly	Arg	Phe	Phe 165	Asn	His	Thr	Leu	Val 170	Leu	Leu	Pro	Asp	Gly 175	Суз			
Gly	Thr	Leu	Leu 180	Arg	Ala	Phe	Tyr	Cys 185	Ile	Leu	Glu	Pro	Arg 190	Ser	Gly			
Asn	His	Cys 195	Pro	Ala	Gly	Asn	Ser 200	Tyr	Thr	Ser	Phe	Ala 205	Thr	Tyr	His			
Thr	Pro 210	Ala	Thr	Asp	Суз	Ser 215	Aab	Gly	Asn	Tyr	Asn 220	Arg	Asn	Ala	Ser			
Leu 225	Asn	Ser	Phe	ГАз	Glu 230	Tyr	Phe	Asn	Leu	Arg 235	Asn	Суз	Thr	Phe	Met 240			
Tyr	Thr	Tyr	Asn	Ile 245	Thr	Glu	Asp	Glu	Ile 250	Leu	Glu	Trp	Phe	Gly 255	Ile			
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Leu	Tyr	Gly 275	Gly	Asn	Met	Phe	Gln 280	Phe	Ala	Thr	Leu	Pro 285	Val	Tyr	Asp			
Thr	Ile 290	Lys	Tyr	Tyr	Ser	Ile 295	Ile	Pro	His	Ser	Ile 300	Arg	Ser	Ile	Gln			
Ser 305	Asp	Arg	Lys	Ala	Trp 310	Ala	Ala	Phe	Tyr	Val 315	Tyr	Lys	Leu	Gln	Pro 320			
Leu	Thr	Phe	Leu	Leu 325	Asp	Phe	Ser	Val	Asp 330	Gly	Tyr	Ile	Arg	Arg 335	Ala			
Ile	Asp	Сув	Gly 340	Phe	Asn	Aab	Leu	Ser 345	Gln	Leu	His	Суз	Ser 350	Tyr	Glu			
Ser	Phe	Asp 355	Val	Glu	Ser	Gly	Val 360	Tyr	Ser	Val	Ser	Ser 365	Phe	Glu	Ala			
Lys	Pro 370	Ser	Gly	Ser	Val	Val 375	Glu	Gln	Ala	Glu	Gly 380	Val	Glu	Сүз	Asp			
Phe 385	Ser	Pro	Leu	Leu	Ser 390	Gly	Thr	Pro	Pro	Gln 395	Val	Tyr	Asn	Phe	Lys 400			
Arg	Leu	Val	Phe	Thr 405	Asn	Сув	Asn	Tyr	Asn 410	Leu	Thr	Lys	Leu	Leu 415	Ser			
Leu	Phe	Ser	Val 420	Asn	Asp	Phe	Thr	Сув 425	Ser	Gln	Ile	Ser	Pro 430	Ala	Ala			
Ile	Ala	Ser 435	Asn	Суз	Tyr	Ser	Ser 440	Leu	Ile	Leu	Asp	Tyr 445	Phe	Ser	Tyr			
Pro	Leu 450	Ser	Met	Гла	Ser	Asp 455	Leu	Ser	Val	Ser	Ser 460	Ala	Gly	Pro	Ile			
Ser 465	Gln	Phe	Asn	Tyr	Lys 470	Gln	Ser	Phe	Ser	Asn 475	Pro	Thr	Сув	Leu	Ile 480			
Leu	Ala	Thr	Val	Pro 485	His	Asn	Leu	Thr	Thr 490	Ile	Thr	Lys	Pro	Leu 495	Lys			
Tyr	Ser	Tyr	Ile 500	Asn	Гуз	Суз	Ser	Arg 505	Leu	Leu	Ser	Asp	Asp 510	Arg	Thr			

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Glu	Val	Pro 515	Gln	Leu	Val	Asn	Ala 520	Asn	Gln	Tyr	Ser	Pro 525	Cys	Val	Ser
Ile	Val 530	Pro	Ser	Thr	Val	Trp 535	Glu	Asp	Gly	Asp	Tyr 540	Tyr	Arg	Lys	Gln
Leu 545	Ser	Pro	Leu	Glu	Gly 550	Gly	Gly	Trp	Leu	Val 555	Ala	Ser	Gly	Ser	Thr 560
Val	Ala	Met	Thr	Glu 565	Gln	Leu	Gln	Met	Gly 570	Phe	Gly	Ile	Thr	Val 575	Gln
Tyr	Gly	Thr	Asp 580	Thr	Asn	Ser	Val	Cys 585	Pro	Lys	Leu	Glu	Phe 590	Ala	Asn
Asp	Thr	Lys 595	Ile	Ala	Ser	Gln	Leu 600	Gly	Asn	Суа	Val	Glu 605	Tyr	Ser	Leu
Tyr	Gly 610	Val	Ser	Gly	Arg	Gly 615	Val	Phe	Gln	Asn	Cys 620	Thr	Ala	Val	Gly
Val 625	Arg	Gln	Gln	Arg	Phe 630	Val	Tyr	Asp	Ala	Tyr 635	Gln	Asn	Leu	Val	Gly 640
Tyr	Tyr	Ser	Aab	Asp 645	Gly	Asn	Tyr	Tyr	Cys 650	Leu	Arg	Ala	Сув	Val 655	Ser
Val	Pro	Val	Ser 660	Val	Ile	Tyr	Asp	Lys 665	Glu	Thr	Lys	Thr	His 670	Ala	Thr
Leu	Phe	Gly 675	Ser	Val	Ala	Сув	Glu 680	His	Ile	Ser	Ser	Thr 685	Met	Ser	Gln
Tyr	Ser 690	Arg	Ser	Thr	Arg	Ser 695	Met	Leu	Lys	Arg	Arg 700	Asp	Ser	Thr	Tyr
Gly 705	Pro	Leu	Gln	Thr	Pro 710	Val	Gly	Суз	Val	Leu 715	Gly	Leu	Val	Asn	Ser 720
Ser	Leu	Phe	Val	Glu 725	Asp	Сүя	Lys	Leu	Pro 730	Leu	Gly	Gln	Ser	Leu 735	Cys
Ala	Leu	Pro	Asp 740	Thr	Pro	Ser	Thr	Leu 745	Thr	Pro	Arg	Ser	Val 750	Arg	Ser
Val	Pro	Gly 755	Glu	Met	Arg	Leu	Ala 760	Ser	Ile	Ala	Phe	Asn 765	His	Pro	Ile
Gln	Val 770	Asp	Gln	Leu	Asn	Ser 775	Ser	Tyr	Phe	Lys	Leu 780	Ser	Ile	Pro	Thr
Asn 785	Phe	Ser	Phe	Gly	Val 790	Thr	Gln	Glu	Tyr	Ile 795	Gln	Thr	Thr	Ile	Gln 800
Lys	Val	Thr	Val	Asp 805	Сув	Lys	Gln	Tyr	Val 810	Сув	Asn	Gly	Phe	Gln 815	Lys
СЛа	Glu	Gln	Leu 820	Leu	Arg	Glu	Tyr	Gly 825	Gln	Phe	СЛа	Ser	Lуа 830	Ile	Asn
Gln	Ala	Leu 835	His	Gly	Ala	Asn	Leu 840	Arg	Gln	Asp	Asp	Ser 845	Val	Arg	Asn
Leu	Phe 850	Ala	Ser	Val	Lys	Ser 855	Ser	Gln	Ser	Ser	Pro 860	Ile	Ile	Pro	Gly
Phe 865	Gly	Gly	Asp	Phe	Asn 870	Leu	Thr	Leu	Leu	Glu 875	Pro	Val	Ser	Ile	Ser 880
Thr	Gly	Ser	Arg	Ser 885	Ala	Arg	Ser	Ala	11e 890	Glu	Asp	Leu	Leu	Phe 895	Asp
Lys	Val	Thr	Ile 900	Ala	Asp	Pro	Gly	Tyr 905	Met	Gln	Gly	Tyr	Asp 910	Asp	Cys
Met	Gln	Gln 915	Gly	Pro	Ala	Ser	Ala 920	Arg	Asp	Leu	Ile	Сув 925	Ala	Gln	Tyr

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Val Ala Gly Tyr Lys Val Leu Pro Pro Leu Met Asp Val Asn Met Glu 930 935 940
Ala Ala Tyr Thr Ser Ser Leu Leu Gly Ser Ile Ala Gly Val Gly Trp 945 950 955 960
Thr Ala Gly Leu Ser Ser Phe Ala Ala Ile Pro Phe Ala Gln Ser Ile 965 970 975
Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu 980 985 990
Asn Gln Lys Leu Ile Ala Asn Lys Phe Asn Gln Ala Leu Gly Ala Met 995 1000 1005
Gln Thr Gly Phe Thr Thr Asn Glu Ala Phe Gln Lys Val Gln 1010 1015 1020
Asp Ala Val Asn Asn Ala Gln Ala Leu Ser Lys Leu Ala Ser 1025 1030 1035
Glu Leu Ser Asn Thr Phe Gly Ala Ile Ser Ala Ser Ile Gly Asp 1040 1045 1050
Ile Ile Gln Arg Leu Asp Val Leu Glu Gln Asp Ala Gln Ile Asp 1055 1060 1065
Arg Leu Ile Asn Gly Arg Leu Thr Thr Leu Asn Ala Phe Val Ala 1070 1075 1080
Gln Gln Leu Val Arg Ser Glu Ser Ala Ala Leu Ser Ala Gln Leu 1085 1090 1095
Ala Lys Asp Lys Val Asn Glu Cys Val Lys Ala Gln Ser Lys Arg 1100 1105 1110
Ser Gly Phe Cys Gly Gln Gly Thr His Ile Val Ser Phe Val Val 1115 1120 1125
Asn Ala Pro Asn Gly Leu Tyr Phe Met His Val Gly Tyr Tyr Pro 1130 1135 1140
Ser Asn His Ile Glu Val Val Ser Ala Tyr Gly Leu Cys Asp Ala 1145 1150 1155
Ala Asn Pro Thr Asn Cys Ile Ala Pro Val Asn Gly Tyr Phe Ile 1160 1165 1170
Lys Thr Asn Asn Thr Arg Ile Val Asp Glu Trp Ser Tyr Thr Gly 1175 1180 1185
Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys 1190 1195 1200
Tyr Val Ala Pro Gln Val Thr Tyr Gln Asn Ile Ser Thr Asn Leu 1205 1210 1215
Pro Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp 1220 1225 1230
Glu Leu Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn 1235 1240 1245
Phe Gly Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr 1250 1255 1260
Tyr Glu Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu 1265 1270 1275
Ser Tyr Ile Asp Leu Lys Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn 1280 1285 1290
Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val 1295 1300 1305

Ala Leu Ala Leu Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys 1310 1315 Leu Lys Cys Asn Arg Cys Cys Asp

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	132	5				133	30				1.	335			
Arg	Tyr 134		u Glu	u Ty:	r Asj	p Lei 134		lu P:	ro H:	is Ly		al 1 350	His '	Val H	His
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Met 1	Ile	His	Ser	Val 5	Phe	Leu	Leu	Met	Phe 10	Leu	Leu	Thr	Pro	Thr 15	Glu
Ser	Asp	Cys	Lys 20	Leu	Pro	Leu	Gly	Gln 25	Ser	Leu	Суз	Ala	Leu 30	Pro	Asp
Thr	Pro	Ser 35	Thr	Leu	Thr	Pro	Arg 40	Ser	Val	Arg	Ser	Val 45	Pro	Gly	Glu
Met	Arg 50	Leu	Ala	Ser	Ile	Ala 55	Phe	Asn	His	Pro	Ile 60	Gln	Val	Aab	Gln
Leu 65	Asn	Ser	Ser	Tyr	Phe 70	Lys	Leu	Ser	Ile	Pro 75	Thr	Asn	Phe	Ser	Phe 80
Gly	Val	Thr	Gln	Glu 85	Tyr	Ile	Gln	Thr	Thr 90	Ile	Gln	Гла	Val	Thr 95	Val
Asp	Сув	Гуз	Gln 100	Tyr	Val	Суя	Asn	Gly 105	Phe	Gln	Lys	Сув	Glu 110	Gln	Leu
Leu	Arg	Glu 115	Tyr	Gly	Gln	Phe	Cys 120	Ser	Lys	Ile	Asn	Gln 125	Ala	Leu	His
Gly	Ala 130	Asn	Leu	Arg	Gln	Asp 135	Asp	Ser	Val	Arg	Asn 140	Leu	Phe	Ala	Ser
Val 145	Гла	Ser	Ser	Gln	Ser 150	Ser	Pro	Ile	Ile	Pro 155	Gly	Phe	Gly	Gly	Asp 160
Phe	Asn	Leu	Thr	Leu 165	Leu	Glu	Pro	Val	Ser 170	Ile	Ser	Thr	Gly	Ser 175	Arg
Ser	Ala	Arg	Ser 180	Ala	Ile	Glu	Aab	Leu 185	Leu	Phe	Asp	Гла	Val 190	Thr	Ile
Ala	Asp	Pro 195	Gly	Tyr	Met	Gln	Gly 200	Tyr	Asp	Asp	САа	Met 205	Gln	Gln	Gly
Pro	Ala 210	Ser	Ala	Arg	Asp	Leu 215	Ile	Сув	Ala	Gln	Tyr 220	Val	Ala	Gly	Tyr
Lys 225	Val	Leu	Pro	Pro	Leu 230	Met	Aab	Val	Asn	Met 235	Glu	Ala	Ala	Tyr	Thr 240
Ser	Ser	Leu	Leu	Gly 245	Ser	Ile	Ala	Gly	Val 250	Gly	Trp	Thr	Ala	Gly 255	Leu
Ser	Ser	Phe	Ala 260	Ala	Ile	Pro	Phe	Ala 265	Gln	Ser	Ile	Phe	Tyr 270	Arg	Leu
Asn	Gly	Val 275	Gly	Ile	Thr	Gln	Gln 280	Val	Leu	Ser	Glu	Asn 285	Gln	гуа	Leu
Ile	Ala 290	Asn	Lys	Phe	Asn	Gln 295	Ala	Leu	Gly	Ala	Met 300	Gln	Thr	Gly	Phe
Thr 305	Thr	Thr	Asn	Glu	Ala 310	Phe	Gln	Гуа	Val	Gln 315	Asp	Ala	Val	Asn	Asn 320
Asn	Ala	Gln	Ala	Leu 325	Ser	Гуз	Leu	Ala	Ser 330	Glu	Leu	Ser	Asn	Thr 335	Phe
Gly	Ala	Ile	Ser		Ser	Ile	Gly	Asp		Ile	Gln	Arg	Leu		Val

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Leu	Glu	Gln 355	Aab	Ala	Gln	Ile	Asp 360	Arg	Leu	Ile	Asn	Gly 365	Arg	Leu	Thr
Thr	Leu 370	Asn	Ala	Phe	Val	Ala 375	Gln	Gln	Leu	Val	Arg 380	Ser	Glu	Ser	Ala
Ala 385	Leu	Ser	Ala	Gln	Leu 390	Ala	Гуа	Asp	Lys	Val 395	Asn	Glu	Суз	Val	Lys 400
Ala	Gln	Ser	Lys	Arg 405	Ser	Gly	Phe	Cys	Gly 410	Gln	Gly	Thr	His	Ile 415	Val
Ser	Phe	Val	Val 420	Asn	Ala	Pro	Asn	Gly 425	Leu	Tyr	Phe	Met	His 430	Val	Gly
Tyr	Tyr	Pro 435	Ser	Asn	His	Ile	Glu 440	Val	Val	Ser	Ala	Tyr 445	Gly	Leu	Cys
Asp	Ala 450	Ala	Asn	Pro	Thr	Asn 455	Суз	Ile	Ala	Pro	Val 460	Asn	Gly	Tyr	Phe
Ile 465	Lya	Thr	Asn	Asn	Thr 470	Arg	Ile	Val	Asp	Glu 475	Trp	Ser	Tyr	Thr	Gly 480
Ser	Ser	Phe	Tyr	Ala 485	Pro	Glu	Pro	Ile	Thr 490	Ser	Leu	Asn	Thr	Lys 495	Tyr
Val	Ala	Pro	Gln 500	Val	Thr	Tyr	Gln	Asn 505	Ile	Ser	Thr	Asn	Leu 510	Pro	Pro
Pro	Leu	Leu 515		Asn	Ser	Thr	Gly 520		Asp	Phe	Gln	Asp 525		Leu	Asp
Glu	Phe 530		Lys	Asn	Val	Ser 535		Ser	Ile	Pro	Asn 540		Gly	Ser	Leu
Thr 545		Ile	Asn	Thr	Thr 550	Leu	Leu	Asp	Leu	Thr 555		Glu	Met	Leu	Ser 560
	Gln	Gln	Val	Val 565		Ala	Leu	Asn	Glu 570		Tyr	Ile	Asp	Leu 575	
Glu	Leu	Gly	Asn 580		Thr	Tyr	Tyr	Asn 585		Trp	Pro	Asp	Lys 590		Glu
Glu	Ile	Leu 595		Lys	Ile	Tyr	His 600		Glu	Asn	Glu	Ile 605		Arg	Ile
ГЛа	Lys 610		Ile	Gly	Glu	Ala 615	000					003			
	910					012									
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Met 1	Ile	His	Ser	Val 5	Phe	Leu	Leu	Met	Phe 10	Leu	Leu	Thr	Pro	Thr 15	Glu
Ser	Tyr	Val	Asp 20	Val	Gly	Pro	Asp	Ser 25	Val	Lys	Ser	Ala	Суа 30	Ile	Glu
Val	Asp	Ile 35	Gln	Gln	Thr	Phe	Phe 40	Asp	Lys	Thr	Trp	Pro 45	Arg	Pro	Ile
Asp	Val 50		ГЛа	Ala	Asp	Gly 55		Ile	Tyr	Pro	Gln 60		Arg	Thr	Tyr
		Ile	Thr	Ile		Tyr	Gln	Gly	Leu			Tyr	Gln	Gly	_
65 His	Gly	Asp	Met	Tyr	70 Val	Tyr	Ser	Ala	Gly	75 His	Ala	Thr	Gly	Thr	80 Thr
				85					90					95	

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											_	con		uea	
Pro	Gln	Lys	Leu 100	Phe	Val	Ala	Asn	Tyr 105	Ser	Gln	Asp	Val	Lys 110	Gln	Phe
Ala	Asn	Gly 115	Phe	Val	Val	Arg	Ile 120	Gly	Ala	Ala	Ala	Asn 125	Ser	Thr	Gly
Thr	Val 130	Ile	Ile	Ser	Pro	Ser 135	Thr	Ser	Ala	Thr	Ile 140	Arg	Lys	Ile	Tyr
Pro 145	Ala	Phe	Met	Leu	Gly 150	Ser	Ser	Val	Gly	Asn 155	Phe	Ser	Asp	Gly	Lys 160
Met	Gly	Arg	Phe	Phe 165	Asn	His	Thr	Leu	Val 170	Leu	Leu	Pro	Asp	Gly 175	Суз
Gly	Thr	Leu	Leu 180	Arg	Ala	Phe	Tyr	Cys 185	Ile	Leu	Glu	Pro	Arg 190	Ser	Gly
Asn	His	Cys 195	Pro	Ala	Gly	Asn	Ser 200	Tyr	Thr	Ser	Phe	Ala 205	Thr	Tyr	His
Thr	Pro 210	Ala	Thr	Asp	Сув	Ser 215	Asp	Gly	Asn	Tyr	Asn 220	Arg	Asn	Ala	Ser
Leu 225	Asn	Ser	Phe	ГЛа	Glu 230	Tyr	Phe	Asn	Leu	Arg 235	Asn	Суз	Thr	Phe	Met 240
Tyr	Thr	Tyr	Asn	Ile 245	Thr	Glu	Asp	Glu	Ile 250	Leu	Glu	Trp	Phe	G1y 255	Ile
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Leu	Tyr	Gly 275	Gly	Asn	Met	Phe	Gln 280		Ala	Thr	Leu	Pro 285		Tyr	Asp
Thr	Ile 290			Tyr	Ser	Ile 295		Pro	His	Ser	Ile 300		Ser	Ile	Gln
Ser 305		Arg	Lys	Ala	Trp 310	Ala	Ala	Phe	Tyr	Val 315		Lys	Leu	Gln	Pro 320
	Thr	Phe	Leu	Leu 325	Asp		Ser	Val	Asp 330		Tyr	Ile	Arg	Arg 335	
Ile	Asp	Сув	Gly 340	Phe	Asn	Asp	Leu	Ser 345		Leu	His	Сув	Ser 350		Glu
Ser	Phe	Asp 355	Val		Ser	Gly	Val 360		Ser	Val	Ser	Ser 365		Glu	Ala
ГÀа	Pro 370			Ser	Val	Val 375		Gln	Ala	Glu	Gly 380		Glu	Суа	Asp
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Ile	Ala	Ser 435	Asn		Tyr	Ser	Ser 440	Leu		Leu	Asp	Tyr 445		Ser	Tyr
Pro				Гуз	Ser				Val	Ser			Gly	Pro	Ile
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GIU	va⊥	F10	eru	пец	Val	АЗП	AIđ	ASU	στΠ	туr	ser	F10	сув	val	ber

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Tyr	Tyr	Ser	Aab	Asp 645	Gly	Asn	Tyr	Tyr	Сув 650	Leu	Arg	Ala	Сув	Val 655	Ser
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Met	Gln	Gln 915	Gly	Pro	Ala	Ser	Ala 920	Arg	Asp	Leu	Ile	Cys 925	Ala	Gln	Tyr
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Phe Tyr Arg Leu Asn Gly Val Gly Ile Thr Gln Gln Val Leu Ser Glu 980 985 990
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Gln Thr Gly Phe Thr Thr Asn Glu Ala Phe Arg Lys Val Gln 1010 1015 1020
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Glu Leu Ser Asn Thr Phe Gly Ala Ile Ser Ala Ser Ile Gly Asp 1040 1045 1050
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Pro Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp 1220 1225 1230
Glu Leu Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn 1235 1240 1245
Phe Gly Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr 1250 1255 1260
Tyr Glu Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu 1265 1270 1275
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Lys Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Val 1295 1300 1305
Ala Leu Ala Leu Cys Val Phe Phe Ile Leu Cys Cys Thr Gly Cys 1310 1315 1320
Gly Thr Asn Cys Met Gly Lys Leu Lys Cys Asn Arg Cys Cys Asp 1325 1330 1335

Arg	Tyr 134	Glu	1 Gl	u Ty:	r Asj	2 Lei 134		lu P:	ro Hi	is Ly		al 1 350	His N	/al H	lis	 	
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Asp	Val 50	Ser	Lys	Ala	Asp	Gly 55	Ile	Ile	Tyr	Pro	Gln 60	Gly	Arg	Thr	Tyr		
Ser 65	Asn	Ile	Thr	Ile	Thr 70	Tyr	Gln	Gly	Leu	Phe 75	Pro	Tyr	Gln	Gly	Asp 80		
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Pro 145	Ala	Phe	Met	Leu	Gly 150	Ser	Ser	Val	Gly	Asn 155	Phe	Ser	Asp	Gly	Lys 160		
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Gly	Thr	Leu	Leu 180	Arg	Ala	Phe	Tyr	Cys 185	Ile	Leu	Glu	Pro	Arg 190	Ser	Gly		
Asn	His	Cys 195	Pro	Ala	Gly	Asn	Ser 200	Tyr	Thr	Ser	Phe	Ala 205	Thr	Tyr	His		
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Leu 225	Asn	Ser	Phe	Гλа	Glu 230	Tyr	Phe	Asn	Leu	Arg 235	Asn	Сув	Thr	Phe	Met 240		
Tyr	Thr	Tyr	Asn	Ile 245	Thr	Glu	Asp	Glu	Ile 250	Leu	Glu	Trp	Phe	Gly 255	Ile		
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Leu	Tyr	Gly 275	Gly	Asn	Met	Phe	Gln 280	Phe	Ala	Thr	Leu	Pro 285	Val	Tyr	Asp		
Thr	Ile 290	Lys	Tyr	Tyr	Ser	Ile 295	Ile	Pro	His	Ser	Ile 300	Arg	Ser	Ile	Gln		
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Ile	Asp	Суя	Gly 340	Phe	Asn	Asp	Leu	Ser 345	Gln	Leu	His	Cys	Ser 350	Tyr	Glu		
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Lys	Pro 370	Ser	Gly	Ser	Val	Val 375	Glu	Gln	Ala	Glu	Gly 380	Val	Glu	Суа	Asp
Phe 385	Ser	Pro	Leu	Leu	Ser 390	Gly	Thr	Pro	Pro	Gln 395	Val	Tyr	Asn	Phe	Lys 400
Arg	Leu	Val	Phe	Thr 405	Asn	Cys	Asn	Tyr	Asn 410	Leu	Thr	гуа	Leu	Leu 415	Ser
Leu	Phe	Ser	Val 420	Asn	Asp	Phe	Thr	Cys 425	Ser	Gln	Ile	Ser	Pro 430	Ala	Ala
Ile	Ala	Ser 435	Asn	Суа	Tyr	Ser	Ser 440	Leu	Ile	Leu	Asp	Tyr 445	Phe	Ser	Tyr
Pro	Leu 450	Ser	Met	Lys	Ser	Asp 455	Leu	Ser	Val	Ser	Ser 460	Ala	Gly	Pro	Ile
Ser 465	Gln	Phe	Asn	Tyr	Lys 470	Gln	Ser	Phe	Ser	Asn 475	Pro	Thr	Сув	Leu	Ile 480
Leu	Ala	Thr	Val	Pro 485	His	Asn	Leu	Thr	Thr 490	Ile	Thr	Гла	Pro	Leu 495	Гла
Tyr	Ser	Tyr	Ile 500	Asn	Lys	Сув	Ser	Arg 505	Leu	Leu	Ser	Asp	Asp 510	Arg	Thr
Glu	Val	Pro 515	Gln	Leu	Val	Asn	Ala 520	Asn	Gln	Tyr	Ser	Pro 525	Cys	Val	Ser
Ile	Val 530	Pro	Ser	Thr	Val	Trp 535	Glu	Asp	Gly	Asp	Tyr 540	Tyr	Arg	Lys	Gln
Leu 545	Ser	Pro	Leu	Glu	Gly 550	Gly	Gly	Trp	Leu	Val 555	Ala	Ser	Gly	Ser	Thr 560
Val	Ala	Met	Thr	Glu 565	Gln	Leu	Gln	Met	Gly 570	Phe	Gly	Ile	Thr	Val 575	Gln
			580	Thr				585					Phe 590		
			580	Thr				585							
Asp	Thr	Lys 595	580 Ile	Thr Ala	Ser	Gln	Leu 600	585 Gly	Asn	Сүз	Val	Glu 605	590	Ser	Leu
Asp Tyr	Thr Gly 610	Lys 595 Val	580 Ile Ser	Thr Ala Gly	Ser Arg	Gln Gly 615	Leu 600 Val	585 Gly Phe	Asn Gln	Cys Asn	Val Cys 620	Glu 605 Thr	590 Tyr	Ser Val	Leu Gly
Asp Tyr Val 625	Thr Gly 610 Arg	Lys 595 Val Gln	580 Ile Ser Gln	Thr Ala Gly Arg	Ser Arg Phe 630	Gln Gly 615 Val	Leu 600 Val Tyr	585 Gly Phe Asp	Asn Gln Ala	Cys Asn Tyr 635	Val Cys 620 Gln	Glu 605 Thr Asn	590 Tyr Ala	Ser Val Val	Leu Gly Gly 640
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Asp Tyr Val 625 Tyr Val Leu Tyr	Thr Gly 610 Arg Tyr Pro Phe Ser 690	Lys 595 Val Gln Ser Val Gly 675 Arg	580 Ile Ser Gln Asp Ser 660 Ser Ser	Thr Ala Gly Arg 645 Val Val Thr	Ser Arg Phe 630 Gly Ile Ala Arg	Gln Gly 615 Val Asn Tyr Cys Ser 695	Leu 600 Val Tyr Tyr Asp Glu 680 Met	585 Gly Phe Asp Tyr Lys 665 His Leu	Asn Gln Ala Cys 650 Glu Ile Lys	Cys Asn Tyr 635 Leu Thr Ser Arg	Val Cys 620 Gln Arg Lys Ser Arg 700	Glu 605 Thr Asn Ala Thr 685 Asp	590 Tyr Ala Leu Cys His 670 Met	Ser Val Val Val 655 Ala Ser Thr	Leu Gly 640 Ser Thr Gln Tyr
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Asp Tyr Val 625 Tyr Val Leu Tyr Gly 705 Ser	Thr Gly 610 Arg Tyr Pro Phe Ser 690 Pro Leu	Lys 595 Val Gln Ser Val Gly 675 Arg Leu Phe	580 Ile Ser Gln Asp Ser Ser Ser Gln Val	Thr Ala Gly Arg 645 Val Val Thr Thr Glu 725	Ser Arg Phe 630 Gly Ile Ala Arg Pro 710 Asp	Gln Gly 615 Val Asn Tyr Cys Ser 695 Val Cys	Leu 600 Val Tyr Tyr Asp Glu 680 Met Gly Lys	585 Gly Phe Asp Tyr Lys 665 His Leu Cys Leu	Asn Gln Ala Cys 650 Glu Ile Lys Val Pro 730	Cys Asn Tyr 635 Leu Thr Ser Arg Leu 715 Leu	Val Cys 620 Gln Arg Lys Ser Arg 700 Gly Gly	Glu 605 Thr Asn Ala Thr Thr 685 Asp Leu Gln	590 Tyr Ala Leu Cys His 670 Met Ser Val	Ser Val Val 655 Ala Ser Thr Asn Leu 735	Leu Gly 640 Ser Thr Gln Tyr Ser 720 Cys
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Ser Ser Phe Tyr Ala Pro Glu Pro Ile Thr Ser Leu Asn Thr Lys	

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)> SE Phe				Leu	Phe	Leu	Thr	Leu 10	. Thr	: Sei	r Gly	7 Sei	r As <u>ı</u> 15	o Leu
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His	Thr	Ser 35	Ser	Met	Arg	Gly	Val 40	Tyr	Tyr	Pro	Asp	9 Glu 45	ı Ile	e Phe	e Arg
Ser	Азр 50	Thr	Leu	Tyr	Leu	Thr 55	Gln	Asp	Leu	. Phe	e Lei 60	ı Pro	> Phe	е Туз	ser
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Ile	Pro	Phe	Lys	Asp 85	Gly	Ile	Tyr	Phe	Ala 90	Ala	1 Thi	r Glu	ı Lyı	95 Sei	: Asn
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Phe	Glu	Tyr	Ile	e Ser 165		Ala	Phe	Ser	Leu 170		va]	l Ser	Glu	1 Lys 179	s Ser
Gly	Asn	Phe	Lys 180		Leu	Arg	Glu	Phe 185		Phe	- Lys	a Asr	n Lys 19(_	Gly
Phe	Leu	Tyr 195			Гуз	Gly	Tyr 200			Ile	Asp	9 Val 205	. Val		l yab
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480

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G1 22		Ile	Asn	Ile	Thr	Asn 230	Phe	Arg	Ala	Ile	Leu 235	Thr	Ala	Phe	Ser	Pro 240
Al	.a	Gln	Asp	Ile	Trp 245	Gly	Thr	Ser	Ala	Ala 250	Ala	Tyr	Phe	Val	Gly 255	Tyr
Le	au	Гуз	Pro	Thr 260	Thr	Phe	Met	Leu	Lys 265	Tyr	Asp	Glu	Asn	Gly 270	Thr	Ile
Τŀ	ır	Asp	Ala 275	Val	Asp	Cys	Ser	Gln 280	Asn	Pro	Leu	Ala	Glu 285	Leu	ГЛа	Суз
Se	er	Val 290	Lys	Ser	Phe	Glu	Ile 295	Asp	Lys	Gly	Ile	Tyr 300	Gln	Thr	Ser	Asn
Ph 30		Arg	Val	Val	Pro	Ser 310	Gly	Asp	Val	Val	Arg 315	Phe	Pro	Asn	Ile	Thr 320
Aε	m	Leu	Сув	Pro	Phe 325	Gly	Glu	Val	Phe	Asn 330	Ala	Thr	Гла	Phe	Pro 335	Ser
Va	1	Tyr	Ala	Trp 340	Glu	Arg	Гла	ГЛа	Ile 345	Ser	Asn	Сүз	Val	Ala 350	Aab	Tyr
Se	er	Val	Leu 355	Tyr	Asn	Ser	Thr	Phe 360	Phe	Ser	Thr	Phe	Lys 365	Cys	Tyr	Gly
Va	1	Ser 370	Ala	Thr	Гла	Leu	Asn 375	Asp	Leu	Сув	Phe	Ser 380	Asn	Val	Tyr	Ala
Ас 38	-	Ser	Phe	Val	Val	Lув 390	Gly	Asp	Asp	Val	Arg 395	Gln	Ile	Ala	Pro	Gly 400
Gl	n	Thr	Gly	Val	Ile 405	Ala	Yab	Tyr	Asn	Tyr 410	Lys	Leu	Pro	Asp	Asp 415	Phe
M€	et	Gly	Сув	Val 420	Leu	Ala	Trp	Asn	Thr 425	Arg	Asn	Ile	Asp	Ala 430	Thr	Ser
Th	ır	Gly	Asn 435	Tyr	Asn	Tyr	Lys	Tyr 440	Arg	Tyr	Leu	Arg	His 445	Gly	Lys	Leu
Ar	g	Pro 450	Phe	Glu	Arg	Asp	Ile 455	Ser	Asn	Val	Pro	Phe 460	Ser	Pro	Asp	Gly
Lу 46		Pro	Сув	Thr	Pro	Pro 470	Ala	Leu	Asn	Сув	Tyr 475	Trp	Pro	Leu	Asn	Asp 480
Ту	r	Gly	Phe	Tyr	Thr 485	Thr	Thr	Gly	Ile	Gly 490	Tyr	Gln	Pro	Tyr	Arg 495	Val
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Pr	0	Lys	Leu 515	Ser	Thr	Asp	Leu	Ile 520	Lys	Asn	Gln	Сүз	Val 525	Asn	Phe	Asn
Pł	he	Asn 530	Gly	Leu	Thr	Gly	Thr 535	Gly	Val	Leu	Thr	Pro 540	Ser	Ser	ГАа	Arg
Ph 54		Gln	Pro	Phe	Gln	Gln 550	Phe	Gly	Arg	Asp	Val 555	Ser	Asp	Phe	Thr	Asp 560
Se	er	Val	Arg	Asp	Pro 565	Lys	Thr	Ser	Glu	11e 570	Leu	Asp	Ile	Ser	Pro 575	Суз
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Gl	.u	Val	Ala 595	Val	Leu	Tyr	Gln	Asp 600	Val	Asn	Сүя	Thr	Asp 605	Val	Ser	Thr
Al	a	Ile 610	His	Ala	Asp	Gln	Leu 615	Thr	Pro	Ala	Trp	Arg 620	Ile	Tyr	Ser	Thr
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Cys	Ala	Ser	Tyr 660		Thr	Val	Ser	Leu 665	Leu	Arg	Ser	Thr	Ser 670	Gln	Lys
Ser	Ile	Val 675	Ala	Tyr	Thr	Met	Ser 680		Gly	Ala	Asp	Ser 685		Ile	Ala
Tyr	Ser 690	Asn	Asn	Thr	Ile	Ala 695		Pro	Thr	Asn	Phe 700	Ser	Ile	Ser	Ile
Thr 705	Thr	Glu	Val	Met	Pro 710	Val	Ser	Met	Ala	Lys 715	Thr	Ser	Val	Asp	Суз 720
Asn	Met	Tyr	Ile	Cys 725	Gly	Asp	Ser	Thr	Glu 730	Суз	Ala	Asn	Leu	Leu 735	Leu
Gln	Tyr	Gly	Ser 740	Phe	Сув	Thr	Gln	Leu 745	Asn	Arg	Ala	Leu	Ser 750	Gly	Ile
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Gln	Met 770	Tyr	Lys	Thr	Pro	Thr 775	Leu	Lys	Tyr	Phe	Gly 780	Gly	Phe	Asn	Phe
Ser 785	Gln	Ile	Leu	Pro	Asp 790	Pro	Leu	Lys	Pro	Thr 795	Lys	Arg	Ser	Phe	Ile 800
Glu	Asp	Leu	Leu	Phe 805	Asn	Lys	Val	Thr	Leu 810	Ala	Asp	Ala	Gly	Phe 815	Met
ГЛЗ	Gln	Tyr	Gly 820	Glu	Суз	Leu	Gly	Asp 825	Ile	Asn	Ala	Arg	Asp 830	Leu	Ile
Суа	Ala	Gln 835	Lys	Phe	Asn	Gly	Leu 840	Thr	Val	Leu	Pro	Pro 845		Leu	Thr
Asp	Asp 850	Met	Ile	Ala	Ala	Tyr 855	Thr	Ala	Ala	Leu	Val 860	Ser	Gly	Thr	Ala
Thr 865	Ala	Gly	Trp	Thr	Phe 870	Gly	Ala	Gly	Ala	Ala 875	Leu	Gln	Ile	Pro	Phe 880
Ala	Met	Gln	Met	Ala 885	Tyr	Arg	Phe	Asn	Gly 890	Ile	Gly	Val	Thr	Gln 895	Asn
Val	Leu	Tyr	Glu 900	Asn	Gln	Lys	Gln	Ile 905	Ala	Asn	Gln	Phe	Asn 910	Lya	Ala
Ile	Ser	Gln 915	Ile	Gln	Glu	Ser	Leu 920	Thr	Thr	Thr	Ser	Thr 925	Ala	Leu	Gly
Lys	Leu 930	Gln	Asp	Val	Val	Asn 935		Asn	Ala	Gln	Ala 940	Leu	Asn	Thr	Leu
Val 945	Гла	Gln	Leu	Ser	Ser 950	Asn	Phe	Gly	Ala	Ile 955	Ser	Ser	Val	Leu	Asn 960
	Ile	Leu	Ser	Arg 965	Leu	Asp	Lys	Val	Glu 970		Glu	Val	Gln	Ile 975	Asp
Arg	Leu	Ile	Thr 980	Gly	Arg	Leu	Gln	Ser 985	Leu	Gln	Thr	Tyr	Val 990	Thr	Gln
Gln	Leu	Ile 995	Arg	Ala	Ala	Glu	Ile 100		g Ala	a Se:	r Al	a As 10		eu A	la Ala
Thr	Lys 1010	Met	: Se	r Glı	u Cy:	s Va 10	1 ь		ly G	ln S				Val i	Asp
Phe	Cys	Gl	у Бу	a Gl	у Ту:	r Hi	s L	eu M	et Se	er Pl	he P:	ro	Gln ź	Ala i	Ala
Pro	1025 His	Glγ	7 Val	l Va	l Ph		u H.	is V	al Tì	hr T	yr V		Pro :	Ser (Gln
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Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His Glu Gly Lys 1055 1060 1065	
Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly Thr Ser 1070 1075 1080	
Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile Thr 1085 1090 1095	
Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly 1100 1105 1110	
Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp 1115 1120 1125	
Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser 1130 1135 1140	
Pro Asp Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val 1145 1150 1155	
Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys 1160 1165 1170	
Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr 1175 1180 1185	
Glu Gln Tyr Ile Lys Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile 1190 1195 1200	
Ala Gly Leu Ile Ala Ile Val Met Val Thr Ile Leu Leu Cys Cys 1205 1210 1215	
Met Thr Ser Cys Cys Ser Cys Leu Lys Gly Ala Cys Ser Cys Gly 1220 1225 1230	
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Pro Pro Pro Ile Ser Thr Asp Thr Val Asp Val Thr Asn Gly Leu Gly 35 40 45	Y
Thr Tyr Tyr Val Leu Asp Arg Val Tyr Leu Asn Thr Thr Leu Phe Lev 50 55 60	u
Asn Gly Tyr Tyr Pro Thr Ser Gly Ser Thr Tyr Arg Asn Met Ala Le 65 70 75 80	u
Lys Gly Ser Val Leu Leu Ser Arg Leu Trp Phe Lys Pro Pro Phe Lev 85 90 95	u
Ser Asp Phe Ile Asn Gly Ile Phe Ala Lys Val Lys Asn Thr Lys Va 100 105 110	1
Ile Lys Asp Arg Val Met Tyr Ser Glu Phe Pro Ala Ile Thr Ile Gly 115 120 125	Y
Ser Thr Phe Val Asn Thr Ser Tyr Ser Val Val Val Gln Pro Arg Th 130 135 140	r

485

486

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											-	con	tin	ued	
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Val	Ser	Val	Суз	Gln 165	Tyr	Asn	Met	Суз	Glu 170	Tyr	Pro	Gln	Thr	Ile 175	Суз
His	Pro	Asn	Leu 180	Gly	Asn	His	Arg	Lys 185	Glu	Leu	Trp	His	Leu 190	Asp	Thr
Gly	Val	Val 195	Ser	Сүз	Leu	Tyr	Lys 200	Arg	Asn	Phe	Thr	Tyr 205	Asp	Val	Asn
Ala	Asp 210	Tyr	Leu	Tyr	Phe	His 215	Phe	Tyr	Gln	Glu	Gly 220	Gly	Thr	Phe	Tyr
Ala 225	Tyr	Phe	Thr	Asp	Thr 230	Gly	Val	Val	Thr	Lys 235	Phe	Leu	Phe	Asn	Val 240
Tyr	Leu	Gly	Met	Ala 245	Leu	Ser	His	Tyr	Tyr 250	Val	Met	Pro	Leu	Thr 255	Cys
Asn	Ser	Lys	Leu 260	Thr	Leu	Glu	Tyr	Trp 265	Val	Thr	Pro	Leu	Thr 270	Ser	Arg
Gln	Tyr	Leu 275	Leu	Ala	Phe	Asn	Gln 280	Asp	Gly	Ile	Ile	Phe 285	Asn	Ala	Glu
Asp	Cys 290	Met	Ser	Asp	Phe	Met 295	Ser	Glu	Ile	Lys	Cys 300	Lys	Thr	Gln	Ser
Ile 305	Ala	Pro	Pro	Thr	Gly 310	Val	Tyr	Glu	Leu	Asn 315	Gly	Tyr	Thr	Val	Gln 320
Pro	Ile	Ala	Asp	Val 325	Tyr	Arg	Arg	Гла	Pro 330	Asn	Leu	Pro	Asn	Сув 335	Asn
Ile	Glu	Ala	Trp 340	Leu	Asn	Aab	ГÀа	Ser 345	Val	Pro	Ser	Pro	Leu 350	Asn	Trp
Glu	Arg	Lys 355	Thr	Phe	Ser	Asn	Сув 360	Asn	Phe	Asn	Met	Ser 365	Ser	Leu	Met
Ser	Phe 370	Ile	Gln	Ala	Asp	Ser 375	Phe	Thr	Суа	Asn	Asn 380	Ile	Asp	Ala	Ala
Lуя 385	Ile	Tyr	Gly	Met	Сув 390	Phe	Ser	Ser	Ile	Thr 395	Ile	Asp	Lys	Phe	Ala 400
Ile	Pro	Asn	Gly	Arg 405	Lys	Val	Aap	Leu	Gln 410	Leu	Gly	Asn	Leu	Gly 415	Tyr
Leu	Gln	Ser	Phe 420	Asn	Tyr	Arg	Ile	Asp 425	Thr	Thr	Ala	Thr	Ser 430	Сүз	Gln
Leu	Tyr	Tyr 435	Asn	Leu	Pro	Ala	Ala 440	Asn	Val	Ser	Val	Ser 445	Arg	Phe	Asn
Pro	Ser 450	Thr	Trp	Asn	Гуз	Arg 455	Phe	Gly	Phe	Ile	Glu 460	Asp	Ser	Val	Phe
Lys 465	Pro	Arg	Pro	Ala	Gly 470	Val	Leu	Thr	Asn	His 475	Asp	Val	Val	Tyr	Ala 480
Gln	His	Cys	Phe	Lys 485	Ala	Pro	Lys	Asn	Phe 490	Cys	Pro	Cys	Lys	Leu 495	Asn
Gly	Ser	Сув	Val 500	Gly	Ser	Gly	Pro	Gly 505	Lys	Asn	Asn	Gly	Ile 510	Gly	Thr
Сүв	Pro	Ala 515	Gly	Thr	Asn	Tyr	Leu 520	Thr	Сув	Asp	Asn	Leu 525	Сув	Thr	Pro
Asp	Pro 530	Ile	Thr	Phe	Thr	Gly 535	Thr	Tyr	Lys	Сув	Pro 540	Gln	Thr	ГЛа	Ser
Leu 545		Gly	Ile	Gly	Glu 550		Суз	Ser	Gly	Leu 555		Val	Lys	Ser	Asp 560
	Сув	Gly	Gly			Суз	Thr	Сув	-		Gln	Ala	Phe		
				565					570					575	

Т	rp	Ser	Ala	Asp 580	Ser	Суз	Leu	Gln	Gly 585	Asp	Lys	САа	Asn	Ile 590	Phe	Ala
A	sn	Phe	Ile 595	Leu	His	Asp	Val	Asn 600	Ser	Gly	Leu	Thr	Cys 605	Ser	Thr	Asp
L	eu	Gln 610	Lys	Ala	Asn	Thr	Asp 615	Ile	Ile	Leu	Gly	Val 620	Сүв	Val	Asn	Tyr
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Т	hr	Tyr	Tyr	Asn	Ser 645	Trp	Gln	Asn	Leu	Leu 650	Tyr	Asp	Ser	Asn	Gly 655	Asn
L	eu	Tyr	Gly	Phe 660	Arg	Asp	Tyr	Ile	Ile 665	Asn	Arg	Thr	Phe	Met 670	Ile	Arg
S	er	Cys	Tyr 675	Ser	Gly	Arg	Val	Ser 680	Ala	Ala	Phe	His	Ala 685	Asn	Ser	Ser
G	lu	Pro 690	Ala	Leu	Leu	Phe	Arg 695	Asn	Ile	Lys	Суя	Asn 700	Tyr	Val	Phe	Asn
	sn 05	Ser	Leu	Thr	Arg	Gln 710	Leu	Gln	Pro	Ile	Asn 715	Tyr	Phe	Asp	Ser	Tyr 720
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Т	hr	Сув	Asp	Leu 740	Thr	Val	Gly	Ser	Gly 745	Tyr	Суя	Val	Asp	Tyr 750	Ser	Lys
A	sn	Arg	Arg 755	Ser	Arg	Gly	Ala	Ile 760	Thr	Thr	Gly	Tyr	Arg 765	Phe	Thr	Asn
Р	he	Glu 770	Pro	Phe	Thr	Val	Asn 775	Ser	Val	Asn	Asp	Ser 780	Leu	Glu	Pro	Val
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la Pro Lys Ser Gly Tyr Phe Val Asn Val Asn Asn Thr Trp Met 1175 1180 1185
yr Thr Gly Ser Gly Tyr Tyr Tyr Pro Glu Pro Ile Thr Glu Asn 1190 1195 1200
sn Val Val Met Ser Thr Cys Ala Val Asn Tyr Thr Lys Ala 1205 1210 1215
ro Tyr Val Met Leu Asn Thr Ser Ile Pro Asn Leu Pro Asp Phe 1220 1225 1230
ys Glu Glu Leu Asp Gln Trp Phe Lys Asn Gln Thr Ser Val Ala 1235 1240 1245
ro Asp Leu Ser Leu Asp Tyr Ile Asn Val Thr Phe Leu Asp Leu 1250 1255 1260
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	Pro	Arg	Ile 35	Ser	Glu	Asp	Val	Val 40	Asp	Val	Ser	Leu	Gly 45	Leu	Gly	Thr
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	225		-		-	230					235	-			Pro	240
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Lys	Asn	Trp 515	Суз	Arg	Суз	Ser	Сув 520	Leu	Pro	Asp	Pro	Ile 525	Ser	Thr	Tyr
Ser	Pro 530	Asn	Thr	Сүя	Pro	Gln 535	Lуя	Гуз	Val	Val	Val 540	Gly	Ile	Gly	Glu
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	-		580		Ser			585	-				590		
		595	-		Asn		600			-		605	_		
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625					Gln 630					635					640
-				645	Asn Leu			-	650			-		655	
-		-	660		Ser			665		-			670		
		675			Asn		680					685			
	690		-	-	Pro	695	-	-		-	700				
705					710 Leu		-		_	715	-		-	-	720
Arg	Met	Gly	Ser	725 Gly	Phe	Сув	Ile	Asp	730 Tyr	Ala	Leu	Pro	Ser	735 Ser	Arg
Arg	Lys		740 Arg	Gly	Ile	Ser		745 Pro	Tyr	Arg	Phe		750 Thr	Phe	Glu
Pro		755 Asn	Val	Ser	Phe		760 Asn	Asp	Ser	Val	Glu	765 Thr	Val	Gly	Gly
Leu	770 Phe	Glu	Ile	Gln	Ile	775 Pro	Thr	Asn	Phe	Thr	780 Ile	Ala	Gly	His	Glu
785 Glu	Phe	Ile	Gln	Thr	790 Ser	Ser	Pro	Гуа	Val	795 Thr	Ile	Asp	Суя	Ser	800 Ala
				805	Tyr			-	810			-	-	815	
		-	820		Asn			825					830		-
στλ		- 11C	-Y8	чар	AGII	- 1C	HOII	0er	E	ueu	лан	JIU	vai	HOII	· ~ F

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		835					840					84	15				
Leu	Leu 850	Asp	Ile	Thr	Gln	Leu 855	Gln	Val	Ala	Asn	86		eu	Met	Gln	Gly	
Val 865	Thr	Leu	Ser	Ser	Asn 870	Leu	Asn	Thr	Asn	Leu 875		s S€	er	Asp	Val	Asp 880	
Asn	Ile	Asp	Phe	Lys 885	Ser	Leu	Leu	Gly	Сув 890		Gl	y S€	er	Gln	Cys 895	Gly	•
Ser	Ser	Ser	Arg 900		Leu	Leu	Glu	Asp 905		Leu	. Ph	e Ae		Lys 910		Lys	•
Leu	Ser	Asp 915		Gly	Phe	Val	Glu 920		Tyr	Asn	As:	n Cy 92		Thr	Gly	Gly	
Ser	Glu 930			Asp		Leu 935		Val	Gln	Ser	Ph 94		'n	Gly	Ile	- Lys	•
Val 945	Leu	Pro	Pro	Ile	Leu 950	Ser	Glu	Thr	Gln	Ile 955		r Gl	y	Tyr	Thr	Thr 960	
Ala	Ala	Thr	Val	Ala 965	Ala	Met	Phe	Pro	Pro 970		Se	r Al	la	Ala	Ala 975	Gly	
Val	Pro	Phe	Ser 980		Asn	Val	Gln	Tyr 985		Ile	As	n Gl		Leu 990		Val	
Thr	Met	Asp 995		Leu	Asn		Asn 1000		n Ly	s Le	u I		Ala 100		sn A	la Pl	he
Asn	Lys 1010		ı Leı	ı Leı	ı Sei	r Il¢ 103		ln A	sn G	ly P		Thr 1020		la	Thr	Asn	
Ser	Ala 1025		ı Ala	a Ly:	∃ Il€	e Glr 103		er V	al V	al A		Ala 1035		sn.	Ala	Gln	
Ala	Leu 1040		n Sei	r Lei	ı Leı	1 Gl1 104		ln L	eu P	he A		Lys 1050		he	Gly	Ala	
Ile	Ser 1055		: Sei	r Lei	ı Glr	n Glu 106		le L	eu S	er A	_	Leu 1065		ab .	Asn	Leu	
Glu	Ala 1070		n Val	l Glı	n Ile	e Asr 107		rg L	eu I	le A		Gly 1080		rg	Leu	Thr	
Ala	Leu 1085		n Ala	а Туз	r Val	L Sei 109		ln G	ln L	eu S		Asp 1095		le	Thr	Leu	
Ile	Lys 1100		a Gly	7 Ala	a Sei	r Arg 11(la I	le G	lu L		Val 1110		sn	Glu	Cys	
Val					r Pro									sn	Gly	Asn	
His	Ile 1130		ı Sei	r Lei	ı Val	l Glr 113		ən A	la P	ro T		Gly 1140		eu	Leu	Phe	
Ile	His 1145		e Sei	r Tyj	r Lys	9 Pro 119		ır S	er P	he L	-	Thr 1155		al	Leu	Val	
Ser	Pro 1160	-	/ Let	і Суя	s Lei	1 Sei 110		ly A	sp A	rg G	-	Ile 1170		la	Pro	Lys	
Gln	Gly 1175	-	: Phe	e Il∢	e Lys	3 Gl1 118		an A	sp S	er T	_	Met 1185		he	Thr	Gly	
Ser	Ser 1190	-	: Туз	r Tyi	r Pro	Glu 119		ro I	le S	er A	-	Lys 1200		sn j	Val	Val	
Phe	Met 1205		n Sei	r Cyi	s Sei	r Val 121		sn Pl	he T	hr L	-	Ala 1215		ro	Phe	Ile	
Tyr	Leu 1220		n Ası	n Sei	r Ile	e Pro 122		en L	eu S	er A	_	Phe 1230		lu .	Ala	Glu	
Leu	Ser 1235		ı Tr <u>ı</u>	p Phe	е Буя	3 ASI 124		is Ti	hr S	er I		Ala 1249		ro.	Asn	Leu	

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Thr	Phe 1250		n Se:	r Hi:	a Ile	e Ası 129		la Tì	nr Pł	ne Le		ap 260	Leu '	[yr]	ſyr
Glu	Met 1269		n Va	l Il(e Glr	n Glu 127		er I	le Ly	∕s S€		eu . 275	Asn :	Ser S	Ser
Phe	Ile 1280		n Lei	u Ly:	; Glu	1 Il. 129		ly Tì	ur Tj	yr G		et 290	Tyr '	Val I	ууа
Trp	Pro 1299		p Ty:	r Ile	e Tr <u>p</u>	Lei 130		∋u I:	le Va	al I:		eu 305	Phe :	Ile :	Ile
Phe	Leu 1310		t 11(e Lei	ı Phe	e Phe 133		le Cy	ya Cj	ya Cj		hr 320	Gly (Cya (Зly
Ser	Ala 1329		s Ph	e Sei	t Lys	5 Cyr 133		is A	an Cl	va Cl		ap 335	Glu '	Tyr (Зly
Gly	His 1340		n Asj	p Phe	e Val	L Il. 134		ys A	la Se	er Hi		ap . 350	Asp		
<21 <21 <21 <22 <22 <22	0 > SI 1 > LI 2 > T 3 > OI 3 > OI 3 > O 3 > O	ENGTI (PE : RGAN) EATUI THER	H: 5: PRT ISM: RE: INF(26 Art: DRMA			-		Poly	pept:	ide				
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Asp	Arg	Ala	Leu 20	Ser	Gly	Ile	Ala	Ala 25	Glu	Gln	Asp	Arg	Asn 30	Thr	Arg
Glu	Val	Phe 35	Ala	Gln	Val	Lys	Gln 40	Met	Tyr	Lys	Thr	Pro 45	Thr	Leu	Lys
Tyr	Phe 50	Gly	Gly	Phe	Asn	Phe 55	Ser	Gln	Ile	Leu	Pro 60	Asp	Pro	Leu	Lys
Pro 65	Thr	Lys	Arg	Ser	Phe 70	Ile	Glu	Asp	Leu	Leu 75	Phe	Asn	Гуз	Val	Thr 80
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Ile	Asn	Ala	Arg 100	Asp	Leu	Ile	Суз	Ala 105	Gln	Lys	Phe	Asn	Gly 110	Leu	Thr
Val	Leu	Pro 115	Pro	Leu	Leu	Thr	Asp 120	Asp	Met	Ile	Ala	Ala 125	Tyr	Thr	Ala
Ala	Leu 130	Val	Ser	Gly	Thr	Ala 135	Thr	Ala	Gly	Trp	Thr 140	Phe	Gly	Ala	Gly
Ala 145	Ala	Leu	Gln	Ile	Pro 150	Phe	Ala	Met	Gln	Met 155	Ala	Tyr	Arg	Phe	Asn 160
Gly	Ile	Gly	Val	Thr 165	Gln	Asn	Val	Leu	Tyr 170	Glu	Asn	Gln	Lys	Gln 175	Ile
Ala	Asn	Gln	Phe 180	Asn	Lys	Ala	Ile	Ser 185	Gln	Ile	Gln	Glu	Ser 190	Leu	Thr
Thr	Thr	Ser 195	Thr	Ala	Leu	Gly	Lув 200	Leu	Gln	Asp	Val	Val 205	Asn	Gln	Asn
Ala	Gln 210	Ala	Leu	Asn	Thr	Leu 215	Val	Гла	Gln	Leu	Ser 220	Ser	Asn	Phe	Gly
Ala 225	Ile	Ser	Ser	Val	Leu 230	Asn	Asp	Ile	Leu	Ser 235	Arg	Leu	Asp	Гуа	Val 240
Glu	Ala	Glu	Val	Gln 245	Ile	Asp	Arg	Leu	Ile 250	Thr	Gly	Arg	Leu	Gln 255	Ser

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Asp	Суз	Lys	Gln 100	Tyr	Val	Суз	Asn	Gly 105	Phe	Gln	Lya	Суз	Glu 110	Gln	Leu	
Leu	Arg	Glu 115	Tyr	Gly	Gln	Phe	Cys 120	Ser	Lys	Ile	Asn	Gln 125	Ala	Leu	His	
Gly	Ala 130	Asn	Leu	Arg	Gln	Asp 135	Asp	Ser	Val	Arg	Asn 140	Leu	Phe	Ala	Ser	
Val 145	Гуз	Ser	Ser	Gln	Ser 150	Ser	Pro	Ile	Ile	Pro 155	Gly	Phe	Gly	Gly	Asp 160	
Phe	Asn	Leu	Thr	Leu 165	Leu	Glu	Pro	Val	Ser 170	Ile	Ser	Thr	Gly	Ser 175	Arg	
Ser	Ala	Arg	Ser 180	Ala	Ile	Glu	Asp	Leu 185	Leu	Phe	Asp	Lys	Val 190	Thr	Ile	
Ala	Asp	Pro 195	Gly	Tyr	Met	Gln	Gly 200	Tyr	Asp	Asp	Сүз	Met 205	Gln	Gln	Gly	
Pro	Ala 210	Ser	Ala	Arg	Asp	Leu 215	Ile	Сув	Ala	Gln	Tyr 220	Val	Ala	Gly	Tyr	
Lys 225	Val	Leu	Pro	Pro	Leu 230	Met	Asp	Val	Asn	Met 235	Glu	Ala	Ala	Tyr	Thr 240	
Ser	Ser	Leu	Leu	Gly 245	Ser	Ile	Ala	Gly	Val 250	Gly	Trp	Thr	Ala	Gly 255	Leu	
Ser	Ser	Phe	Ala 260	Ala	Ile	Pro	Phe	Ala 265	Gln	Ser	Ile	Phe	Tyr 270	Arg	Leu	
Asn	Gly	Val 275	Gly	Ile	Thr	Gln	Gln 280	Val	Leu	Ser	Glu	Asn 285	Gln	ГАз	Leu	
Ile	Ala 290	Asn	Lys	Phe	Asn	Gln 295	Ala	Leu	Gly	Ala	Met 300	Gln	Thr	Gly	Phe	
Thr 305	Thr	Thr	Asn	Glu	Ala 310	Phe	Gln	Lys	Val	Gln 315	Asp	Ala	Val	Asn	Asn 320	
Asn	Ala	Gln	Ala	Leu 325	Ser	Гуз	Leu	Ala	Ser 330	Glu	Leu	Ser	Asn	Thr 335	Phe	
Gly	Ala	Ile	Ser 340	Ala	Ser	Ile	Gly	Asp 345	Ile	Ile	Gln	Arg	Leu 350	Aap	Val	
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Thr	Leu 370	Asn	Ala	Phe	Val	Ala 375	Gln	Gln	Leu	Val	Arg 380	Ser	Glu	Ser	Ala	
Ala 385	Leu	Ser	Ala	Gln	Leu 390	Ala	Lys	Asp	Lys	Val 395	Asn	Glu	Cys	Val	Lys 400	
Ala	Gln	Ser	ГАа	Arg 405	Ser	Gly	Phe	Cys	Gly 410	Gln	Gly	Thr	His	Ile 415	Val	
Ser	Phe	Val	Val 420	Asn	Ala	Pro	Asn	Gly 425	Leu	Tyr	Phe	Met	His 430	Val	Gly	
Tyr	Tyr	Pro 435	Ser	Asn	His	Ile	Glu 440	Val	Val	Ser	Ala	Tyr 445	Gly	Leu	Cys	
Asp	Ala 450	Ala	Asn	Pro	Thr	Asn 455	Сув	Ile	Ala	Pro	Val 460	Asn	Gly	Tyr	Phe	
Ile 465	ГЛа	Thr	Asn	Asn	Thr 470	Arg	Ile	Val	Asp	Glu 475	Trp	Ser	Tyr	Thr	Gly 480	
Ser	Ser	Phe	Tyr	Ala 485	Pro	Glu	Pro	Ile	Thr 490	Ser	Leu	Asn	Thr	Lys 495	Tyr	
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Pro Leu Leu Gly Asn Ser Thr Gly Ile Asp Phe Gln Asp Glu Leu Asp Glu Phe Phe Lys Asn Val Ser Thr Ser Ile Pro Asn Phe Gly Ser Leu Thr Gln Ile Asn Thr Thr Leu Leu Asp Leu Thr Tyr Glu Met Leu Ser Leu Gln Gln Val Val Lys Ala Leu Asn Glu Ser Tyr Ile Asp Leu Lys Glu Leu Gly Asn Tyr Thr Tyr Tyr Asn Lys Trp Pro <210> SEQ ID NO 34 <211> LENGTH: 526 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic Polypeptide <400> SEQUENCE: 34 Met Phe Ile Phe Leu Leu Phe Leu Thr Leu Thr Ser Gly Ser Asp Leu Asp Arg Ala Leu Ser Gly Ile Ala Ala Glu Gln Asp Arg Asn Thr Arg 20 25 30 Glu Val Phe Ala Gln Val Lys Gln Met Tyr Lys Thr Pro Thr Leu Lys Tyr Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro Asp Pro Leu Lys Pro Thr Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Met Lys Gln Tyr Gly Glu Cys Leu Gly Asp Ile Asn Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Asp Met Ile Ala Ala Tyr Thr Ala Ala Leu Val Ser Gly Thr Ala Thr Ala Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn Gln Lys Gln Ile Ala Asn Gln Phe Asn Lys Ala Ile Ser Gln Ile Gln Glu Ser Leu Thr Thr Thr Ser Thr Ala Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn 195 200 205 Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu Cys Val Leu Gly

506

Concinaca
Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly Tyr His Leu Met Ser 290 295 300
Phe Pro Gln Ala Ala Pro His Gly Val Val Phe Leu His Val Thr Tyr 305 310 315 320
Val Pro Ser Gln Glu Arg Asn Phe Thr Thr Ala Pro Ala Ile Cys His 325 330 335
Glu Gly Lys Ala Tyr Phe Pro Arg Glu Gly Val Phe Val Phe Asn Gly 340 345 350
Thr Ser Trp Phe Ile Thr Gln Arg Asn Phe Phe Ser Pro Gln Ile Ile 355 360 365
Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly 370 375 380
Ile Ile Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser
385 390 395 400 Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp
405 410 415 Val Asp Leu Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile
420 425 430 Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu
435 440 445 Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys
450 455 460
Trp Pro Trp Tyr Val Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala Ile 465 470 475 480
Val Met Val Thr Ile Leu Leu Cys Cys Met Thr Ser Cys Cys Ser Cys 485 490 495
Leu Lys Gly Ala Cys Ser Cys Gly Ser Cys Cys Lys Phe Asp Glu Asp 500 505 510
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tetetaagat aggggtagta ggaataggaa gtgeaageta eaaagttatg aetegtteea 240 geeateaate attagteata aaattaatge eeaatataae teteeteaat aaetgeaega 300
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cacttaatgc aatgacccag aacataaggc cggttcagag cgtagcttca agtaggagac 420
acaagagatt tgegggagta gteetggeag gtgeggeeet aggtgttgee acagetgete 480
agataacago oggoattgoa ottoacoggt ocatgotgaa ototoaggoo atogacaato 540
tgagagegag cetggaaact actaateagg caattgagge aateagacaa geagggeagg 600
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eguarrayor accorgegar claarogger ayaayeteyy yereaaarey eerayatadt - 720

507

508

atacagaaat cetgteatta tttggeeeea geetaeggga eeeeatatet geggagatat	780
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519

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	geeg cteattttet taettttate		1680
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<210> SEQ ID NO 43 <211> LENGTH: 2126

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<210> SEQ ID NO 44 <211> LENGTH: 2065 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic Polynucleotide <400> SEQUENCE: 44 tcaagetttt ggaceetegt acagaageta ataegaetea etatagggaa ataagagaga 60 aaagaagagt aagaagaaat ataagagcca ccatgtcacc acaacgagac cggataaatg 120 cettetacaa agacaaceee cateetaagg gaagtaggat agttattaac agagaacate 180 ttatgattga tagacettat gttttgetgg etgttetatt egteatgttt etgagettga 240 tegggttget agecattgea ggeattagae tteateggge agecatetae acegeagaga 300 tecataaaag eeteageace aatetggatg taactaacte aategageat caggttaagg 360 420 acgtgetgae accactette aagateateg gtgatgaagt gggettgagg acaceteaga gattcactga cetagtgaag ttcatetetg acaagattaa attcettaat ceggacaggg 480 aatacgactt cagagatete aettggtgta teaaceegee agagagaate aaattggatt 540 600 atgatcaata ctgtgcagat gtggctgctg aagaactcat gaatgcattg gtgaactcaa etetaetgga gaccagggea accaateagt teetagetgt eteaaaggga aactgeteag 660 ggeccactac aatcagagge caatteteaa acatgteget gteeetgttg gaettgtatt 720 taagtegagg ttacaatgtg teatetatag teactatgae ateceaggga atgtaegggg 780 qaacttacct aqtqqaaaaq cctaatctqa qcaqcaaaqq qtcaqaqttq tcacaactqa 840 gcatgcaccg agtgtttgaa gtaggtgtta tcagaaatcc gggtttgggg gctccggtat 900 tecatatgae aaactatett gageaaceag teagtaatga ttteageaae tgeatggtgg 960 etttgggggga geteaagtte geageeetet gteacaggga agattetate acaatteeet 1020 atcagggate agggaaaggt gteagettee agettgteaa getaggtgte tggaaateee 1080 caacegacat geaateetgg gteeceetat caacggatga teeagtgata gacaggettt 1140 acctctcatc tcacagagge gttatcgetg acaatcaage aaaatggget gteecgacaa 1200 cacggacaga tgacaagttg cgaatggaga catgottoca gcaggogtgt aagggtaaaa 1260 tecaageact ttgegagaat eeegagtgga caccattgaa ggataacagg atteetteat 1320 acggggtett gtetgttgat etgagtetga cagttgaget taaaateaaa attgttteag 1380 gattegggee attgateaca caeggtteag ggatggaeet atacaaatee aaceacaaca 1440 atatgtattg getgactate eegecaatga agaacetgge ettaggtgta ateaacacat 1500 tggagtggat accgagatte aaggttagte ceaacetett cactgtteea attaaggaag 1560 caggegagga etgecatgee ceaacatace tacetgegga ggtggatggt gatgteaaac 1620 1680 tcaqttccaa tctqqtqatt ctacctqqtc aaqatctcca atatqttctq qcaacctacq atactteeag agttgaacat getgtagttt attacgttta cageceaage egeteatttt 1740 ettaetttta teettttagg ttgeetgtaa gggggggteee eattgaatta caagtggaat 1800 getteacatg ggaccaaaaa etetggtgee gteacttetg tgtgettgeg gacteagaat 1860 etggtggaca tateacteac tetgggatgg tgggcatggg agteagetge acagecaete 1920 gggaagatgg aaccagcogc agatagtgat aataggotgg agootoggtg gocaagotto 1980 ttgeccettg ggeeteeeee cageceetee teeeetteet geaceegtae eeeegtggte 2040 tttgaataaa gtetgagtgg gegge 2065

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<210> SEQ ID NO 45 <211> LENGTH: 1854 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Synthetic Polynucleotide <400> SEQUENCE: 45 atgtcaccac aacgagaccg gataaatgcc ttctacaaag acaaccecca tectaaggga agtaggatag ttattaacag agaacatett atgattgata gaeettatgt tttgetgget gttetatteg teatgtttet gagettgate gggttgetag ceattgeagg eattagaett categggeag ceatetaeae egeagagate cataaaagee teageaeeaa tetggatgta actaactcaa tegageatca ggttaaggae gtgetgaeae caetetteaa gateateggt gatgaagtgg gettgaggae aceteagaga tteactgaee tagtgaagtt catetetgae aagattaaat teettaatee ggacagggaa taegaettea gagateteae ttggtgtate aacccgccag agagaatcaa attggattat gatcaatact gtgcagatgt ggctgctgaa gaactcatga atgcattggt gaactcaact ctactggaga ccagggcaac caatcagttc ctagetgtet caaagggaaa etgeteaggg ceeactacaa teagaggeea atteteaaae atgtegetgt ceetgttgga ettgtattta agtegaggtt acaatgtgte atetatagte actatgacat cccagggaat gtacggggga acttacctag tggaaaagcc taatctgagc agcaaagggt cagagttgtc acaactgagc atgcaccgag tgtttgaagt aggtgttatc agaaateegg gtttgggggge teeggtatte catatgaeaa actatettga geaaceagte agtaatgatt teageaactg catggtgget ttgggggage teaagttege ageestetgt cacagggaag attetateac aatteestat cagggateag ggaaaggtgt cagetteeag ettgtcaage taggtgtetg gaaateeeca acegacatge aateetgggt eeeetatea 1020 acggatgate cagtgataga caggetttae eteteatete acagaggegt tategetgae 1080 aatcaagcaa aatgggetgt eeegacaaca eggacagatg acaagttgeg aatggagaca 1140 tgetteeage aggegtgtaa gggtaaaate caageaettt gegagaatee egagtggaca 1200 ccattgaagg ataacaggat teetteatae ggggtettgt etgttgatet gagtetgaca 1260 gttgagetta aaatcaaaat tgtttcagga ttegggeeat tgatcacaca eggttcaggg 1320 atggacetat acaaateeaa eeacaacaat atgtattgge tgactateee gecaatgaag 1380 aacctggcot taggtgtaat caacacattg gagtggatac cgagattcaa ggttagtcoc 1440 aacctettea etgtteeaat taaggaagea ggegaggaet geeatgeeee aacataeeta 1500 cctgcggagg tggatggtga tgtcaaactc agttccaatc tggtgattct acctggtcaa 1560 gatetecaat atgttetgge aacetaegat aettecagag ttgaacatge tgtagtttat 1620 tacgtttaca geocaageeg eteatttet taetttate ettttaggtt geetgtaagg 1680 ggggteecca ttgaattaca agtggaatge tteacatggg accaaaaaet etggtgeegt 1740 cacttetgtg tgettgegga etcagaatet ggtggacata teacteacte tgggatggtg 1800 ggcatgggag tcagctgcac agccactcgg gaagatggaa ccagccgcag atag 1854

<210> SEQ ID NO 46 <211> LENGTH: 2126 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE:

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<210> SEQ ID NO 47 <211> LENGTH: 550

529

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Ala	Gln 130	Ile	Thr	Ala	Gly	Ile 135	Ala	Leu	His	Arg	Ser 140	Met	Leu	Asn	Ser	
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Leu	Ser	Суя 195	Asp	Leu	Ile	Gly	Gln 200	гуз	Leu	Gly	Leu	Lув 205	Leu	Leu	Arg	
Tyr	Tyr 210	Thr	Glu	Ile	Leu	Ser 215	Leu	Phe	Gly	Pro	Ser 220	Leu	Arg	Asp	Pro	
Ile 225	Ser	Ala	Glu	Ile	Ser 230	Ile	Gln	Ala	Leu	Ser 235	Tyr	Ala	Leu	Gly	Gly 240	
Asp	Ile	Asn	Lys	Val 245	Leu	Glu	Lys	Leu	Gly 250	Tyr	Ser	Gly	Gly	Asp 255	Leu	
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Asn 385	Leu	Ile	Ala	Asn	Cys 390	Ala	Ser	Ile	Leu	Cys 395	ГЛЗ	Суз	Tyr	Thr	Thr 400
Gly	Thr	Ile	Ile	Asn 405	Gln	Asp	Pro	Asp	Lys 410	Ile	Leu	Thr	Tyr	Ile 415	Ala
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						55		-		nec	60	ASII	110		Lea
Leu 65	Asn	Asn	Сув	Thr			Gly	-			60				
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Gly Val Gln Asp Tyr Ile Asn Asn Glu Leu Ile Pro Ser Met Asn Gln

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Met Ser Pro Gln Arg Asp Arg Ile Asn Ala Phe Tyr Lys Asp Asn Pro 1 10 15 Tyr Pro Lys Gly Ser Arg Ile Val Ile Asn Arg Glu His Leu Met Ile 25 Asp Arg Pro Tyr Val Leu Leu Ala Val Leu Phe Val Met Phe Leu Ser 35 40 45 Leu Ile Gly Leu Leu Ala Ile Ala Gly Ile Arg Leu His Arg Ala Ala 50 55 60 Ile Tyr Thr Ala Glu Ile His Lys Ser Leu Ser Thr Asn Leu Asp Val65707580 Thr Asn Ser Ile Glu His Gln Val Lys Asp Val Leu Thr Pro Leu Phe 85 90 95 Lys Ile Ile Gly Asp Glu Val Gly Leu Arg Thr Pro Gln Arg Phe Thr 100 105 110 Asp Leu Val Lys Phe Ile Ser Asp Lys Ile Lys Phe Leu Asn Pro Asp 115 120 125 Arg Glu Tyr Asp Phe Arg Asp Leu Thr Trp Cys Ile Asn Pro Pro Glu130135140 Arg Ile Lys Leu Asp Tyr Asp Gln Tyr Cys Ala Asp Val Ala Ala Glu 145 150 155 160 Glu Leu Met Asn Ala Leu Val Asn Ser Thr Leu Leu Glu Thr Arg Thr 165 175 170 Thr Thr Gln Phe Leu Ala Val Ser Lys Gly Asn Cys Ser Gly Pro Thr 180 185 190 Thr Ile Arg Gly Gln Phe Ser Asn Met Ser Leu Ser Leu Leu Asp Leu 195 200 2.05 Tyr Leu Gly Arg Gly Tyr Asn Val Ser Ser Ile Val Thr Met Thr Ser 215 210 220 Gln Gly Met Tyr Gly Gly Thr Tyr Leu Val Glu Lys Pro Asn Leu Asn 230 235 225 240 Ser Lys Gly Ser Glu Leu Ser Gln Leu Ser Met Tyr Arg Val Phe Glu 245 250 Val Gly Val Ile Arg Asn Pro Gly Leu Gly Ala Pro Val Phe His Met 265 Thr Asn Tyr Phe Glu Gln Pro Val Ser Asn Gly Leu Gly Asn Cys Met 275 280 285 Val Ala Leu Gly Glu Leu Lys Leu Ala Ala Leu Cys His Gly Asp Asp 290 295 300 Ser Ile Ile Ile Pro Tyr Gln Gly Ser Gly Lys Gly Val Ser Phe Gln305310315320 Leu Val Lys Leu Gly Val Trp Lys Ser Pro Thr Asp Met Gln Ser Trp 325 330 335 Val Pro Leu Ser Thr Asp Asp Pro Val Val Asp Arg Leu Tyr Leu Ser 340 345 350 Ser His Arg Gly Val Ile Ala Asp Asn Gln Ala Lys Trp Ala Val Pro 355 360 365 Thr Thr Arg Thr Asp Asp Lys Leu Arg Met Glu Thr Cys Phe Gln Gln 370 375 380 Ala Cys Lys Gly Lys Ile Gln Ala Leu Cys Glu Asn Pro Glu Trp Val 390 400 385 395 Pro Leu Lys Asp Asn Arg Ile Pro Ser Tyr Gly Val Leu Ser Val Asp 405 410 415 Leu Ser Leu Thr Val Glu Leu Lys Ile Lys Ile Ala Ser Gly Phe Gly

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Gly 465	Val	Ile	Asn	Thr	Leu 470	Glu	Trp	Ile	Pro	Arg 475	Phe	Гуз	Val	Ser	Pro 480
Asn	Leu	Phe	Thr	Val 485	Pro	Ile	ГАз	Glu	Ala 490	Gly	Glu	Asp	Сув	His 495	Ala
Pro	Thr	Tyr	Leu 500	Pro	Ala	Glu	Val	Asp 505	Gly	Aab	Val	Lys	Leu 510	Ser	Ser
Asn	Leu	Val 515	Ile	Leu	Pro	Gly	Gln 520	Asp	Leu	Gln	Tyr	Val 525	Leu	Ala	Thr
Tyr	Asp 530	Thr	Ser	Arg	Val	Glu 535	His	Ala	Val	Val	Tyr 540	Tyr	Val	Tyr	Ser
Pro 545	Ser	Arg	Ser	Phe	Ser 550	Tyr	Phe	Tyr	Pro	Phe 555	Arg	Leu	Pro	Ile	Lys 560
Gly	Val	Pro	Ile	Glu 565	Leu	Gln	Val	Glu	Cys 570	Phe	Thr	Trp	Asp	Gln 575	Lys
Leu	Trp	Cys	Arg 580	His	Phe	Cys	Val	Leu 585	Ala	Asp	Ser	Glu	Ser 590	Gly	Gly
Leu	Ile	Thr 595	His	Ser	Gly	Met	Val 600	Gly	Met	Gly	Val	Ser 605	Сув	Thr	Ala
Thr	Arg 610	Glu	Asp	Gly	Thr	Asn 615	Arg	Arg							
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Met 1	Ser	Pro	Gln	Arg 5	Asp	Arg	Ile	Asn	Ala 10	Phe	Tyr	Lys	Asp	Asn 15	Pro
His	Pro	Lys	Gly 20	Ser	Arg	Ile	Val	Ile 25	Asn	Arg	Glu	His	Leu 30	Met	Ile
Asp	Arg	Pro 35	Tyr	Val	Leu	Leu	Ala 40	Val	Leu	Phe	Val	Met 45	Phe	Leu	Ser
Leu	Ile 50	Gly	Leu	Leu	Ala	11e 55	Ala	Gly	Ile	Arg	Leu 60	His	Arg	Ala	Ala
Ile 65	Tyr	Thr	Ala	Glu	Ile 70	His	ГАа	Ser	Leu	Ser 75	Thr	Asn	Leu	Yab	Val 80
Thr	Asn	Ser	Ile	Glu 85	His	Gln	Val	Lys	Asp 90	Val	Leu	Thr	Pro	Leu 95	Phe
Lys	Ile	Ile	Gly 100	Asp	Glu	Val	Gly	Leu 105	Arg	Thr	Pro	Gln	Arg 110	Phe	Thr
Asp	Leu	Val 115	Lys	Phe	Ile	Ser	Asp 120	Lys	Ile	Lys	Phe	Leu 125	Asn	Pro	Asp
Arg	Glu 130	Tyr	Asp	Phe	Arg	Asp 135	Leu	Thr	Trp	Сув	Ile 140	Asn	Pro	Pro	Glu
Arg 145	Ile	Lys	Leu	Asp	Tyr 150	Aab	Gln	Tyr	Сув	Ala 155	Asp	Val	Ala	Ala	Glu 160

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Thr	Asn	Gln	Phe 180	Leu	Ala	Val	Ser	Lys 185	Gly		Суз		Gly 190	Pro	Thr
Thr	Ile	Arg 195		Gln	Phe	Ser	Asn 200	Met	Ser	Leu	Ser	Leu 205	Leu	Asp	Leu
Tyr	Leu 210	Ser	Arg	Gly	Tyr	Asn 215		Ser	Ser	Ile	Val 220	Thr	Met	Thr	Ser
Gln 225	Gly	Met	Tyr	Gly	Gly 230	Thr	Tyr	Leu	Val	Glu 235		Pro	Asn	Leu	Ser 240
Ser	Lys	Gly	Ser	Glu 245		Ser	Gln	Leu	Ser 250	Met	His	Arg	Val	Phe 255	Glu
Val	Gly	Val	Ile 260		Asn	Pro	Gly	Leu 265		Ala	Pro	Val	Phe 270	His	Met
Thr	Asn	Tyr 275		Glu	Gln	Pro	Val 280	Ser	Asn	Asp	Phe	Ser 285	Asn	Cys	Met
Val	Ala 290	Leu	Gly	Glu	Leu	Lys 295		Ala	Ala	Leu	Суз 300	His	Arg	Glu	Asp
Ser 305	Ile	Thr	Ile	Pro	Tyr 310	Gln	Gly	Ser	Gly	Lys 315		Val	Ser	Phe	Gln 320
Leu	Val	Lys	Leu	Gly 325		Trp	Lys	Ser	Pro 330	Thr	Asp	Met	Gln	Ser 335	Trp
Val	Pro	Leu	Ser 340	Thr		Asp		Val 345	Ile		Arg		Tyr 350	Leu	Ser
Ser	His	Arg 355		Val	Ile	Ala	Asp 360	Asn		Ala		Trp 365	Ala	Val	Pro
Thr	Thr 370	Arg	Thr	Asp	Asp	Lys 375	Leu	Arg	Met	Glu	Thr 380	Cys	Phe	Gln	Gln
Ala 385	Cys	Гуа	Gly	Lys	Ile 390	Gln	Ala	Leu	Суз	Glu 395	Asn	Pro	Glu	Trp	Thr 400
Pro	Leu	Гуз	Asp	Asn 405		Ile	Pro	Ser	Tyr 410	Gly	Val	Leu	Ser	Val 415	Asp
Leu	Ser	Leu	Thr 420	Val	Glu	Leu	Lya	Ile 425		Ile	Val	Ser	Gly 430	Phe	Gly
Pro	Leu	Ile 435		His	Gly	Ser	Gly 440		Asp	Leu	Tyr	Lys 445	Ser	Asn	His
Asn	Asn 450					Thr 455		Pro			-		Leu	Ala	Leu
Gly 465	Val					Glu							Val	Ser	Pro 480
	Leu	Phe	Thr	Val 485	Pro	Ile	ГЛа	Glu	Ala 490	Gly	Glu	Asp	Сув	His 495	Ala
Pro	Thr	Tyr	Leu 500		Ala	Glu	Val	Asp 505		Asp	Val	Lys	Leu 510		Ser
Asn	Leu	Val 515	Ile	Leu	Pro	Gly	Gln 520	Asp	Leu	Gln	Tyr	Val 525	Leu	Ala	Thr
Tyr	Asp 530		Ser	Arg	Val	Glu 535		Ala	Val	Val	Tyr 540		Val	Tyr	Ser
		Arg	Ser	Phe		Tyr	Phe	Tyr	Pro			Leu	Pro	Val	_
545 Gly	Val	Pro	Ile		550 Leu	Gln	Val	Glu	-	555 Phe	Thr	Trp	Asp		560 Lys
Leu	Trp	Сув	Arg	565 His	Phe	Cys	Val	Leu	570 Ala	Asp	Ser	Glu	Ser	575 Gly	Gly
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546

ucccagucug accucgacuc	cauccaggcu gaaau	caccc agcgccugaa	cgaaaucgac 420
cguguauccg gccagacuca	guucaacggc gugaa	agucc uggegeagga	caacacccug 480
accauccagg uuggugccaa	cgacggugaa acuau	cgaua uugauuuaaa	agaaaucage 540
ucuaaaacac ugggacuuga	uaagcuuaau gucca	agaug ccuacacece	gaaagaaacu 600
gcuguaaccg uugauaaaac	uaccuauaaa aaugg	uacag auccuauuac	ageccagage 660
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aaauuuaaag auggucaaua	cuauuuagau guuaa	aggeg gugeuueuge	ugguguuuau 780
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Ser Ser Gly Leu Arg I 35	le Asn Ser Ala Ly 40	s Asp Asp Ala Al 45	a Gly Gln
Ala Ile Ala Asn Arg Pi 50	he Thr Ala Asn Il 55	e Lys Gly Leu Th: 60	r Gln Ala
Ser Arg Asn Ala Asn A 65 7		e Ala Gln Thr Th 75	r Glu Gly 80
Ala Leu Asn Glu Ile A 85	sn Asn Asn Leu Gl 90	n Arg Val Arg Gl	u Leu Ala 95
Val Gln Ser Ala Asn G 100	ly Thr Asn Ser Gl 105	n Ser Asp Leu Asj 11	

Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly

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Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu Lys Glu Ile Ser Ser Lys Thr Leu Gly Leu Asp Lys Leu Asn Val Gln Asp Ala Tyr Thr Pro Lys Glu Thr Ala Val Thr Val Asp Lys Thr Thr Tyr Lys Asn Gly Thr Asp Pro Ile Thr Ala Gln Ser Asn Thr Asp Ile 195 200 205 Gln Thr Ala Ile Gly Gly Gly Ala Thr Gly Val Thr Gly Ala Asp Ile 210 215 220 Lys Phe Lys Asp Gly Gln Tyr Tyr Leu Asp Val Lys Gly Gly Ala Ser 225 230 235 240 Ala Gly Val Tyr Lys Ala Thr Tyr Asp Glu Thr Thr Lys Lys Val Asn 245 250 255 Ile Asp Thr Thr Asp Lys Thr Pro Leu Ala Thr Ala Glu Ala Thr Ala260265270 Ile Arg Gly Thr Ala Thr Ile Thr His Asn Gln Ile Ala Glu Val Thr Lys Glu Gly Val Asp Thr Thr Thr Val Ala Ala Gln Leu Ala Ala Ala Gly Val Thr Gly Ala Asp Lys Asp Asn Thr Ser Leu Val Lys Leu Ser Phe Glu Asp Lys Asn Gly Lys Val Ile Asp Gly Gly Tyr Ala Val Lys Met Gly Asp Asp Phe Tyr Ala Ala Thr Tyr Asp Glu Lys Thr Gly Ala Ile Thr Ala Lys Thr Thr Thr Tyr Thr Asp Gly Thr Gly Val Ala Gln Thr Gly Ala Val Lys Phe Gly Gly Ala Asn Gly Lys Ser Glu Val Val Thr Ala Thr Asp Gly Lys Thr Tyr Leu Ala Ser Asp Leu Asp Lys His 385 390 395 400 Asn Phe Arg Thr Gly Gly Glu Leu Lys Glu Val Asn Thr Asp Lys Thr Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg Phe Asn Ser Ala Ile 435 440 445 Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Ser Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu Ser Leu Leu Arg

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)> SI Ala				Asn	Thr	Asn	Ser	Leu	Ser	Leu	Leu	Thr	Gln	Asn
1				5					10					15	
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Ser	Ser	Gly 35	Leu	Arg	Ile	Asn	Ser 40	Ala	Гла	Aab	Asp	Ala 45	Ala	Gly	Gln
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Ala	Leu	Asn	Glu	Ile 85	Asn	Asn	Asn	Leu	Gln 90	Arg	Val	Arg	Glu	Leu 95	Ala
Val	Gln	Ser	Ala 100	Asn	Ser	Thr	Asn	Ser 105	Gln	Ser	Asp	Leu	Asp 110	Ser	Ile
Gln	Ala	Glu 115	Ile	Thr	Gln	Arg	Leu 120	Asn	Glu	Ile	Asp	Arg 125	Val	Ser	Gly
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Thr 145	Ile	Gln	Val	Gly	Ala 150	Asn	Asp	Gly	Glu	Thr 155	Ile	Asp	Ile	Aab	Leu 160
ГЛЗ	Gln	Ile	Asn	Ser 165	Gln	Thr	Leu	Gly	Leu 170	Asp	Thr	Leu	Asn	Val 175	Gln
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Asp	Thr	Thr 195	Ile	Ala	Leu	Asp	Asn 200	Ser	Thr	Phe	Lys	Ala 205	Ser	Ala	Thr
Gly	Leu 210	Gly	Gly	Thr	Asp	Gln 215	Lys	Ile	Asp	Gly	Asp 220	Leu	Lys	Phe	Asp
Asp 225	Thr	Thr	Gly	ГЛа	Tyr 230	Tyr	Ala	Гла	Val	Thr 235	Val	Thr	Gly	Gly	Thr 240
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Ala	Thr	Ala 275	Thr	Glu	Asp	Val	ГАа 780	Asn	Val	Gln	Val	Ala 285	Asn	Ala	Asp
Leu	Thr 290	Glu	Ala	Lys	Ala	Ala 295	Leu	Thr	Ala	Ala	Gly 300	Val	Thr	Gly	Thr
Ala 305	Ser	Val	Val	Lys	Met 310	Ser	Tyr	Thr	Asp	Asn 315	Asn	Gly	Lys	Thr	Ile 320
Asp	Gly	Gly	Leu	Ala 325	Val	Гла	Val	Gly	Asp 330	Asp	Tyr	Tyr	Ser	Ala 335	Thr
Gln	Asn	Lys	Asp 340	Gly	Ser	Ile	Ser	Ile 345	Asn	Thr	Thr	Lys	Tyr 350	Thr	Ala
Asp	Asp	-		Ser	Lys	Thr			Asn	Lys	Leu	-		Ala	Asp
Gly	Гуз	355 Thr	Glu	Val	Val	Ser	360 Ile	Gly	Gly	Lys	Thr	365 Tyr	Ala	Ala	Ser
-	370					375		-	-		380				

Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro Asp Leu Ala Glu Ala 385 390 395 400

A	la	Ala	Thr	Thr	Thr 405	Glu	Asn	Pro	Leu	Gln 410	Lys	Ile	Asp	Ala	Ala 415	Leu
A	la	Gln	Val	Asp 420		Leu	Arg	Ser	Asp 425		Gly	Ala	Val	Gln 430		Arg
P	he	Asn	Ser 435		Ile	Thr	Asn	Leu 440		Asn	Thr	Val	Asn 445		Leu	Thr
S	er	Ala 450		Ser	Arg	Ile	Glu 455		Ser	Asp	Tyr	Ala 460	Thr	Glu	Val	Ser
	sn 65		Ser	Arg	Ala	Gln 470		Leu	Gln	Gln	Ala 475		Thr	Ser	Val	Leu 480
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A	la	Asn	Pro 515		Ala	Asn	Pro	Asn 520		Asn	Pro	Asn	Ala 525		Pro	Asn
A	la	Asn 530		Asn	Ala	Asn	Pro 535		Ala	Asn	Pro	Asn 540	Ala	Asn	Pro	Asn
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		Asn	Pro	Asn	Ala 565		Pro	Asn	Ala	Asn 570	Pro	Asn	Ala	Asn	Pro 575	
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	lu 25	Pro	Ser	Asp	Lys	His 630	Ile	Glu	Gln	Tyr	Leu 635	Lys	Гуз	Ile	Lys	Asn 640
S	er	Ile	Ser	Thr	Glu 645	Trp	Ser	Pro	Суз	Ser 650	Val	Thr	Cys	Gly	Asn 655	Gly
I	le	Gln	Val	Arg 660	Ile	Lys	Pro	Gly	Ser 665	Ala	Asn	Lys	Pro	Lys 670	Asp	Glu
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C	Уa	Ser 690	Ser	Val	Phe	Asn	Val 695	Val	Asn	Ser						
	211 212 213 220 223	L> LH 2> TY 3> OH 0> FH 3> OY	CATUR THER	I: 69 PRT SM: XE: INF(92 Art: DRMA	ific: FION		-		9 0 1y	pepti	ide				
			EQUER Ala			Dara	A ~~~	7 1-	3.00	Dma	D ~~~	<u>م</u> ام	A ~~~	Dme	7.000	مام
1					5					10			Asn		15	
A	sn	Pro	Asn	Ala 20	Asn	Pro	Asn	Ala	Asn 25	Pro	Asn	Ala	Asn	Pro 30	Asn	Ala
A	sn	Pro	Asn 35	Ala	Asn	Pro	Asn	Ala 40	Asn	Pro	Asn	Ala	Asn 45	Pro	Asn	Ala

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Asn	Pro 50	Asn	Ala	Asn	Pro	Asn 55	Ala	Asn	Pro	Asn	Ala 60	Asn	Pro	Asn	Ala
Asn 65	Pro	Asn	Ala	Asn	Pro 70	Asn	Ala	Asn	Pro	Asn 75	Ala	Asn	Pro	Asn	Ala 80
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Val	Lys	Asn 115	Asn	Asn	Asn	Glu	Glu 120	Pro	Ser	Asp	Lya	His 125	Ile	Glu	Gln
Tyr	Leu 130	Гуа	ГАа	Ile	Lys	Asn 135	Ser	Ile	Ser	Thr	Glu 140	Trp	Ser	Pro	Суз
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ГАз	Ile	Сув	Lys 180	Met	Glu	ГАЗ	САа	Ser 185	Ser	Val	Phe	Asn	Val 190	Val	Asn
Ser	Arg	Pro 195	Val	Thr	Met	Ala	Gln 200	Val	Ile	Asn	Thr	Asn 205	Ser	Leu	Ser
Leu	Leu 210	Thr	Gln	Asn	Asn	Leu 215	Asn	Гла	Ser	Gln	Ser 220	Ala	Leu	Gly	Thr
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Thr	Gly	Gly	Leu	Pro	Ala	Thr	Ala	Thr	Glu	Asp	Val	Lys	Asn	Val	Gln

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										-	con	tin	ued					
465				470					475					480				
Val Ala	Asn	Ala	Asp 485	Leu	Thr	Glu	Ala	Lys 490	Ala	Ala	Leu	Thr	Ala 495	Ala				
Gly Val	. Thr	Gly 500		Ala	Ser	Val	Val 505	Lys	Met	Ser	Tyr	Thr 510	Asp	Asn				
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Tyr Tyr 530		Ala	Thr	Gln	Asn 535	Lys	Asp	Gly	Ser	Ile 540	Ser	Ile	Asn	Thr				
Thr Lys		Thr	Ala		Aab	Gly	Thr	Ser			Ala	Leu	Asn					
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_		580		-			585				-	590						
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Ala Val 625	Gln	Asn	Arg	Phe 630		Ser	Ala	Ile	Thr 635	Asn	Leu	Gly	Asn	Thr 640				
Val Asn	ı Asn	Leu	Thr 645	Ser	Ala	Arg	Ser	Arg 650	Ile	Glu	Asp	Ser	Asp 655	Tyr				
Ala Thr	Glu	Val 660	Ser	Asn	Met	Ser	Arg 665	Ala	Gln	Ile	Leu	Gln 670	Gln	Ala				
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cugaaga	iccg i	uguc	cgcc	ga c	cage	uggco	c aga	agag	gaac	aga	ucga	gaa d	eccu	eggeag	300			
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acacccugcu gga	ucgugaa	ggccgcuccu	ageugeuceg	agaagaaagg	aaacuaugcc	900	
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cucaaaacag ucu	cugcuga	ucaguuggcg	agagaggagc	aaauugaaaa	ucccagacaa	300	
ucaagauuug ucu						360	
ggcauugcaa uag						420	
cucaaacaaa cua						480	
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cugaugacug aug	cugaguu	ggccagagcu	guaucauaca	ugccaacauc	ugcagggcag	720	
auaaaacuga ugu	uggagaa	ccgcgcaaug	guaaggagaa	aaggauuugg	aauccugaua	780	
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acaccuuguu gga	ucaucaa	ggcagcuccc	ucuugcucag	aaaaaacgg	gaauuaugcu	900	
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ccaaaugaaa aag	acugcga	aacaagaggu	gaucauguuu	uuugugacac	agcagcaggg	1020	
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cuuggucuaa ccaugauuuc	agugagcauc	aucaucauaa	ucaagaaaac	aaggaagccc	1560	
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ucaagguuug uccuaggugc	aauagcucuu	ggaguugcca	cagcagcagc	agucacagca	360	
ggcauugcaa uagccaaaac	uauaaggcuu	gagagugaag	ugaaugcaau	caaaggugcu	420	
cucaaaacaa ccaaugaggc	aguaucaaca	cuaggaaaug	gagugcgggu	ccuagccacu	480	
gcaguaagag agcugaaaga	auuugugagc	aaaaaccuga	cuagugegau	caacaagaac	540	
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cuuggguuaa ccaugauuuc	agugagcauc	aucaucauaa	ucaaaaaaaac	aaggaageee	1560	
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LENGTH: 1725
<212> TYPE: RNA
<213> ORGANISM: Human respiratory syncytial virus

<400> SEQUENCE: 60

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aauaccaaaa auaccaaugu					420
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uuaucaaaug gaguuagugu					600
aaacaguugu uaccuauugu					660
auagaguucc aacaaaagaa					720
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guuagacago aaaguuacuc	uaucaugucc	auaauaaagg	aggaagucuu	agcauaugua	900
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aacucuugug gugaccaaca					240
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<223> OTHER INFORMATION: Synthetic Polynucleotide

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-	COL	ιt	1	n	u	ed.

uccccgcuuu aauauguugc ugcagggggc guuguaacaa gaagggagaa caaguuggua	1680
ugucaagacc aggccuaaag ccugaucuua caggaacauc aaaauccuau guaaggucac	1740
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geagugugue uuggaggauu gauagggaue eeegeuuuaa uauguugeug cagggggegu	1560
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<210> SEQ ID NO 76 <211> LENGTH: 1854 <212> TYPE: RNA

<400> SEQUENCE: 77

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<213> ORGANISM: Artificial Sequence

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US 10,702,600 B1

596

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597

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cugagaacac	cucagagauu	cacugaccua	gugaaauuca	ucucggacaa	gauuaaauuc	420
cuuaauccgg	auagggagua	cgacuucaga	gaucucacuu	ggugcaucaa	cccgccagag	480
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

<223> OTHER INFORMATION: Synthetic Polynucleotide

<220> FEATURE:

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gaacucauga augcauuggu gaacucaacu cuacuggaga ccagggcaac caaucaguuc	540
cuageugueu caaagggaaa cugeucaggg eecacuacaa ucagaggeea auucucaaac	600
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603

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Asn Pro Gly	Ser Gly S 100	er Phe Val	Leu Gly Al 105	a Ile Ala Le 11	-	
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Ile	Ile			Thr	Lys	гуз			Gly	Ala	Pro			Leu	Ser
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nec 1	Ser	тр	гув	5 5	vai	те	тте	Pne	ser 10	Leu	Leu	IIe	III	Pro 15	GIN
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Pro Asn Glu	Lys As 32		Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сүя 335	Asp
Thr Ala Ala	Gly I1 340	e Asn	Val	Ala	Glu 345	Gln	Ser	Lys	Glu	Суя 350	Asn	Ile
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Lys Gln Leu	Asn Ly 40	-	Суя	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr Val Thr	Ile As 420	p Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu Gln His 435	Val Il	e Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
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Glu Asn Ile 465	Glu As	n Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Arg	Ile 480
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Glu Gly Tyr 35	Leu Se	r Val	Leu	Arg 40	Thr	Gly	Trp	Tyr	Thr 45	Asn	Val	Phe
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Ser Leu Ile 65	Lys Th	r Glu 70	Leu	Азр	Leu	Leu	Lys 75	Ser	Ala	Leu	Arg	Glu 80
Leu Lys Thr	Val Se	r Ala	Asp	Gln	Leu	Ala	Arg	Glu	Glu	Gln	Ile	Glu

Leu Lys Thr Val Ser Ala Asp Gl
n Leu Ala Arg Glu Glu Glu Gln Ile Glu 85 90 95

Asn Pro Gly Ser Gly Ser Phe Val Leu Gly Ala Ile Ala Leu Gly Val 100 105 110

Ala	Ala	Ala 115	Ala	Ala	Val	Thr	Ala 120	Gly	Val	Ala	Ile	Ala 125	Lys	Thr	Ile
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Ala	Val	Arg	Glu	Leu 165	Lys	Asp	Phe	Val	Leu 170	Lys	Asn	Leu	Thr	Arg 175	Ala
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Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
Ala 225	Glu	Leu	Ala	Arg	Ala 230	Val	Pro	Asn	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
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Gly	Ile	Leu	Ile 260	Gly	Val	Tyr	Gly	Ser 265	Ser	Val	Ile	Tyr	Met 270	Val	Gln
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Thr	Ala	Ala	Gly 340	Ile	Asn	Val	Ala	Glu 345	Gln	Ser	Lys	Glu	Сув 350	Asn	Ile
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Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Суз
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Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
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Asn															
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Tyr 385	Lys	Gly	Val	Ser	Суз 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
Lys	Gln	Leu	Asn	Lys 405	Gly	Cys	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	11e 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
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Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
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Glu	Gly	Tyr 35	Leu	Ser	Val	Leu	Arg 40	Thr	Gly	Trp	Tyr	Thr 45	Asn	Val	Phe
Thr	Leu 50	Glu	Val	Gly	Asp	Val 55	Glu	Asn	Leu	Thr	Сүз 60	Ser	Asp	Gly	Pro
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Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
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Ala	Val	Arg	Glu	Leu 165		Asp	Phe	Val	Leu 170		Asn	Leu	Thr	Arg 175	Ala
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Pro	Asn	Glu	Гуз	Asp 325		Glu	Thr	Arg	Gly 330	Aap	His	Val	Phe	Суз 335	Asp
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Asn	Ile	Ser 355	Thr			-	Pro 360	Суз	-				Gly	Arg	His
Pro	Ile 370			_	_		Ser			_	_		_	Ala	Сув
Tyr 385		Gly	Val	Ser	Cys 390		Ile	Gly	Ser	Asn 395		Val	Gly	Ile	Ile 400
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Glu	Gln		420 Val	Ile	Гуз	Gly	Arg	425 Pro	Val	Ser	Ser		430 Phe	Asp	Pro
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Leu	Ser	ser	AIa	485	цув	GIÝ	Asn	Inr	490	Pne	тте	ITé	var	11e 495	ITe

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Tyr Ly 385	s Gly	Val	Ser	Cys 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
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Thr Va	l Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Гуз	Val 430	Glu	Gly
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Leu Se	r Ser	Ala	Glu 485	Гла	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
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Ser Le			m la sa	Glu	Leu	Asp	Leu	Leu	Lys	Ser	Ala	Leu	Arg	
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650

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Glu	Gly	Tyr 35	Leu	Ser	Val	Leu	Arg 40	Thr	Gly	Trp	Tyr	Thr 45	Asn	Val	Phe
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Leu	Гла	Thr	Val	Ser 85	Ala	Asp	Gln	Leu	Ala 90	Arg	Glu	Glu	Gln	Ile 95	Glu
Asn	Pro	Gly	Ser 100	Gly	Ser	Phe	Val	Leu 105	Gly	Ala	Ile	Ala	Leu 110	Gly	Val
Ala	Ala	Ala 115	Ala	Ala	Val	Thr	Ala 120	Gly	Val	Ala	Ile	Ala 125	Lys	Thr	Ile
Arg	Leu 130	Glu	Ser	Glu	Val	Thr 135	Ala	Ile	Asn	Asn	Ala 140	Leu	Lys	Lys	Thr
Asn 145	Glu	Ala	Val	Ser	Thr 150	Leu	Gly	Asn	Gly	Val 155	Arg	Val	Leu	Ala	Thr 160
Ala	Val	Arg	Glu	Leu 165	Lys	Aab	Phe	Val	Ser 170	Lys	Asn	Leu	Thr	Arg 175	Ala
Ile	Asn	Lys	Asn 180	Lys	Cys	Asp	Ile	Pro 185	Asp	Leu	Lys	Met	Ala 190	Val	Ser
Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser

Asp As 2	3n 10	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
Ala G 225	lu	Leu	Ala	Arg	Ala 230	Val	Pro	Asn	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
Ile Ly	ys	Leu	Met	Leu 245	Glu	Asn	Arg	Ala	Met 250	Val	Arg	Arg	Lys	Gly 255	Phe
Gly I	le	Leu	Ile 260	Gly	Val	Tyr	Gly	Ser 265	Ser	Val	Ile	Tyr	Met 270	Val	Gln
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Ala Pr 29	ro 90	Ser	Cys	Ser	Glu	Lys 295	Lys	Gly	Asn	Tyr	Ala 300	Суз	Leu	Leu	Arg
Glu A: 305	ab	Gln	Gly	Trp	Tyr 310	Cys	Gln	Asn	Ala	Gly 315	Ser	Thr	Val	Tyr	Tyr 320
Pro As	sn	Glu	Lys	Asp 325	Сув	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сув 335	Авр
Thr A	la	Ala	Gly 340	Ile	Asn	Val	Ala	Glu 345	Gln	Ser	ГЛа	Glu	Сув 350	Asn	Ile
Asn II		Ser 355	Thr	Thr	Asn	Tyr	Pro 360	Суз	Lys	Val	Ser	Thr 365	Gly	Arg	His
Pro II 3	le 70	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Сув
Tyr Ly 385	γs	Gly	Val	Ser	Сув 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
Lys G	ln	Leu	Asn	Lys 405	Gly	Сув	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	deV
Thr Va	al	Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu G		His 435	Val	Ile	Гλа	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
Ile L ₃ 49	78 50	Phe	Pro	Glu	Asp	Gln 455	Phe	Gln	Val	Ala	Leu 460	Asp	Gln	Val	Phe
Glu As 465	₹n	Ile	Glu	Asn	Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Arg	Ile 480
Leu Se	∍r	Ser	Ala	Glu 485	Lys	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
Leu I	le	Ala	Val 500	Leu	Gly	Ser	Ser	Met 505	Ile	Leu	Val	Ser	Ile 510	Phe	Ile
Ile I		Lys 515	Lya	Thr	Lys	Lys	Pro 520	Thr	Gly	Ala	Pro	Pro 525	Glu	Leu	Ser
Gly Va 5:	al 30	Thr	Asn	Asn	Gly	Phe 535	Ile	Pro	His	Asn					
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1 His G	ly	Leu	-	5 Glu	Ser	Tyr	Leu		10 Glu	Ser	Суз	Ser		15 Ile	Thr
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Glu	Gly	Tyr 35	Leu	Ser	Val	Leu	Arg 40	Thr	Gly	Trp	Tyr	Thr 45	Asn	Val	Phe
Thr	Leu 50	Glu	Val	Gly	Asp	Val 55	Glu	Asn	Leu	Thr	Cys 60	Ser	Asp	Gly	Pro
Ser 65	Leu	Ile	Гλа	Thr	Glu 70	Leu	Asp	Leu	Thr	Lys 75	Ser	Ala	Leu	Arg	Glu 80
Leu	Гуз	Thr	Val	Ser 85	Ala	Asp	Gln	Leu	Ala 90	Arg	Glu	Glu	Gln	Ile 95	Glu
Asn	Pro	Gly	Ser 100	Gly	Ser	Phe	Val	Leu 105	Gly	Ala	Ile	Ala	Leu 110	Gly	Val
Ala	Ala	Ala 115	Ala	Ala	Val	Thr	Ala 120	Gly	Val	Ala	Ile	Ala 125	Lys	Thr	Ile
Arg	Leu 130	Glu	Ser	Glu	Val	Thr 135	Ala	Ile	Asn	Asn	Ala 140	Leu	Lys	Lys	Thr
Asn 145	Glu	Ala	Val	Ser	Thr 150	Leu	Gly	Asn	Gly	Val 155	Arg	Val	Leu	Ala	Thr 160
Ala	Val	Arg	Glu	Leu 165	Lys	Yab	Phe	Val	Ser 170	Lys	Asn	Leu	Thr	Arg 175	Ala
Ile	Asn	Lys	Asn 180	Lys	Cys	Pro	Ile	Asp 185	Asp	Leu	Lys	Met	Ala 190	Val	Ser
Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
Ala 225	Glu	Leu	Ala	Arg	Ala 230	Val	Pro	Asn	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
Ile	Lys	Leu	Met	Leu 245	Glu	Asn	Arg	Ala	Met 250	Val	Arg	Arg	Lys	Gly 255	Phe
Gly	Ile	Leu	Ile 260	Gly	Val	Tyr	Gly	Ser 265	Ser	Val	Ile	Tyr	Met 270	Val	Gln
Leu	Pro	Ile 275	Phe	Gly	Val	Ile	Asp 280	Thr	Pro	Суя	Trp	Ile 285	Val	Lys	Ala
Ala	Pro 290	Ser	Суа	Ser	Glu	Lys 295	ГЛа	Gly	Asn	Tyr	Ala 300	Суз	Leu	Leu	Arg
Glu 305	Asp	Gln	Gly	Trp	Tyr 310	Суа	Gln	Asn	Ala	Gly 315	Ser	Thr	Val	Tyr	T yr 320
Pro	Asn	Glu	Lys	Asp 325	Сув	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сув 335	Asp
Thr	Ala	Ala	Gly 340	Ile	Asn	Val	Ala	Glu 345	Gln	Ser	Гуз	Glu	Cys 350	Asn	Ile
Asn	Ile	Ser 355	Thr	Thr	Asn	Tyr	Pro 360	Суз	Гуз	Val	Ser	Thr 365	Gly	Arg	His
Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Cys
Tyr 385	Гла	Gly	Val	Ser	Cys 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
Lys	Gln	Leu	Asn	Lys 405	Gly	Суя	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	Ile 420		Asn	Thr	Val	Tyr 425		Leu	Ser	Гуа	Val 430		Gly
Glu	Gln			Ile	Lys	Gly	-		Val	Ser	Ser			Asp	Pro
Ile	Lys	435 Phe	Pro	Glu	Asp	Gln	440 Phe	Gln	Val	Ala	Leu	445 Asp	Gln	Val	Phe

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Pro	Asn	Glu	Гүз	Asp 325	Суз	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сув 335	Asp
Thr	Ala	Ala	Gly 340		Asn	Val	Ala	Glu 345	Gln	Ser	Lys	Glu	Суз 350	Asn	Ile
Asn	Ile	Ser 355	Thr	Thr	Asn	Tyr	Pro 360	Суз	Lys	Val	Ser	Thr 365	Gly	Arg	His
Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Суз
Tyr 385	Гла	Gly	Val	Ser	Сув 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
ГЛЗ	Gln	Leu	Asn	Lys 405	Gly	Сув	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	Ile 420		Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
Ile	Lув 450	Phe	Pro	Glu	Asp	Gln 455	Phe	Gln	Val	Ala	Leu 460	Asp	Gln	Val	Phe
Glu 465	Asn	Ile	Glu	Asn	Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Arg	Ile 480
Leu	Ser	Ser	Ala	Glu 485	Lys	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
Leu	Ile	Ala	Val 500		Gly	Ser	Ser	Met 505	Ile	Leu	Val	Ser	Ile 510	Phe	Ile
Ile	Ile	Lys 515	Lys	Thr	Гуз	Гуз	Pro 520	Thr	Gly	Ala	Pro	Pro 525	Glu	Leu	Ser
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Glu	Gly	Tyr 35	Leu	Ser	Val	Leu	Arg 40	Thr	Gly	Trp	Tyr	Thr 45	Asn	Val	Phe
Thr	Leu 50	Glu	Val	Gly	Asp	Val 55	Glu	Asn	Leu	Thr	Cys 60	Ser	Asp	Gly	Pro
Ser 65	Leu	Ile	Гүз	Thr	Glu 70	Leu	Asp	Leu	Thr	Lys 75	Ser	Ala	Leu	Arg	Glu 80
Leu	Lys	Thr	Val	Ser 85	Ala	Yab	Gln	Leu	Ala 90	Arg	Glu	Glu	Gln	Ile 95	Glu
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Arg	Leu 130	Glu	Ser	Glu	Val	Thr 135	Ala	Ile	Asn	Asn	Ala 140	Leu	Гуз	Гλа	Thr
Asn 145	Glu	Ala	Val	Ser	Thr 150	Leu	Gly	Asn	Gly	Val 155	Arg	Val	Leu	Ala	Thr 160
Ala	Val	Arg	Glu	Leu 165	Гла	Aab	Phe	Val	Ser 170	Lys	Asn	Leu	Thr	Arg 175	Ala
Ile	Asn	Lys	Asn 180	ГЛа	Суз	Yab	Ile	Asp 185	Asp	Leu	ГЛа	Met	Ala 190	Val	Ser
Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
Ala 225	Glu	Leu	Ala	Arg	Ala 230	Val	Pro	Asn	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
Ile	Lys	Leu	Met	Leu 245	Glu	Asn	Arg	Ala	Met 250	Val	Arg	Arg	Lys	Gly 255	Phe
Gly	Ile	Leu	Ile 260	Gly	Val	Tyr	Gly	Ser 265	Ser	Val	Ile	Tyr	Met 270	Val	Gln
Leu	Pro	Ile 275	Phe	Gly	Val	Ile	Asp 280	Thr	Pro	Суз	Trp	Ile 285	Val	Гλа	Ala
Ala	Pro 290	Ser	САа	Ser	Glu	Lys 295	ГÀа	Gly	Asn	Tyr	Ala 300	Суз	Leu	Leu	Arg
Glu 305	Asp	Gln	Gly	Trp	Tyr 310	Cys	Gln	Asn	Ala	Gly 315	Ser	Thr	Val	Tyr	Tyr 320
Pro	Asn	Glu	ГЛа	Asp 325	Cys	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Сув 335	Asp
Thr	Ala	Ala	Gly 340	Ile	Asn	Val	Ala	Glu 345	Gln	Ser	Lys	Glu	Сув 350	Asn	Ile
Asn	Ile	Ser 355	Thr	Thr	Asn	Tyr	Pro 360	Суз	Lys	Val	Ser	Thr 365	Gly	Arg	His
Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Cys
Tyr 385	Гуз	Gly	Val	Ser	Сув 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
Гүз	Gln	Leu	Asn	Lys 405	Gly	Суя	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Гла	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Pro	Pro
Ile	Lys 450	Phe	Pro	Glu	Asp	Gln 455	Phe	Gln	Val	Ala	Leu 460	Asp	Gln	Val	Phe
Glu 465	Asn	Ile	Glu	Asn	Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Arg	Ile 480
Leu	Ser	Ser	Ala	Glu 485	Lys	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
Leu	Ile	Ala	Val 500	Leu	Gly	Ser	Ser	Met 505	Ile	Leu	Val	Ser	Ile 510	Phe	Ile
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n260 265 270Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile

Asn															
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Pro	Ile 370	Ser	Met	Val	Ala	Leu 375	Ser	Pro	Leu	Gly	Ala 380	Leu	Val	Ala	Суз
Tyr 385	Гла	Gly	Val	Ser	Сув 390	Ser	Ile	Gly	Ser	Asn 395	Arg	Val	Gly	Ile	Ile 400
Lys	Gln	Leu	Asn	Lys 405	Gly	Cys	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	Lys	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Asp	Pro
Ile	Lys 450	Phe	Pro	Glu	Asn	Gln 455	Phe	Gln	Val	Ala	Leu 460	Asp	Gln	Val	Phe
Glu 465	Asn	Ile	Glu	Asn	Ser 470	Gln	Ala	Leu	Val	Asp 475	Gln	Ser	Asn	Arg	Ile 480
Leu	Ser	Ser	Ala	Glu 485	Lys	Gly	Asn	Thr	Gly 490	Phe	Ile	Ile	Val	Ile 495	Ile
Leu	Ile	Ala	Val 500	Leu	Gly	Ser	Ser	Met 505	Ile	Leu	Val	Ser	Ile 510	Phe	Ile
Ile	Ile	Lуя 515	Гла	Thr	Гла	Lys	Pro 520	Thr	Gly	Ala	Pro	Pro 525	Glu	Leu	Ser
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Phe	Ser	Gln 195	Phe	Asn	Arg	Arg	Phe 200	Leu	Asn	Val	Val	Arg 205	Gln	Phe	Ser
Asp	Asn 210	Ala	Gly	Ile	Thr	Pro 215	Ala	Ile	Ser	Leu	Asp 220	Leu	Met	Thr	Asp
Ala 225	Glu	Leu	Ala	Arg	Ala 230	Val	Pro	Asn	Met	Pro 235	Thr	Ser	Ala	Gly	Gln 240
Ile	Lys	Leu	Met	Leu 245	Glu	Asn	Arg	Ala	Met 250	Val	Arg	Arg	Lys	G1y 255	Phe
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Ala	Pro 290	Ser	Сүз	Ser	Glu	Lys 295	Гла	Gly	Asn	Tyr	Ala 300	Сув	Leu	Leu	Arg
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Pro	Asn	Glu	Lys	Asp 325	Cys	Glu	Thr	Arg	Gly 330	Asp	His	Val	Phe	Cys 335	Asp
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Гуз	Gln	Leu	Asn	Lys 405	Gly	Сүз	Ser	Tyr	Ile 410	Thr	Asn	Gln	Asp	Ala 415	Asp
Thr	Val	Thr	Ile 420	Asp	Asn	Thr	Val	Tyr 425	Gln	Leu	Ser	гда	Val 430	Glu	Gly
Glu	Gln	His 435	Val	Ile	Lys	Gly	Arg 440	Pro	Val	Ser	Ser	Ser 445	Phe	Aab	Pro
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 Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr

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Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Fhe Ile 500 11 E Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser 515 520 520 520 520 520 520 520	er Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile	
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675

676

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692

180

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709

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717

718

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600

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What is claimed is:

1. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

2. The composition of claim 1, wherein the open reading ³⁰ frame encodes a BetaCoV S protein.

3. The composition of claim 1, wherein the open reading frame encodes an S protein subunit selected from an S1 subunit and an S2 subunit.

4. The composition of claim **1**, wherein the mRNA further 35 comprising a 5' untranslated region (UTR) and a 3' UTR.

5. The composition of claim 4, wherein the mRNA further comprises a poly(A) tail.

6. The composition of claim 4, wherein the mRNA further comprises a 5' cap analog.

7. The composition of claim 6, wherein the 5' cap analog is 7mG(5')ppp(5')NImpNp.

8. The composition of claim 1, wherein the mRNA comprises a chemical modification.

9. The composition of claim **8**, wherein the chemical 45 modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.

10. The composition of claim 8, wherein at least 80% of the uracil in the open reading frame has a chemical modification.

11. The composition of claim 1, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.

12. The composition of claim 11, wherein the lipid nanoparticle comprises 20-60% ionizable cationic lipid, 55 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

13. The composition of claim 12, wherein the lipid nanoparticle comprises 50% ionizable cationic lipid, 10% neutral lipid, 38.5% sterol, and 1.5% PEG-modified lipid.

14. The composition of claim 11, wherein the ionizable cationic lipid is Compound 25.

15. The composition of claim **11**, wherein the neutral lipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), the sterol is cholesterol, and the PEG-modified lipid is 1,2-65 dimyristoyl-racalycero-3-methoxypolyethylene glycol-2000 (PEG-DMG) or PEG-cDMA.

16. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

17. The composition of claim 16, wherein the open reading frame encodes a BetaCoV S protein.

18. The composition of claim 16, wherein the open reading frame encodes an S protein subunit selected from an S1 subunit and an S2 subunit.

19. The composition of claim **16**, wherein the mRNA further comprises 5' cap analog 7mG(5')ppp(5')NlmpNp.

20. The composition of claim **16**, wherein at least 80% of the uracil in the open reading frame has a chemical modification.

21. The composition of claim **20**, wherein the chemical modification is a 1-methylpseudouridine modification or a 1-ethylpseudouridine modification.

22. The composition of claim 16, wherein the ionizable cationic lipid is Compound 25.

23. The composition of claim **16**, wherein the neutral lipid is DSPC, the sterol is cholesterol, and the PEG-modified lipid is PEG-DMG.

24. A composition, comprising: a messenger ribonucleic acid (mRNA) comprising a 5' cap analog, a 5' untranslated region (UTR), an open reading frame encoding a betacoronavirus (BetaCoV) S protein, a 3' UTR, and a poly(A) tail, formulated in a lipid nanoparticle that comprises 20-60% ionizable cationic lipid, 5-25% DSPC, 25-55% cholesterol, and 0.5-15% PEG-DMG, wherein the ionizable cationic lipid has the structure of Compound 25, and wherein at least 80% of the uracil in the open reading frame has a 1-meth-ylpseudouridine modification.

25. The composition of claim **24**, wherein the 5' cap analog is 7mG(5')ppp(5')NlmpNp.

26. A lipid nanoparticle, comprising: a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit; wherein the lipid nanoparticle comprises

20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% cholesterol, and 0.5-15% PEG-modified lipid.

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