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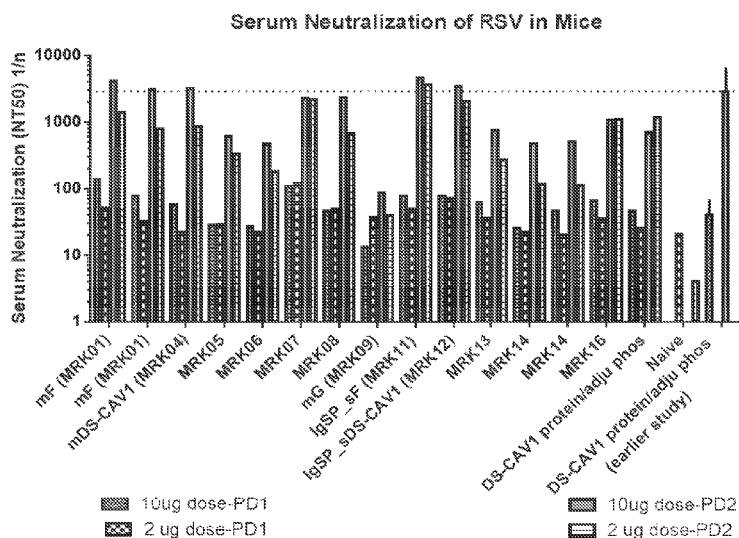
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(54) Title: RESPIRATORY SYNCYTIAL VIRUS VACCINE

Fig. 1



(57) Abstract: The disclosure relates to respiratory syncytial virus (RSV) ribonucleic acid (RNA) vaccines, as well as methods of using the vaccines and compositions comprising the vaccines.



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RESPIRATORY SYNCYTIAL VIRUS VACCINE

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application number 62/245,208, filed October 22, 2015, U.S. provisional application number 62/247,563, filed October 28, 2015, and U.S. provisional application number 62/248,250, filed October 29, 2015, each of which is incorporated by reference herein in its entirety. This application also claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application number 62/245,031, filed October 22, 2015, which is incorporated by reference herein in its entirety.

BACKGROUND

The human respiratory syncytial virus (RSV) 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.

Deoxyribonucleic acid (DNA) vaccination is one technique used to stimulate humoral and cellular immune responses to foreign antigens, such as RSV antigens. The direct injection of genetically engineered DNA (*e.g.*, naked plasmid DNA) into a living host results in a small number of host 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

The RNA vaccines of the present disclosure may be used to induce a balanced immune response against RSV, comprising both cellular and humoral immunity, without risking the possibility of insertional mutagenesis, for example.

5 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 vaccines may be utilized to treat and/or prevent an infection by various genotypes, strains, and isolates of RSV. The RNA vaccines as provided herein have superior properties in that they produce much larger antibody titers and produce responses earlier than commercially-
10 available anti-viral therapeutic treatments. While not wishing to be bound by theory, it is believed that the RNA vaccines of the present disclosure are better designed to produce the appropriate protein conformation upon translation, as the RNA vaccines co-opt natural cellular machinery. Unlike traditional vaccines, which are manufactured *ex vivo* and may trigger unwanted cellular responses, RNA vaccines as provided herein are presented to the
15 cellular system in a more native fashion.

Some embodiments of the present disclosure provide respiratory syncytial virus (RSV) vaccines that include (i) at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide or an immunogenic fragment thereof (*e.g.*, an immunogenic fragment capable of raising an immune response to
20 RSV), and (ii) a pharmaceutically acceptable carrier.

In some embodiments, the at least one RNA polynucleotide has at least one chemical modification.

In some embodiments, an antigenic polypeptide is glycoprotein G or an immunogenic fragment thereof.

25 In some embodiments, an antigenic polypeptide is glycoprotein F or an immunogenic fragment thereof.

In some embodiments, at least one antigenic polypeptide is glycoprotein F and at least one antigenic polypeptide is selected from G, M, N, P, L, SH, M2, NS1 and NS2.

30 In some embodiments, at least one antigenic polypeptide is glycoprotein F and at least two antigenic polypeptides are selected from G, M, N, P, L, SH, M2, NS1 and NS2.

In some embodiments, the RNA vaccines further comprise an adjuvant.

In some embodiments, at least one RNA polynucleotide is encoded by at least one nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259, or homologs having at least 80% identity with a nucleic acid

sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259. In some embodiments, at least one RNA polynucleotide is encoded by at least one nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259, or homologs having at least 90% (*e.g.* 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.8% or 99.9%) identity with a nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259. In some embodiments, at least one RNA polynucleotide is encoded by at least one fragment of a nucleic acid sequence (*e.g.*, a fragment having at least one antigenic sequence or at least one epitope) set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259.

In some embodiments, at least one RNA polynucleotide comprises at least one nucleic acid sequence set forth as any of SEQ ID NO: 260-280, or homologs having at least 80% identity with a nucleic acid sequence set forth as any of SEQ ID NO: 260-280. In some embodiments, at least one RNA polynucleotide comprises at least one nucleic acid sequence set forth as any of SEQ ID NO: 260-280, or homologs having at least 90% (*e.g.* 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.8% or 99.9%) identity with a nucleic acid sequence set forth as any of SEQ ID NO: 260-280. In some embodiments, at least one RNA polynucleotide comprises at least one fragment of a nucleic acid sequence (*e.g.*, a fragment having at least one antigenic sequence or at least one epitope) set forth as any of SEQ ID NO: 260-280.

In some embodiments, the amino acid sequence of the RSV antigenic polypeptide is, or is a fragment of, or is a homolog having at least 80% (*e.g.*, 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence set forth as SEQ ID NO: 3 or SEQ ID NO: 4.

In some embodiments, the amino acid sequence of the RSV antigenic polypeptide is, or is a fragment of, or is a homolog having at least 80% (*e.g.*, 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence set forth as SEQ ID NO: 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 243, or 245.

In some embodiments, at least one RNA (*e.g.*, mRNA) polynucleotide encodes an antigenic polypeptide having at least 90% identity to an amino acid sequence of the present disclosure and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having at least 95% identity to an amino acid sequence of the present disclosure and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having at least 96% identity to an amino acid sequence of the present disclosure and having membrane

fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having at least 97% identity to an amino acid sequence of the present disclosure and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having at least 98% identity to an amino acid sequence of the present disclosure and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having at least 99% identity to an amino acid sequence of the present disclosure and having membrane fusion activity. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having 95-99% identity to an amino acid sequence of the present disclosure and having membrane fusion activity.

In some embodiments, at least one RNA (*e.g.*, mRNA) polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and is codon optimized mRNA.

In some embodiments, at least one RNA (*e.g.*, mRNA) polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and has less than 80% identity to (corresponding) wild-type mRNA sequence. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and has less than 75%, 85% or 95% identity to wild-type mRNA sequence. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and has 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and has 30-85%, 40-85%, 50-85%, 60-85%, 70-85%, 75-85%, or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one RNA polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and has 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 (*e.g.*, mRNA) polynucleotide is encoded by a nucleic acid (*e.g.*, DNA) having at least 90% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having at least 95% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having at least 96% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having at least

97% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having at least 98% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having at least 99% identity to a nucleic acid sequence of the present disclosure. In some embodiments, at least one RNA polynucleotide is encoded by a nucleic acid having 95-99% identity to a nucleic acid sequence of the present disclosure.

In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence of the present disclosure and has 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 of the present disclosure and has 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 of the present disclosure and has less than 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 75-80% or 78-80% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence of the present disclosure and has less than 30-85%, 40-85%, 50-85%, 60-85%, 70-85%, 75-85% or 80-85% identity to wild-type mRNA sequence. In some embodiments, at least one mRNA polynucleotide is encoded by a nucleic acid having a sequence of the present disclosure and has less than 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 (*e.g.*, mRNA) polynucleotide encodes an antigenic polypeptide having an amino acid sequence of the present disclosure and having at least 80% identity to wild-type mRNA sequence, but does not include wild-type mRNA sequence.

In some embodiments, the RSV vaccine includes at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide, said RNA polynucleotide having at least one chemical modification.

In some embodiments, the RSV vaccine includes at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide, said RNA polynucleotide having at least one chemical modification and at least one 5' terminal cap, wherein the RSV vaccine is formulated within a lipid nanoparticle.

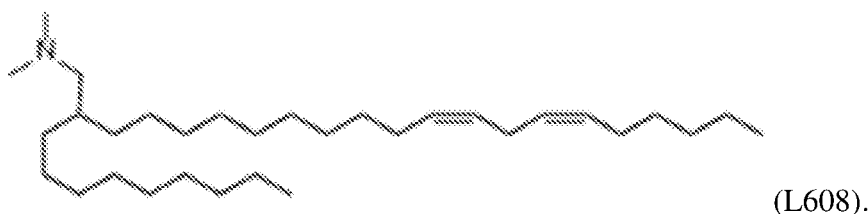
In some embodiments, a 5' terminal cap is 7mG(5')ppp(5')NlmpNp.

In some embodiments, at least one chemical modification is selected from the group consisting of pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine,

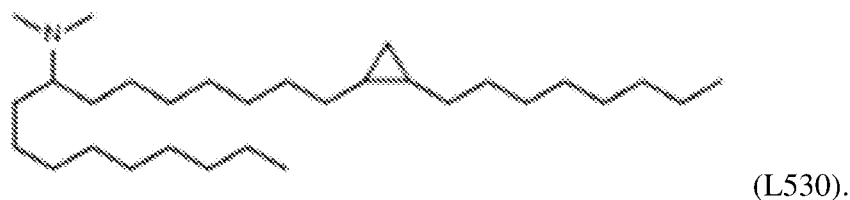
4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methoxyuridine and 2'-O-methyl uridine.

In some embodiments, a lipid nanoparticle comprises a cationic lipid, a PEG-modified lipid, a sterol and a non-cationic lipid. In some embodiments, a 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, 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-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530).

In some embodiments, the lipid is



In some embodiments, the lipid is



Some embodiments of the present disclosure provide a respiratory syncytial virus (RSV) vaccine that includes at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide, wherein at least 80% of the uracil in the open reading frame have a chemical modification, optionally wherein the RSV vaccine is formulated in a lipid nanoparticle.

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, a chemical modification is a N1-methyl pseudouridine in the 5-position

of the uracil. In some embodiments, 100% of the uracil in the open reading frame are modified to include N1-methyl pseudouridine.

Some embodiments of the present disclosure provide methods of inducing an antigen specific immune response in a subject, comprising administering to the subject a RSV RNA
5 (e.g., mRNA) vaccine in an amount effective to produce an antigen specific immune response.

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

In some embodiments, a method of producing an antigen specific immune response
10 involves a single administration of the RSV RNA (e.g., mRNA) vaccine. In some embodiments, a method further includes administering to the subject a booster dose of the RSV RNA (e.g., mRNA) vaccine. A booster vaccine according to this invention may comprise any RSV RNA (e.g., mRNA) vaccine disclosed herein and may be the same as the RSV RNA vaccine initially administered. In some embodiments, the same RSV RNA
15 vaccine is administered annually for every RSV season.

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

Also provided herein are RSV RNA (e.g., mRNA) vaccines for use in a method of
20 inducing an antigen specific immune response in a subject, the method comprising administering the RSV vaccine to the subject in an amount effective to produce an antigen specific immune response.

Further provided herein are uses of RSV RNA (e.g., mRNA) vaccines in the manufacture of a medicament for use in a method of inducing an antigen specific immune
25 response in a subject, the method comprising administering the RSV vaccine to the subject in an amount effective to produce an antigen specific immune response.

Some aspects of the present disclosure provide RSV RNA (e.g., mRNA) vaccines formulated in an effective amount to produce an antigen specific immune response in a subject.

30 Other aspects of the present disclosure provide methods of inducing an antigen specific immune response in a subject, the method comprising administering to a subject the RSV RNA (e.g., mRNA) vaccine described herein in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, an anti-RSV antigenic polypeptide antibody titer produced in the subject is increased by at least 1 log relative to a control (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control (*e.g.*, a control vaccine).

5 In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased at least 2 times relative to a control (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased at least 5 times relative to a control (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased at least
10 10 times relative to a control (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased 2-10 times relative to a control (*e.g.*, a control vaccine).

In some embodiments, the control is an anti-RSV antigenic polypeptide antibody titer produced in a subject who has not been administered RSV vaccine. In some embodiments,
15 the control is an anti-RSV antigenic polypeptide antibody titer produced in a subject who has been administered a live attenuated or inactivated RSV vaccine. In some embodiments, the control is an anti-RSV antigenic polypeptide antibody titer produced in a subject who has been administered a recombinant or purified RSV protein vaccine. In some embodiments, the control is an anti-RSV antigenic polypeptide antibody titer produced in a subject who has
20 been administered an RSV virus-like particle (VLP) vaccine.

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

In some embodiments, the effective amount is a dose equivalent to at least a 4-fold reduction in the standard of care dose of a recombinant RSV protein vaccine, wherein an anti-RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard
30 of care dose of a recombinant or purified RSV protein vaccine, a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine.

In some embodiments, the effective amount is a dose equivalent to at least a 10-fold reduction in the standard of care dose of a recombinant RSV protein vaccine, wherein an anti-

RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified RSV protein vaccine, a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine.

5 In some embodiments, the effective amount is a dose equivalent to at least a 100-fold reduction in the standard of care dose of a recombinant RSV protein vaccine, wherein an anti-RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified RSV protein vaccine, a live attenuated or
10 inactivated RSV vaccine, or a RSV VLP vaccine.

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

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

In some embodiments, the effective amount is a total dose of 25 μ g to 1000 μ g, or 50 μ g to 1000 μ g, or 25 to 200 μ g. In some embodiments, the effective amount is a total dose of
25 50 μ g, 100 μ g, 200 μ g, 400 μ g, 800 μ g, or 1000 μ g. In some embodiments, the effective amount is a dose of 25 μ g administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 50 μ g administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 μ g administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 200
30 μ g administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 μ g administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 μ g administered to the subject a total of two times.

In some embodiments, the effective amount administered to a subject is a total dose (of RSV RNA, *e.g.*, mRNA, vaccine) of 50 µg to 1000 µg.

In some embodiments, the efficacy (or effectiveness) of the RSV RNA (*e.g.*, mRNA) vaccine against RSV is greater than 60%.

5 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
10 among the vaccinated group with use of the following formulas:

Efficacy = (ARU – ARV)/ARU x 100; and

Efficacy = (1-RR) x 100.

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
15 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
20 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 rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

25 Effectiveness = (1 – OR) x 100.

In some embodiments, the efficacy (or effectiveness) of the RSV RNA (*e.g.*, mRNA) vaccine against RSV is greater than 65%. In some embodiments, the efficacy (or effectiveness) of the vaccine against RSV is greater than 70%. In some embodiments, the efficacy (or effectiveness) of the vaccine against RSV is greater than 75%. In some
30 embodiments, the efficacy (or effectiveness) of the vaccine against RSV is greater than 80%. In some embodiments, the efficacy (or effectiveness) of the vaccine against RSV is greater than 85%. In some embodiments, the efficacy (or effectiveness) of the vaccine against RSV is greater than 90%.

In some embodiments, the vaccine immunizes the subject against RSV up to 1 year (*e.g.* for a single RSV season). In some embodiments, the vaccine immunizes the subject against RSV for up to 2 years. In some embodiments, the vaccine immunizes the subject against RSV for more than 2 years. In some embodiments, the vaccine immunizes the subject against RSV for more than 3 years. In some embodiments, the vaccine immunizes the subject against RSV for more than 4 years. In some embodiments, the vaccine immunizes the subject against RSV for 5-10 years.

In some embodiments, the subject administered an RSV RNA (*e.g.*, mRNA) vaccine is about 5 years old or younger, is between the ages of about 1 year and about 5 years (*e.g.*, about 1, 2, 3, 4, 5 or 6 years), is between the ages of about 6 months and about 1 year (*e.g.*, about 6, 7, 8, 9, 10, 11 or 12 months), is about 6 months or younger, or 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 was born full term (*e.g.*, about 37-42 weeks). In some embodiments, the subject was born prematurely 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), the subject was born prematurely at about 32 weeks of gestation or earlier, or the subject was born prematurely between about 32 weeks and about 36 weeks of gestation.

In some embodiments, the subject is pregnant (*e.g.*, in the first, second or third trimester) when administered an RSV RNA (*e.g.*, mRNA) vaccine. RSV causes infections of the lower respiratory tract, mainly in infants and young children. One-third of RSV related deaths 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 RSV vaccines for maternal immunization to improve mother-to-child transmission of protection against RSV.

In some embodiments, the subject 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 RSV RNA (*e.g.*, mRNA) vaccine may have chronic bronchitis or emphysema.

In some embodiments, the subject has been exposed to RSV, is infected with (has) RSV, or is at risk of infection by RSV.

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 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 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).

5 Some aspects of the present disclosure provide Respiratory Syncytial Virus (RSV) RNA (*e.g.*, mRNA) vaccines containing a signal peptide linked to a RSV antigenic polypeptide. Thus, in some embodiments, the RSV RNA (*e.g.*, mRNA) vaccines contain at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding a signal peptide linked to a RSV antigenic peptide. Also provided herein are nucleic acids
10 encoding the RSV RNA (*e.g.*, mRNA) vaccines disclosed herein.

 In some embodiments, the RSV antigenic peptide is RSV attachment protein (G) or an immunogenic fragment thereof. In some embodiments, the RSV antigenic peptide is RSV Fusion (F) glycoprotein or an immunogenic fragment thereof. In some embodiments, the RSV antigenic peptide is nucleoprotein (N) or an immunogenic fragment thereof. In some
15 embodiments, the RSV antigenic peptide is phosphoprotein (P) or an immunogenic fragment thereof. In some embodiments, the RSV antigenic peptide is large polymerase protein (L) or an immunogenic fragment thereof. In some embodiments, the RSV antigenic peptide is matrix protein (M) or an immunogenic fragment thereof. In some
20 embodiments, the RSV antigenic peptide is nonstructural protein1(NS1) or an immunogenic fragment thereof. In some embodiments, the RSV antigenic peptide is nonstructural protein 2 (NS2) or an immunogenic fragment thereof.

 In some embodiments, the signal peptide is a IgE signal peptide. In some
embodiments, the signal peptide is an IgE HC (Ig heavy chain epsilon-1) signal peptide. In
25 some embodiments, the signal peptide has the sequence MDWTWILFLVAAATRVHS (SEQ ID NO: 281). In some embodiments, the signal peptide is an IgGκ signal peptide. In some
embodiments, the signal peptide has the sequence METPAQLLFLLLLWLPDTTG (SEQ ID NO: 282). In some embodiments, the signal peptide is encoded by sequence
TGGAGACTCCCGCTCAGCTGCTGTTTTTGCTCCTCCTATGGCTGCCGGATACCACC
30 GGC (SEQ ID NO: 287) or AUGGAGACUCCCGCUCAGCUGCUGUUUUUGCUCCU
CCUAUGGCUGCCGGAUACCACCGGC (SEQ ID NO: 288). In some embodiments, the
signal peptide is selected from: a Japanese encephalitis PRM signal sequence
(MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 283), VSVg protein signal sequence
(MKCLLYLAFLFIGVNCA; SEQ ID NO: 284) and Japanese encephalitis JEV signal sequence

(MWLVSLAIVTACAGA; SEQ ID NO: 285). In some embodiments, the signal peptide is MELLILKANAITTILTAVTFC (SEQ ID NO: 289).

Also provided herein are respiratory syncytial virus (RSV) vaccines, comprising at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding membrane-bound RSV F protein, membrane-bound DS-Cav1 (stabilized prefusion of RSV F protein), or a combination of membrane-bound RSV F protein and membrane-bound DS-Cav1, and a pharmaceutically acceptable carrier.

In some embodiments, a RNA polynucleotide comprises the sequence of SEQ ID NO: 5 and/or the sequence of SEQ ID NO: 7.

In some embodiments, an effective amount of an RSV RNA (*e.g.*, mRNA) vaccine (*e.g.*, a single dose of the RSV vaccine) results in a 2 fold to 200 fold (*e.g.*, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 fold) increase in serum neutralizing antibodies against RSV, relative to a control (*e.g.*, a control vaccine). In some embodiments, a single dose of the RSV RNA (*e.g.*, mRNA) vaccine results in an about 5 fold, 50 fold, or 150 fold increase in serum neutralizing antibodies against RSV, relative to a control (*e.g.*, a control vaccine). In some embodiments, a single dose of the RSV RNA (*e.g.*, mRNA) vaccine results in an about 2 fold to 10 fold, or an about 40 to 60 fold increase in serum neutralizing antibodies against RSV, relative to a control (*e.g.*, a control vaccine).

In some embodiments, the serum neutralizing antibodies are against RSV A and/or RSV B.

In some embodiments, the RSV vaccine is formulated in a MC3 lipid nanoparticle (*see, e.g.*, U.S. Publication No. 2013/0245107 A1 and International Publication No. WO 2010/054401).

Also provided herein are methods of inducing an antigen specific immune response in a subject, the method comprising administering to a subject the RSV RNA (*e.g.*, mRNA) vaccine comprising at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding membrane-bound RSV F protein, membrane-bound DS-Cav1 (stabilized prefusion of RSV F protein), or a combination of membrane-bound RSV F protein and membrane-bound DS-Cav1, and a pharmaceutically acceptable carrier, in an effective amount to produce an antigen specific immune response in a subject.

In some embodiments, the methods further comprise administering a booster dose of the RSV RNA (*e.g.*, mRNA) vaccine. In some embodiments, the methods further comprise administering a second booster dose of the RSV vaccine.

In some embodiments, efficacy of RNA vaccines RNA (*e.g.*, mRNA) 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-
5 encoded flagellin adjuvant) have superior properties in that they may produce much larger antibody titers and produce responses earlier than commercially available vaccine formulations. While not wishing to be bound by theory, it is believed that the RNA 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
10 (*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
15 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
20 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
25 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 of SEQ ID NO: 173-175.

In some embodiments the nucleic acid vaccines described herein are chemically
30 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 element, 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 ug/kg and 400 ug/kg of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 μ g, 5-10 μ g, 10-15 μ g, 15-20 μ g, 10-25 μ g, 20-25 μ g, 20-50 μ g, 30-50 μ g, 40-50 μ g, 40-60 μ g, 60-80 μ g, 60-100 μ g, 50-100 μ g, 80-120 μ g, 40-120 μ g, 40-150 μ g, 50-150 μ g, 50-200 μ g, 80-200 μ g, 100-200 μ g, 120-250 μ g, 150-250 μ g, 180-280 μ g, 200-300 μ g, 50-300 μ g, 80-300 μ g, 100-300 μ g, 40-300 μ g, 50-350 μ g, 100-350 μ g, 200-350 μ g, 300-350 μ g, 320-400 μ g, 40-380 μ g, 40-100 μ g, 100-400 μ g, 200-400 μ g, or 300-400 μ g 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 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 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. 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 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 a histone stem-loop. In some embodiments, the stabilization element is a nucleic acid sequence having increased GC content relative to wild type sequence.

5 Aspects of the invention provide nucleic acid vaccines comprising one or more RNA polynucleotides having an 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 subjects. In some embodiments, the antibody titer
10 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 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-
15 10,000, 1,400- 10,000, 1,500- 10,000, 1,000- 5,000, 1,000- 4,000, 1,800- 10,000, 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 or more RNA
20 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 having a stabilizing element or formulated with an adjuvant and encoding the first antigenic polypeptide. In some embodiments, the RNA polynucleotide is formulated to
25 produce a neutralizing antibodies within one week of a single administration. In some embodiments, the adjuvant is 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 comprising at least one chemical modification or optionally no
30 nucleotide modification, the open reading frame encoding 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 10ug 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 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 the invention. Both chemically modified and unmodified RNA vaccines are useful in 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 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 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 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 treating a young subject age 17 years or younger 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 other aspects the invention encompasses a method of 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 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 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
5 embodiments, the combined dosage is 75 micrograms of the RNA polynucleotide in the 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 nucleic acid vaccine administered to the subject. In some
10 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 modified and in other embodiments the nucleic acid vaccine is not chemically modified.

In some embodiments, the RNA polynucleotide is one of SEQ ID NO: 1, 2, 5, 7, 9,
15 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259 and includes at least one chemical modification. In other embodiments, the RNA polynucleotide is one of SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259 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: 3, 4, 6, 8, 10,
20 12, 14, 16, 18, 20, 22, 24, 26, 28, 243, or 245 and includes at least one chemical modification. In other embodiments, the RNA polynucleotide encodes an antigenic protein of any of SEQ ID NO: 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 243, or 245 and does not include any nucleotide modifications, or is unmodified.

The details of various embodiments of the invention are set forth in the description
25 below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages will be apparent from the
30 following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the 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 invention.

Fig. 1 shows data from an immunogenicity study in mice, designed to evaluate the immune response to RSV vaccine antigens delivered using various mRNA vaccines formulated with MC3 LNP in comparison to protein antigens. The data demonstrated strong neutralizing antibody titers.

Fig. 2 shows that that RNA/LNP vaccines gave much higher cellular immune responses than the protein antigen.

Figs. 3A-3C show data from an intracellular cytokine staining assay to test immunogenicity in mice, demonstrating that RSV-F mRNA/NLP vaccines and RSV-G mRNA/LNP vaccines, but not DS-CAV1 protein antigens, elicit robust Th1 biased CD4+ immune responses in mice.

Figs. 4A-4C show data from an intracellular cytokine staining assay to test immunogenicity in mice, demonstrating that RSV-F mRNA/NLP vaccines and RSV-G mRNA/LNP vaccines, but not DS-CAV1 protein antigens, elicit robust Th1 biased CD8+ immune responses in mice.

Fig. 5 shows data from an immunogenicity study in mice, demonstrating strong neutralizing antibody titers equivalent to those achieved with a protein antigen adjuvanted with ADJU-PHOS®.

Figs. 6A-6C show data from an intracellular cytokine staining assay to test immunogenicity in mice, demonstrating that RSV-F mRNA/LNP vaccines and RSV-G mRNA/LNP vaccines, but not DS-CAV1 protein antigens, elicit robust Th1 biased CD4+ immune responses in mice.

Figs. 7A-7C show data from an intracellular cytokine staining assay to test immunogenicity in mice, confirming that RSV-F mRNA/LNP vaccines, but not RSV-G mRNA/LNP vaccines or DS-CAV1 protein antigens, elicit robust TH1 biased CD8+ immune responses in mice.

Fig. 8 shows data from an assay, demonstrating that no virus was recovered from lungs of any of mice immunized with RSV mRNA vaccines formulated with MC3 LNP, and only one animal at the lower dose of DS-CAV1 protein /ADJU-PHOS® vaccine had any virus detectable in the nose.

Fig. 9 shows data from an immunogenicity study in cotton rats, demonstrating strong neutralizing antibody titers in animals immunized with various RSV mRNA vaccines formulated with MC3 LNP.

Fig. 10 shows data from a cotton rat competition ELISA, characterizing the antigenic Ø and antigenic site II response to various RSV mRNA vaccines.

Fig. 11 shows data from a cotton rat challenge assay, demonstrating protective effects of RSV mRNA vaccines formulated with MC3 LNP.

Fig. 12 shows a graph representative of serum neutralizing antibody titers (NT50 individual and GMT with 95% confidence intervals) to RSV A induced in African Green Monkeys by RSV mRNA vaccines and control formulations.

Figs. 13A-13B show graphs representative of serum antibody competition ELISA titers (IT50 individual and GMT with 95% confidence intervals) against palivizumab (site II) (Fig. 13A) and D25 (site Ø) (Fig. 13B) measured at week 10 (2 weeks PD3).

Figs. 14A-14B show graphs representative of mean lung viremia detected post challenge (Fig. 13A) and mean nasal viremia detected post challenge (Fig. 13B) in African Green Monkeys with 95% confidence intervals.

Fig. 15 shows a graph representative of serum neutralizing antibody titers (NT50 individual and GMT with 95% confidence intervals) to RSV A induced in RSV-experienced African Green Monkeys by various RSV mRNA vaccine and control formulations at 2 weeks post vaccination.

Fig. 16 shows a graph representative of serum neutralizing antibody titers (GMT with 95% confidence intervals) to RSV A induced in RSV-experienced African Green Monkeys by various RSV mRNA vaccine and control formulations.

Figs. 17A-17B show graphs representative of serum antibody competition ELISA titers (IT50 individual and GMT with 95% confidence intervals) against palivizumab (site II) (Fig. 17A) and D25 (site Ø) (Fig. 17B) measured at baseline and 4 weeks post immunization.

Figs. 18A-18B show graphs representative of RSV F-specific CD4+ (Fig. 18A) and CD8+ (Fig. 18B) T cell responses induced in RSV experienced African Green Monkeys by various vaccine and control formulations.

Fig. 19 shows a graph representative of serum neutralizing antibody titers (NT50 individual and GMT with 95% confidence intervals) to RSV A and RSV B induced in cotton rats at weeks 4 (4 weeks post dose 1 against RSV A (circle) and RSV B (square)) and 8 (4 weeks post dose 2 against RSV A (triangle pointing up) and RSV B (triangle pointing down)) by various vaccine and control formulations.

Fig. 20 shows a graph representative of mean lung (circles) and nose (squares) viral copies with 95% confidence intervals measured in cotton rats post challenge with RSV B 18357.

DETAILED DESCRIPTION

Embodiments of the present disclosure provide RNA (*e.g.*, mRNA) vaccines that include a (at least one) polynucleotide encoding a respiratory syncytial virus (RSV) antigen. 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 formation 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 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.

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 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 glycosaminoglycans to mediate fusion and delivery of the RSV virion contents into the host cell (Krzyzaniak MA *et al. PLoS Pathog* 2013;9(4)).

RSV RNA (*e.g.*, mRNA) vaccines, as provided herein, 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 content of International Application No. PCT/US2015/02740 is incorporated herein by reference.

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. Various mRNA vaccines formulated with MC3 LNP were compared in mice to protein antigen vaccination. The data demonstrated that in comparison to existing vaccines, the mRNA vaccines produced stronger neutralizing

antibody titers, much higher cellular immune responses than the protein antigen, elicited robust Th1 biased CD4+ and CD8+ immune responses in mice and reduction in virus in the lungs. No virus was recovered from lungs of any of mice immunized with RSV mRNA vaccines formulated with MC3 LNP, in contrast to only one animal at the lower dose of protein/adjuvant vaccine formulation. Significant neutralizing antibody titers were also achieved in rats and monkeys.

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, 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 compromised 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

RSV vaccines, as provided herein, comprise at least one (one or more) ribonucleic acid (RNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide. The term “nucleic acid,” in its broadest sense, includes any compound and/or substance that comprises a polymer of nucleotides. These polymers are referred to as polynucleotides.

In some embodiments, at least one RNA polynucleotide is encoded by at least one nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259, or homologs having at least 80% identity with a nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259. In some embodiments, at least one RNA polynucleotide is encoded by at least one nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259, or homologs having at least 90% (*e.g.* 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.8% or 99.9%) identity with a nucleic acid sequence set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 242, 246, 257, 258, or 259. In some embodiments, at least one RNA polynucleotide is encoded by at least one fragment of a nucleic acid sequence (*e.g.*, a fragment having at least one antigenic sequence or at least one epitope) set forth as SEQ ID NO: 1, 2, 5, 7, 9, 11, 13, 15, 17, 19, 21,

23, 25, 27, 242, 246, 257, 258, or 259. In some embodiments, the at least one RNA polynucleotide has at least one chemical modification. In some embodiments, the at least one RNA polynucleotide is an mRNA polynucleotide, wherein each uracil (100% of the uracils) of the mRNA polynucleotide is chemically modified. In some embodiments, the at least one
5 RNA polynucleotide is an mRNA polynucleotide, wherein each uracil (100% of the uracils) of the mRNA polynucleotide is chemically modified to include a N1-methyl pseudouridine.

In some embodiments, the amino acid sequence of the RSV antigenic polypeptide is, or is a (antigenic) fragment of, or is a homolog having at least 80% (*e.g.*, 85%, 90%, 95%, 98%, 99%) identity to, the amino acid sequence set forth as SEQ ID NO: 3, 4, 6, 8, 10, 12,
10 14, 16, 18, 20, 22, 24, 26, 28, 243, or 245.

Nucleic acids (also referred to as polynucleotides) may be or may include, for example, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), 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
15 configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 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). "Messenger RNA" (mRNA) refers to any polynucleotide that
20 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 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
25 "T"s would be substituted for "U"s. Thus, any of the RNA polynucleotides 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
30 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 (*e.g.*, mRNA) of a RSV 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 polynucleotide (*e.g.*, mRNA) of a RSV RNA (*e.g.*, mRNA) vaccine encodes at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 antigenic polypeptides. In some embodiments, a RNA polynucleotide (*e.g.*, mRNA) of a RSV vaccine encodes at least 100 antigenic polypeptides, or at least 200 antigenic polypeptides. In some embodiments, a RNA polynucleotide (*e.g.*, mRNA) of a RSV vaccine encodes 1-10, 5-15, 10-20, 15-25, 20-30, 25-35, 30-40, 35-45, 40-50, 1-50, 1-100, 2-50 or 2-100 antigenic polypeptides.

Polynucleotides (*e.g.*, mRNAs) 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 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 CA) 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 to a naturally-occurring 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 sequence shares less than 90% sequence identity to a naturally-occurring 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 sequence shares less than 85% sequence identity to a naturally-occurring 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 sequence shares less than 80% sequence identity to a naturally-occurring 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 sequence shares less than 75% sequence identity to a naturally-occurring 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 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 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 sequence shares between 65% and 75% or about 80% sequence identity to a naturally-occurring 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, the RSV vaccine includes at least one RNA polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide having at least one modification, at least one 5' terminal cap, and is formulated within a lipid nanoparticle. 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 protocols: 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, MA). 5'-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). 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-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'-preantepenultimate nucleotide using a 2'-O methyl-transferase. Enzymes may be derived from a recombinant source.

When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours, or greater than 18 hours, *e.g.*, 24, 36, 48, 60, 72, or greater than 72 hours.

In some embodiments a codon optimized RNA may be one in which the levels of G/C are enhanced. The G/C-content of nucleic acid molecules (*e.g.*, mRNA) 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 RNA containing a large amount of adenine (A) and thymine (T) or uracil (U) nucleotides. As an example, 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 RNA stability without changing the resulting amino acid. The approach is limited to coding regions of the RNA.

Antigens/Antigenic Polypeptides

At least two antigenic subgroups (A and B) of RSV are known to exist. This antigenic dimorphism is due primarily to difference in the surface G glycoproteins. Two surface glycoproteins, G and F, are present in the envelope and mediate attachment and fusion with cells of the respiratory epithelium. The F proteins also mediate coalescence of neighboring cells to form the characteristic syncytial cells for which the virus receives its name. The epidemiologic and biologic significance of the two antigenic variants of RSV is uncertain. Nonetheless, there is some evidence to suggest that Group A infections tend to be more severe.

The RSV genome is ~15,000 nucleotides in length and is composed of a single strand of RNA with negative polarity. It has 10 genes encoding 11 proteins—there are 2 open reading frames of M2. The genome is transcribed sequentially from NS1 to L with reduction in expression levels along its length.

NS1 and NS2 inhibit type I interferon activity. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding products of NS1, NS2, or an immunogenic fragment thereof.

N encodes nucleocapsid protein that associates with the genomic RNA forming the nucleocapsid. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding nucleocapsid protein or an immunogenic fragment thereof.

M encodes the Matrix protein required for viral assembly. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding Matrix protein or an immunogenic fragment thereof.

SH, G and F form the viral coat. The G protein is a surface protein that is heavily glycosylated and functions as the attachment protein. The F protein is another important surface protein that mediates fusion, allowing entry of the virus into the cell cytoplasm and also allowing the formation of syncytia. The F protein is homologous in both subtypes of RSV; antibodies directed at the F protein are neutralizing. In contrast, the G protein differs considerably between the two subtypes. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding SH, G or F protein, or a combination thereof, or an immunogenic fragment thereof.

Nucleolin at the cell surface is the receptor for the RSV fusion protein. Interference with the nucleolin-RSV fusion protein interaction has been shown to be therapeutic against RSV infection in cell cultures and animal models. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding nucleolin or an immunogenic fragment thereof.

M2 is the second matrix protein also required for transcription and encodes M2-1 (elongation factor) and M2-2 (transcription regulation). M2 contains CD8 epitopes. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding the second matrix protein or an immunogenic fragment thereof.

L encodes the RNA polymerase. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding the RNA polymerase (L) or an immunogenic fragment thereof.

The phosphoprotein P is a cofactor for the L protein. In some embodiments, a RSV vaccine comprises at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding phosphoprotein P or an immunogenic fragment thereof.

Some embodiments of the present disclosure provide RSV vaccines that include at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding glycoprotein G or an immunogenic fragment thereof (*e.g.*, an immunogenic fragment capable of raising an immune response to RSV).

Some embodiments of the present disclosure provide RSV vaccines that include at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding glycoprotein F or an immunogenic fragment thereof (*e.g.*, an immunogenic fragment capable of raising an immune response to RSV).

Some embodiments of the present invention disclose RSV vaccines that include at least one RNA (*e.g.* mRNA) polynucleotide having an open reading frame encoding a

polypeptide or an immunogenic fragment thereof in the post-fusion form. Further embodiments of the present invention disclose RSV vaccines that include at least one RNA (*e.g.* mRNA) polynucleotide having an open reading frame encoding a polypeptide or an immunogenic fragment thereof in the pre-fusion form. In some embodiments, the

5 polypeptides or antigenic fragments thereof comprise glycoproteins in a prefusion conformation, for example, but not limited to, prefusion glycoprotein F or DS-CAV1.

Without wishing to be bound by theory, certain polypeptides or antigenic fragments thereof, when in a prefusion conformation, may contain more epitopes for neutralizing antibodies relative to the postfusion conformation of the same proteins or immunogenic fragments

10 thereof. For example, prefusion glycoprotein F or an immunogenic fragment thereof has a unique antigen site ("antigenic site 0") at its membrane distal apex. Antigenic site 0 may, but not necessarily, comprise residues 62-69 and 196-209 of a RSV F protein sequence. In some instances, such as, but not limited to, prefusion glycoprotein F or immunogenic fragments thereof, prefusion polypeptides or immunogenic fragments thereof may exhibit many fold
15 greater immune responses than those achieved with post-fusion polypeptides or immunogenic fragments thereof. Prefusion RSV glycoproteins and their methods of use are described in WO/2014/160463, incorporated by reference herein its entirety.

In some embodiments, RSV vaccines include at least one RNA (*e.g.*, mRNA) polynucleotide having an open reading frame encoding glycoprotein F or glycoprotein G or
20 an immunogenic fragment thereof obtained from RSV strain A2 (RSV A2). Other RSV strains are encompassed by the present disclosure, including subtype A strains and subtype B strains.

In some embodiments, a RSV vaccine has at least one RNA (*e.g.*, mRNA) having at least one modification, including but not limited to at least one chemical modification.

25 In some embodiments, a RSV antigenic polypeptide is longer than 25 amino acids and shorter than 50 amino acids. Thus, 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 single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. Polypeptides may
30 also comprise single chain or multichain polypeptides such as antibodies or insulin and may be associated or linked. Most commonly, disulfide linkages are 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.

The term “polypeptide variant” refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants possess at least 50% identity to a native or reference sequence. In some embodiments, variants share at least 80%, or at least 90% identity with a native or reference sequence.

In some embodiments “variant mimics” are provided. As used herein, 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 phosphoro-serine. Alternatively, variant mimics may result in deactivation 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.

“Orthologs” refers to genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is critical for reliable prediction of gene function in newly sequenced genomes.

“Analog” 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.

“Paralogs” are genes (or proteins) related by duplication within a genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.

The present disclosure provides several types of compositions that are polynucleotide or polypeptide based, including variants and derivatives. These include, for example, substitutional, insertional, deletion and covalent variants and derivatives. The term “derivative” is used synonymously with the term “variant,” but generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or 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 or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support. In alternative embodiments, sequences for (or encoding) signal sequences, termination sequences, transmembrane domains, linkers, multimerization domains (such as, *e.g.*, foldon regions) and the like may be substituted with alternative sequences that achieve the same or a similar function. Such sequences are readily identifiable to one of skill in the art. It should also be understood that some of the sequences provided herein contain sequence tags or terminal peptide sequences (*e.g.*, at the N-terminal or C-terminal ends) that may be deleted, for example, prior to use in the preparation of an RNA (*e.g.*, mRNA) vaccine.

“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 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 non-conservative substitutions include the substitution of a non-polar (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 polynucleotide 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, termini or any combination 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 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 polynucleotide that may be modified, manipulated, altered, derivatized or varied within the polypeptide or polynucleotide based molecules.

As used herein, the terms “termini” or “terminus,” when referring to polypeptides or polynucleotides, refers to an 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 having 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 forces (multimers, oligomers). These proteins have multiple N-termini 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 acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or greater than 100 amino acids in length. In another example, any protein that includes a stretch of 20, 30, 40, 50, or 100 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 present 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 provided or referenced herein. In some

embodiments, a protein fragment is longer than 25 amino acids and shorter than 50 amino acids.

Polypeptide or polynucleotide molecules of the present disclosure may share a certain degree of sequence similarity 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 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 them as determined by the number of matches between strings of two or more amino acid residues 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 calculated by known methods. “% identity” as it applies to polypeptide or polynucleotide sequences is defined as the 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. It is understood that 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) has been 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
5 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
10 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”
15 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
20 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.

25 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 sequence by descent from a common ancestral sequence. The term “homolog” may apply to the relationship between genes and/or proteins separated by the
30 event of speciation or to the relationship between genes and/or proteins separated by the event of genetic duplication.

Multiprotein and Multicomponent Vaccines

The present disclosure encompasses RSV vaccines comprising multiple RNA (*e.g.*, mRNA) polynucleotides, each encoding a single antigenic polypeptide, as well as RSV vaccines comprising a single RNA polynucleotide encoding more than one antigenic polypeptide (*e.g.*, as a fusion polypeptide). Thus, it should be understood that a vaccine composition comprising a RNA polynucleotide having an open reading frame encoding a first RSV antigenic polypeptide and a RNA polynucleotide having an open reading frame encoding a second RSV antigenic polypeptide encompasses (a) vaccines that comprise a first RNA polynucleotide encoding a first RSV antigenic polypeptide and a second RNA polynucleotide encoding a second RSV antigenic polypeptide, and (b) vaccines that comprise a single RNA polynucleotide encoding a first and second RSV antigenic polypeptide (*e.g.*, as a fusion polypeptide). RSV RNA 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 RSV antigenic polypeptide (or a single RNA polynucleotide encoding 2-10, or more, different RSV antigenic polypeptides). In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV Fusion (F) glycoprotein, a RNA polynucleotide having an open reading frame encoding a RSV attachment (G) protein, a RNA polynucleotide having an open reading frame encoding a RSV nucleoprotein (N), a RNA polynucleotide having an open reading frame encoding a RSV phosphoprotein (P), a RNA polynucleotide having an open reading frame encoding a RSV large polymerase protein (L), a RNA polynucleotide having an open reading frame encoding a RSV matrix protein (M), a RNA polynucleotide having an open reading frame encoding a RSV small hydrophobic protein (SH), a RNA polynucleotide having an open reading frame encoding a RSV nonstructural protein 1 (NS1), and a RNA polynucleotide having an open reading frame encoding a RSV nonstructure protein 2 (NS2). In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV fusion (F) protein and a RNA polynucleotide having an open reading frame encoding a RSV attachment protein (G). In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV F protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV N protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV M protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV L protein.

In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV P protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV SH protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV NS1 protein. In some embodiments, a RSV RNA vaccine comprises a RNA polynucleotide having an open reading frame encoding a RSV NS2 protein.

In some embodiments, a RNA polynucleotide encodes a RSV antigenic polypeptide fused to a signal peptide (*e.g.*, SEQ ID NO: 281 or SEQ ID NO:282). Thus, RSV vaccines comprising at least one ribonucleic acid (RNA) polynucleotide having an open reading frame encoding a signal peptide linked to a RSV antigenic peptide are provided.

Further provided herein are RSV vaccines comprising any RSV antigenic polypeptides disclosed herein (*e.g.*, F, G, M, N, L, P, SH, NS1, NS2, or any antigenic fragment thereof) fused to signal peptides. The signal peptide may be fused to the N- or C-terminus of the RSV antigenic polypeptides.

Signal peptides

In some embodiments, antigenic polypeptides encoded by RSV 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 of three 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 endoplasmic reticulum (ER) membrane and initiates the transport of the growing peptide chain across it. The signal peptide is not responsible for the final destination of the mature protein, however. Secretory proteins devoid of further address tags in their sequence are by default secreted to the external environment. Signal peptides are cleaved from precursor proteins by an endoplasmic reticulum (ER)-resident signal peptidase or they remain uncleaved and function as a membrane anchor. 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.

Signal peptides typically function to facilitate the targeting of newly synthesized protein to the endoplasmic reticulum (ER) for processing. ER processing produces a mature Envelope protein, wherein the signal peptide is cleaved, typically by a signal peptidase of the host cell. A signal peptide may also facilitate the targeting of the protein to the cell membrane. RSV vaccines of the present disclosure may comprise, for example, RNA 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 RSV antigenic polypeptide. Thus, RSV vaccines of the present disclosure, in some embodiments, produce an antigenic polypeptide comprising a RSV antigenic polypeptide fused to a signal peptide.

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

In some embodiments, the signal peptide fused to the RSV antigenic polypeptide is an artificial signal peptide. In some embodiments, an artificial signal peptide fused to the RSV antigenic polypeptide encoded by the RSV 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 RSV antigenic polypeptide encoded by a RSV RNA (*e.g.*, mRNA) vaccine is an Ig heavy chain epsilon-1 signal peptide (IgE HC SP) having the sequence of: MDWTWILFLVAAATRVHS (SEQ ID NO: 281). In some embodiments, a signal peptide fused to a RSV antigenic polypeptide encoded by the RSV RNA (*e.g.*, mRNA) vaccine is an IgGk chain V-III region HAH signal peptide (IgGk SP) having the sequence of METPAQLLFLLLLWLPDTTG (SEQ ID NO: 282). In some embodiments, the RSV antigenic polypeptide encoded by a RSV RNA (*e.g.*, mRNA) vaccine has an amino acid sequence set forth in one of SEQ ID NO: 1 to SEQ ID NO: 28 fused to a signal peptide of SEQ ID NO: 281 or SEQ ID NO: 282. The examples disclosed herein are not meant to be 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 may have 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 RSV antigenic polypeptide produced by RSV

5 RNA vaccine of the present disclosure typically does not comprise a signal peptide.

Chemical Modifications

RNA (*e.g.*, mRNA) vaccines of the present disclosure comprise, in some embodiments, at least one ribonucleic acid (RNA) polynucleotide having an open reading
10 frame encoding at least one respiratory syncytial virus (RSV) antigenic polypeptide, wherein said RNA comprises at least one 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 deoxyribonucleosides in at least one of their position, pattern, percent or
15 population. Generally, these terms do not refer to the ribonucleotide modifications in naturally occurring 5'-terminal mRNA cap moieties.

Modifications of polynucleotides include, without limitation, those described herein, and include, but are expressly not limited to, those modifications that comprise chemical modifications. Polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides)
20 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).

25 With respect to a polypeptide, the term “modification” refers to a modification relative to the canonical set of 20 amino acids. Polypeptides, as provided herein, are also considered “modified” if they contain amino acid substitutions, insertions or a combination of substitutions and insertions.

Polynucleotides (*e.g.*, RNA polynucleotides, such as mRNA polynucleotides), in
30 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. In some embodiments, a modified RNA 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).

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 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 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 derivative thereof (also referred to herein as “nucleobase”). A nucleotide” refers to a nucleoside, including a phosphate group. Modified nucleotides may be synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or 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 phosphodiester linkages, in which case the polynucleotides would comprise regions of nucleotides.

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 arrangement 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, such as, for example, in those polynucleotides having at least one chemical modification. One example of such non-standard base pairing is the base pairing between the modified nucleotide 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), including but not limited to chemical modification, that are useful in the compositions, vaccines, methods and synthetic processes 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 carbamoyl adenosine; N6-glyciny carbamoyl adenosine; N6-isopentenyladenosine; N6-methyladenosine; N6-threonyl carbamoyl adenosine; 1,2'-O-dimethyladenosine; 1-methyladenosine; 2'-O-methyladenosine; 2'-O-ribosyladenosine (phosphate); 2-methyladenosine; 2-methylthio-N6 isopentenyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyl adenosine; 2'-O-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-acetyl adenosine; N6-hydroxynorvalyl carbamoyl adenosine; N6-methyl-N6-threonyl carbamoyl adenosine; 2-methyladenosine; 2-methylthio-N6-isopentenyladenosine; 7-deaza-adenosine; N1-methyladenosine; N6, N6 (dimethyl)adenine; N6-cis-hydroxy-isopentenyl-adenosine; α -thioadenosine; 2 (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; 2'-Deoxy-2'-a-azidoadenosine TP; 6 (alkyl)adenine; 6 (methyl)adenine; 6-(alkyl)adenine; 6-(methyl)adenine; 7 (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; 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'-a-thiomethoxyadenosine 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'-b-thiomethoxyadenosine TP; 2-Fluoroadenosine TP; 2-Iodoadenosine TP; 2-Mercaptadenosine 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'-a-aminocytidine 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'-O-dimethylcytidine; 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-methyl-pseudoisocytidine; 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-1-methyl-pseudoisocytidine; 4-thio-pseudoisocytidine; 5-aza-zebularine; 5-methyl-zebularine; pyrrolo-pseudoisocytidine; Zebularine; (E)-5-(2-Bromovinyl)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-mercaptopcytidine 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'-b-chlorocytidine TP; 2'-Deoxy-2'-b-fluorocytidine TP; 2'-Deoxy-2'-b-iodocytidine TP; 2'-Deoxy-2'-b-mercaptopcytidine 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 TP; 5-(1-Propynyl)ara-cytidine TP; 5-(2-Chloro-phenyl)-2-thiocytidine 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; 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; 2'-O-ribosylguanosine (phosphate); 7-aminomethyl-7-deazaguanosine; 7-cyano-7-deazaguanosine;
- 5 Archaeosine; Methylwyosine; N2,7-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; N2,N2,7-trimethylguanosine; N2,N2-dimethylguanosine; N2,7,2'-O-trimethylguanosine; 6-thio-guanosine; 7-deaza-guanosine; 8-oxo-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
- 10 (methyl)guanine; 6-(alkyl)guanine; 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; 8-(amino)guanine; 8-(halo)guanine; 8-(hydroxyl)guanine; 8-(thioalkyl)guanine; 8-(thiol)guanine; aza guanine;
- 15 deaza guanine; N (methyl)guanine; N-(methyl)guanine; 1-methyl-6-thio-guanosine; 6-methoxy-guanosine; 6-thio-7-deaza-8-aza-guanosine; 6-thio-7-deaza-guanosine; 6-thio-7-methyl-guanosine; 7-deaza-8-aza-guanosine; 7-methyl-8-oxo-guanosine; N2,N2-dimethyl-6-thio-guanosine; N2-methyl-6-thio-guanosine; 1-Me-GTP; 2'Fluoro-N2-isobutyl-guanosine TP; 2'O-methyl-N2-isobutyl-guanosine TP; 2'-a-Ethynylguanosine TP; 2'-a-
- 20 Trifluoromethylguanosine TP; 2'-b-Ethynylguanosine TP; 2'-b-Trifluoromethylguanosine TP; 2'-Deoxy-2',2'-difluoroguanosine TP; 2'-Deoxy-2'-a-mercaptoguanosine TP; 2'-Deoxy-2'-a-thiomethoxyguanosine TP; 2'-Deoxy-2'-b-aminoguanosine TP; 2'-Deoxy-2'-b-azidoguanosine TP; 2'-Deoxy-2'-b-bromoguanosine TP; 2'-Deoxy-2'-b-chloroguanosine TP; 2'-Deoxy-2'-b-fluoroguanosine TP; 2'-Deoxy-2'-b-iodoguanosine TP; 2'-Deoxy-2'-b-mercaptoguanosine TP;
- 25 2'-Deoxy-2'-b-thiomethoxyguanosine TP; 4'-Azidoguanosine TP; 4'-Carbocyclic guanosine TP; 4'-Ethynylguanosine TP; 5'-Homo-guanosine TP; 8-bromo-guanosine TP; 9-Deazaguanosine TP; N2-isobutyl-guanosine TP; 1-methylinosine; Inosine; 1,2'-O-dimethylinosine; 2'-O-methylinosine; 7-methylinosine; 2'-O-methylinosine; Epoxyqueuosine; galactosyl-queuosine; Mannosylqueuosine; Queuosine; allyamino-thymidine; aza thymidine;
- 30 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-amino-3-carboxypropyl)uridine; 1-methyl-3-(3-amino-5-carboxypropyl)pseudouridine; 1-methylpseudouridine; 1-ethyl-pseudouridine; 2'-O-methyluridine; 2'-O-methylpseudouridine; 2'-O-methyluridine; 2-thio-2'-

O-methyluridine; 3-(3-amino-3-carboxypropyl)uridine; 3,2'-O-dimethyluridine; 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; 5-carboxyhydroxymethyluridine; 5-carboxyhydroxymethyluridine methyl ester; 5-carboxymethylaminomethyl-2'-O-methyluridine; 5-carboxymethylaminomethyl-2-thiouridine; 5-carboxymethylaminomethyluridine; 5-carboxymethylaminomethyluridine; 5-Carbamoylmethyluridine TP; 5-methoxycarbonylmethyl-2'-O-methyluridine; 5-methoxycarbonylmethyl-2-thiouridine; 5-methoxycarbonylmethyluridine; 5-methyluridine, 5-methoxyuridine; 5-methyl-2-thiouridine; 5-methylaminomethyl-2-selenouridine; 5-methylaminomethyl-2-thiouridine; 5-methylaminomethyluridine; 5-Methyldihydrouridine; 5-Oxyacetic acid-Uridine TP; 5-Oxyacetic acid-methyl ester-Uridine TP; N1-methyl-pseudo-uracil; N1-ethyl-pseudo-uracil; 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 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil; 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil; 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil; 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil; 1 (aminocarbonylethylenyl)-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; 1-Ethyl-pseudo-UTP; 2 (thio)pseudouracil; 2' deoxy uridine; 2' fluorouridine; 2-(thio)uracil; 2,4-(dithio)pseudouracil; 2' methyl, 2' amino, 2' azido, 2' fluoro-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-(2-
 aminopropyl)uracil; 5-(alkyl)-2-(thio)pseudouracil; 5-(alkyl)-2,4 (dithio)pseudouracil; 5-
 5 (alkyl)-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-
 10 (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;
 15 deaza uracil; N3 (methyl)uracil; P pseudo-UTP-1-2-ethanoic acid; Pseudouracil; 4-Thio-
 pseudo-UTP; 1-carboxymethyl-pseudouridine; 1-methyl-1-deaza-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-1-methyl-pseudouridine; 2-thio-5-aza-uridine; 2-thio-dihydropseudouridine; 2-thio-
 20 dihydrouridine; 2-thio-pseudouridine; 4-methoxy-2-thio-pseudouridine; 4-methoxy-
 pseudouridine; 4-thio-1-methyl-pseudouridine; 4-thio-pseudouridine; 5-aza-uridine;
 Dihydropseudouridine; ($\pm$)1-(2-Hydroxypropyl)pseudouridine TP; (2R)-1-(2-
 Hydroxypropyl)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-
 25 uridine TP; (Z)-5-(2-Bromo-vinyl)uridine TP; 1-(2,2,2-Trifluoroethyl)-pseudo-UTP; 1-
 (2,2,3,3,3-Pentafluoropropyl)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-Hydroxyethyl)pseudouridine TP; 1-(2-Methoxyethyl)pseudouridine
 30 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-Amino-
 4-carboxybutyl)pseudo-UTP; 1-(4-Amino-benzyl)pseudo-UTP; 1-(4-Amino-butyl)pseudo-
 UTP; 1-(4-Amino-phenyl)pseudo-UTP; 1-(4-Azidobenzyl)pseudouridine TP; 1-(4-

- Bromobenzyl)pseudouridine TP; 1-(4-Chlorobenzyl)pseudouridine TP; 1-(4-Fluorobenzyl)pseudouridine TP; 1-(4-Iodobenzyl)pseudouridine TP; 1-(4-Methanesulfonylbenzyl)pseudouridine TP; 1-(4-Methoxybenzyl)pseudouridine TP; 1-(4-Methoxy-benzyl)pseudo-UTP; 1-(4-Methoxy-phenyl)pseudo-UTP; 1-(4-Methylbenzyl)pseudouridine TP; 1-(4-Methyl-benzyl)pseudo-UTP; 1-(4-Nitrobenzyl)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-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-Acetylpsudouridine TP; 1-Alkyl-6-(1-propynyl)-pseudo-UTP; 1-Alkyl-6-(2-propynyl)-pseudo-UTP; 1-Alkyl-6-allyl-pseudo-UTP; 1-Alkyl-6-ethynyl-pseudo-UTP; 1-Alkyl-6-homoallyl-pseudo-UTP; 1-Alkyl-6-vinyl-pseudo-UTP; 1-Allylpseudouridine TP; 1-Aminomethyl-pseudo-UTP; 1-Benzoylpseudouridine TP; 1-Benzyloxymethylpseudouridine TP; 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-Cycloheptylmethyl-pseudo-UTP; 1-Cycloheptyl-pseudo-UTP; 1-Cyclohexylmethyl-pseudo-UTP; 1-Cyclohexyl-pseudo-UTP; 1-Cyclooctylmethyl-pseudo-UTP; 1-Cyclooctyl-pseudo-UTP; 1-Cyclopentylmethyl-pseudo-UTP; 1-Cyclopentyl-pseudo-UTP; 1-Cyclopropylmethyl-pseudo-UTP; 1-Cyclopropyl-pseudo-UTP; 1-Ethyl-pseudo-UTP; 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; 1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP; 1-Methyl-6-(4-morpholino)-pseudo-UTP; 1-Methyl-6-(4-thiomorpholino)-pseudo-UTP; 1-Methyl-6-(substituted phenyl)pseudo-UTP; 1-Methyl-6-amino-pseudo-UTP; 1-Methyl-6-azido-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-ethyl-pseudo-UTP; 1-Methyl-6-fluoro-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-phenyl-pseudo-UTP; 1-Methyl-6-propyl-pseudo-

UTP; 1-Methyl-6-tert-butyl-pseudo-UTP; 1-Methyl-6-trifluoromethoxy-pseudo-UTP; 1-Methyl-6-trifluoromethyl-pseudo-UTP; 1-Morpholinomethylpseudouridine TP; 1-Pentyl-pseudo-UTP; 1-Phenyl-pseudo-UTP; 1-Pivaloylpseudouridine TP; 1-Propargylpseudouridine TP; 1-Propyl-pseudo-UTP; 1-propynyl-pseudouridine; 1-p-tolyl-pseudo-UTP; 1-tert-Butyl-pseudo-UTP; 1-Thiomethoxymethylpseudouridine TP; 1-Thiomorpholinomethylpseudouridine TP; 1-Trifluoroacetylpsudouridine 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-mercaptopuridine TP; 2'-Deoxy-2'-a-thiomethoxyuridine TP; 2'-Deoxy-2'-b-aminouridine TP; 2'-Deoxy-2'-b-azidouridine TP; 2'-Deoxy-2'-b-bromouridine TP; 2'-Deoxy-2'-b-chlorouridine TP; 2'-Deoxy-2'-b-fluorouridine TP; 2'-Deoxy-2'-b-iodouridine TP; 2'-Deoxy-2'-b-mercaptopuridine 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-Chloro-pseudo-UTP; 6-Cyano-pseudo-UTP; 6-Dimethylamino-pseudo-UTP; 6-Ethoxy-pseudo-UTP; 6-Ethylcarboxylate-pseudo-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-Phenyl-pseudo-UTP; 6-Phenyl-pseudo-UTP; 6-Propyl-pseudo-UTP; 6-tert-Butyl-pseudo-UTP; 6-Trifluoromethoxy-pseudo-UTP; 6-Trifluoromethyl-pseudo-UTP; Alpha-thio-pseudo-UTP; Pseudouridine 1-(4-methylbenzenesulfonic acid) TP; Pseudouridine 1-(4-methylbenzoic acid) TP; Pseudouridine TP 1-[3-(2-ethoxy)]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy)-ethoxy]-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxy}]propionic acid; Pseudouridine TP 1-[3-{2-(2-ethoxy)-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; Hydroxywybutosine; Isowyosine; Peroxywybutosine; undermodified hydroxywybutosine; 4-

5 demethylwyosine; 2,6-(diamino)purine; 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 1,3,5-(triaz)-2,6-(diox)-naphthalene; 2 (amino)purine; 2,4,5-(trimethyl)phenyl; 2' methyl, 2' amino, 2' azido, 2' fluoro-cytidine; 2' methyl, 2' amino, 2' azido, 2' fluoro-adenine; 2' methyl, 2' amino, 2' azido, 2' fluoro-uridine; 2'-amino-2'-deoxyribose; 2-amino-6-Chloro-purine; 2-aza-inosinyl; 2'-azido-2'-

10 deoxyribose; 2'fluoro-2'-deoxyribose; 2'-fluoro-modified bases; 2'-O-methyl-ribose; 2-oxo-7-aminopyridopyrimidin-3-yl; 2-oxo-pyridopyrimidine-3-yl; 2-pyridinone; 3 nitropyrrole; 3-(methyl)-7-(propynyl)isocarbostyryl; 3-(methyl)isocarbostyryl; 4-(fluoro)-6-(methyl)benzimidazole; 4-(methyl)benzimidazole; 4-(methyl)indolyl; 4,6-(dimethyl)indolyl; 5 nitroindole; 5 substituted pyrimidines; 5-(methyl)isocarbostyryl; 5-nitroindole; 6-

15 (aza)pyrimidine; 6-(azo)thymine; 6-(methyl)-7-(aza)indolyl; 6-chloro-purine; 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(aza)indolyl; 7-

20 (guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl; 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-

25 (oxo)-phenoxazin-1-yl; 7-(propynyl)isocarbostyryl; 7-(propynyl)isocarbostyryl, propynyl-7-(aza)indolyl; 7-deaza-inosinyl; 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl; 7-substituted 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl; 9-(methyl)-imidizopyridinyl; Aminoindolyl; Anthracenyl; bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; Difluorotolyl; Hypoxanthine;

30 Imidizopyridinyl; Inosinyl; Isocarbostyryl; Isoguanisine; N2-substituted purines; N6-methyl-2-amino-purine; N6-substituted purines; N-alkylated derivative; Napthalenyl; Nitrobenzimidazolyl; Nitroimidazolyl; Nitroindazolyl; Nitropyrazolyl; Nubularine; O6-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

TP; para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl; 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-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; 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), 2-thiouridine (s2U), 4'-thiouridine, 5-methylcytosine, 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-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methyluridine, 5-methoxyuridine, 2'-O-methyl uridine, 1-methyl-pseudouridine (m1 ψ), 1-ethyl-pseudouridine (e1 ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), α -thio-guanosine, α -thio-adenosine, 5-cyano uridine, 4'-thio uridine 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), N6-methyl-adenosine (m6A), and 2,6-Diaminopurine, (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 2,8-dimethyladenosine, 2-geranylthiouridine, 2-lysidine, 2-selenouridine, 3-(3-amino-3-carboxypropyl)-5,6-dihydrouridine, 3-(3-amino-3-carboxypropyl)pseudouridine, 3-methylpseudouridine, 5-(carboxyhydroxymethyl)-2'-O-methyluridine methyl ester, 5-aminomethyl-2-geranylthiouridine, 5-aminomethyl-2-selenouridine, 5-aminomethyluridine, 5-carbamoylhydroxymethyluridine, 5-carbamoylmethyl-2-thiouridine, 5-carboxymethyl-2-thiouridine, 5-carboxymethylaminomethyl-2-geranylthiouridine, 5-carboxymethylaminomethyl-2-selenouridine, 5-cyanomethyluridine, 5-hydroxycytidine, 5-

5 methylaminomethyl-2-geranylthiouridine, 7-aminocarboxypropyl-demethylwyosine, 7-aminocarboxypropylwyosine, 7-aminocarboxypropylwyosine methyl ester, 8-methyladenosine, N⁴,N⁴-dimethylcytidine, N⁶-formyladenosine, N⁶-hydroxymethyladenosine, agmatidine, cyclic N⁶-threonylcarbamoyladenosine, glutamyl-queuosine, methylated undermodified hydroxywybutosine, N⁴,N⁴,2'-O-trimethylcytidine, geranylated 5-methylaminomethyl-2-thiouridine, geranylated 5-carboxymethylaminomethyl-2-thiouridine, Qbase, preQ⁰base, preQ¹base, and combinations of two or more thereof. In some embodiments, the at least one chemically modified nucleoside is selected from the group consisting of pseudouridine, 1-methyl-pseudouridine, 1-ethyl-pseudouridine, 5-methylcytosine, 5-methoxyuridine, and a combination thereof. In some embodiments, the polyribonucleotide (*e.g.*, RNA polyribonucleotide, such as mRNA polyribonucleotide) 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) include a combination of at least two (*e.g.*, 2, 3, 4 or more) of the
10
15 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 (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), pseudouridine (ψ), α-thio-guanosine and α-thio-adenosine. In some
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25 embodiments, the polyribonucleotide 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 (ψ) and 5-methyl-cytidine (m5C). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 1-methyl-pseudouridine (m1ψ). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 1-ethyl-pseudouridine (e1ψ). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 1-methyl-pseudouridine (m1ψ) and 5-methyl-cytidine (m5C). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 1-ethyl-pseudouridine (e1ψ) and 5-methyl-cytidine (m5C). In
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some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 2-thiouridine (s2U). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 2-thiouridine and 5-methyl-cytidine (m5C). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise methoxy-uridine (mo5U). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 5-methoxy-

uridine (mo5U) and 5-methyl-cytidine (m5C). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 2'-O-methyl uridine. In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise 2'-O-methyl uridine and 5-methyl-cytidine (m5C). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) comprise N6-methyl-adenosine (m6A). In some embodiments, the polyribonucleotides (*e.g.*, RNA, such as mRNA) 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 1-methyl-pseudouridine, meaning that all uridine residues in the mRNA sequence are replaced with 1-methyl-pseudouridine. 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 modified cytosine include N4-acetyl-cytidine (ac4C), 5-methyl-cytidine (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 nucleosides having a modified uridine include 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy uridine, 2-thio uridine, 5-cyano uridine, 2'-O-methyl uridine and 4'-thio uridine.

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

In some embodiments, a modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, and 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 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 invention, or in a given predetermined sequence region thereof (*e.g.*, in the mRNA including or excluding the polyA tail). In some

embodiments, all nucleotides X in a polynucleotide of the present disclosure (or in a given sequence region thereof) are modified nucleotides, wherein X may be 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.

5 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 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 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 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%). It will be understood that 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% 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). 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 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).

 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 (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (*e.g.*, 5-iodo-uridine or 5-bromo-uridine), 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine (τm^5U), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine (τm^5s^2U), 1-taurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m^5U , *i.e.*, having the nucleobase deoxythymine), 1-methyl-pseudouridine ($m^1\psi$), 1-ethyl-pseudouridine ($e1\psi$), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α -thio-uridine, 2'-O-methyl-uridine (Um), 5,2'-O-dimethyl-uridine (m^5Um), 2'-O-methyl-pseudouridine (ψm), 2-thio-2'-O-methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2'-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2'-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2'-O-methyl-uridine ($cmnm^5Um$), 3,2'-O-dimethyl-uridine (m^3Um), and 5-(isopentenylaminomethyl)-2'-O-methyl-uridine (inm^5Um), 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 having a modified cytosine include 5-aza-cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (ac^4C), 5-formyl-cytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (*e.g.*, 5-

iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s^2C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k_2C), α -thio-cytidine, 2'-O-methyl-cytidine (Cm), 5,2'-O-dimethyl-cytidine (m^5Cm), N4-acetyl-2'-O-methyl-cytidine (ac^4Cm), N4,2'-O-dimethyl-cytidine (m^4Cm), 5-formyl-2'-O-methyl-cytidine (f^5Cm), N4,N4,2'-O-trimethyl-cytidine (m^4_2Cm), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine.

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-6-chloro-purine), 6-halo-purine (*e.g.*, 6-chloro-purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m^1A), 2-methyl-adenine (m^2A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine ($\text{ms}^2\text{m}^6\text{A}$), N6-isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine ($\text{ms}^2\text{i}^6\text{A}$), N6-(cis-hydroxyisopentenyl)adenosine (io^6A), 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine ($\text{ms}^2\text{io}^6\text{A}$), N6-glycylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6-methyl-N6-threonylcarbamoyl-adenosine ($\text{m}^6\text{t}^6\text{A}$), 2-methylthio-N6-threonylcarbamoyl-adenosine ($\text{ms}^2\text{g}^6\text{A}$), N6,N6-dimethyl-adenosine (m^6_2A), N6-hydroxynorvalylcarbamoyl-adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine ($\text{ms}^2\text{hn}^6\text{A}$), N6-acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α -thio-adenosine, 2'-O-methyl-adenosine (Am), N6,2'-O-dimethyl-adenosine (m^6Am), N6,N6,2'-O-trimethyl-adenosine (m^6_2Am), 1,2'-O-dimethyl-adenosine (m^1Am), 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-pentaoxonadecyl)-adenosine.

In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m^1I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o_2yW), 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-deaza-guanosine (preQ₁), archaeosine (G⁺), 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-azaguanosine, 7-methyl-guanosine (m⁷G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (m¹G), N2-methyl-guanosine (m²G), 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-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, α-thio-guanosine, 2'-O-methyl-guanosine (Gm), N2-methyl-2'-O-methyl-guanosine (m²Gm), N2,N2-dimethyl-2'-O-methyl-guanosine (m²₂Gm), 1-methyl-2'-O-methyl-guanosine (m¹Gm), N2,7-dimethyl-2'-O-methyl-guanosine (m^{2,7}Gm), 2'-O-methyl-inosine (Im), 1,2'-O-dimethyl-inosine (m¹Im), 2'-O-ribosylguanosine (phosphate) (Gr(p)), 1-thio-guanosine, O6-methyl-guanosine, 2'-F-ara-guanosine, and 2'-F-guanosine.

In some embodiments, the RNA 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.

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

RSV 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, the at least one RNA polynucleotide has at least one chemical modification. The at least one chemical modification may include, but is expressly not limited to, any modification described herein.

In vitro transcription of RNA is known in the art and is described in International Publication WO/2014/152027, which is incorporated by reference herein in its entirety. For example, in some embodiments, the RNA transcript is generated using a non-amplified, linearized DNA template in an *in vitro* transcription reaction to generate the RNA transcript. In some embodiments the RNA transcript is capped *via* enzymatic capping. In some embodiments the RNA transcript is purified via chromatographic methods, e.g., use of an oligo dT substrate. Some embodiments exclude the use of DNase. In some embodiments the RNA transcript is synthesized from a non-amplified, linear DNA template coding for the gene of interest via an enzymatic *in vitro* transcription reaction utilizing a T7 phage RNA polymerase and nucleotide triphosphates of the desired chemistry. Any number of RNA

polymerases or variants may be used in the method of the present invention. The polymerase may be selected from, but is not limited to, a phage RNA polymerase, *e.g.*, a T7 RNA polymerase, a T3 RNA polymerase, a SP6 RNA polymerase, and/or mutant polymerases such as, but not limited to, polymerases able to incorporate modified nucleic acids and/or modified nucleotides, including chemically modified nucleic acids and/or nucleotides.

In some embodiments a non-amplified, linearized plasmid DNA is utilized as the template DNA for *in vitro* transcription. In some embodiments, the template DNA is isolated DNA. In some embodiments, the template DNA is cDNA. In some embodiments, the cDNA is formed by reverse transcription of a RNA polynucleotide, for example, but not limited to RSV RNA, *e.g.* RSV mRNA. In some embodiments, Cells, *e.g.*, bacterial cells, *e.g.*, *E. coli*, *e.g.*, DH-1 cells are transfected with the plasmid DNA template. In some embodiments, the transfected cells are cultured to replicate the plasmid DNA which is then isolated and purified. In some embodiments, the DNA template includes a RNA polymerase promoter, *e.g.*, a T7 promoter located 5' to and operably linked to the gene of interest.

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” (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” (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 degradation, *e.g.*, in the cytoplasm, and aids in transcription termination, and/or 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 to 3000 nucleotides).

Methods of Treatment

Provided herein are compositions (*e.g.*, pharmaceutical compositions), methods, kits and reagents for prevention and/or treatment of RSV in humans and other mammals. RSV 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 exemplary aspects, the RSV RNA vaccines of the present disclosure are used to provide prophylactic protection from RSV. Prophylactic protection from RSV can be achieved following administration of a RSV RNA vaccine of the present disclosure. 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 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 a RSV is provided in aspects of the invention. The method involves administering to the subject a RSV RNA vaccine comprising at least one RNA polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to RSV antigenic polypeptide or an immunogenic fragment thereof, wherein anti-antigenic polypeptide antibody titer in the subject is increased following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional (*e.g.*, non-nucleic acid) vaccine against the RSV. An “anti-antigenic polypeptide antibody” is a serum antibody the binds specifically to the antigenic polypeptide.

A prophylactically effective dose is a therapeutically effective dose that prevents infection with the virus at a 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 mRNA vaccines of the invention. For instance, a traditional vaccine includes but is not limited to live

microorganism vaccines, killed microorganism vaccines, subunit vaccines, protein antigen vaccines, DNA vaccines, *etc.*

5 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 the RSV.

10 In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 1 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the RSV.

In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 2 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the RSV.

15 In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 3 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the RSV.

20 In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 5 log following vaccination relative to anti-antigenic polypeptide antibody titer in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the RSV.

25 In some embodiments the anti-antigenic polypeptide antibody titer in the subject is increased 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 the RSV.

30 A method of eliciting an immune response in a subject against a RSV is provided in other aspects of the invention. The method involves administering to the subject a RSV RNA vaccine comprising at least one RNA polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to RSV 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 RSV at 2 times to 100 times the dosage level relative to the RNA 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 twice the dosage level relative to the RSV RNA vaccine.

5 In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at three times the dosage level relative to the RSV RNA 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 4 times the dosage level relative to the RSV RNA vaccine.

10 In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 5 times the dosage level relative to the RSV RNA 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 times the dosage level
15 relative to the RSV RNA 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 50 times the dosage level relative to the RSV RNA vaccine.

20 In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 100 times the dosage level relative to the RSV RNA 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 times to 1000 times the dosage level relative to the RSV RNA vaccine.

25 In some embodiments the immune response in the subject is equivalent to an immune response in a subject vaccinated with a traditional vaccine at 100 times to 1000 times the dosage level relative to the RSV RNA vaccine.

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

30 In other aspects the invention is a method of eliciting an immune response in a subject against a RSV by administering to the subject a RSV RNA vaccine comprising at least one RNA polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide or an immunogenic fragment thereof, thereby inducing in the subject an immune response specific to RSV antigenic polypeptide or an immunogenic fragment thereof,

wherein the immune response in the subject is induced 2 days to 10 weeks earlier relative to an immune response induced in a subject vaccinated with a prophylactically effective dose of a traditional vaccine against the RSV. 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 vaccine.

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

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

Broad spectrum RSV vaccines

It is envisioned that there may be situations where persons are at risk for infection with more than one strain of RSV. 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 RSV, a combination vaccine can be administered that includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a first RSV and further
5 includes RNA encoding at least one antigenic polypeptide protein (or antigenic portion thereof) of a second RSV. RNAs (mRNAs) can be co-formulated, for example, in a single lipid nanoparticle (LNP) or can be formulated in separate LNPs destined for co-administration.

10 *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 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
15 (dendritic cells, macrophages, *etc.*) is mediated by the Toll-like receptor 5 (TLR5) as well as by Nod-like receptors (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 known flagellin polypeptides are
20 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. burgdorferi*, *C. difficile*, *R. meliloti*, *A. tumefaciens*, *R. lupini*, *B. clarridgeiae*, *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,
25 immunogenic fragments thereof, and peptides having at least 50% sequence identify to a flagellin protein or immunogenic fragments thereof. Exemplary flagellin proteins include flagellin from *Salmonella typhi* (UniPro Entry number: Q56086), *Salmonella typhimurium* (A0A0C9DG09), *Salmonella enteritidis* (A0A0C9BAB7), and *Salmonella choleraesuis*
30 (Q6V2X8), and SEQ ID NO: 173-175. 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 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.

5 Hinge regions of a flagellin are also referred to as “D3 domain or region,” “propeller 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, 25, 30, 35, or 40 amino acid C-terminal fragment of flagellin.

10 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 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
15 the D1 domain 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
20 *Salmonella* sequence in 88-100 of FliC (LQRVRELAVQSAN; SEQ ID NO: 286).

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
25 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
30 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 includes at least two separate RNA polynucleotides, one 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.

Therapeutic and Prophylactic Compositions

Provided herein are compositions (*e.g.*, pharmaceutical compositions), methods, kits and reagents for prevention, treatment or diagnosis of RSV in humans and other mammals, for example. RSV 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 RSV vaccines of the invention can be envisioned for use in 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 exemplary embodiments, a RSV vaccine containing RNA polynucleotides as described herein can be administered to a subject (*e.g.*, a mammalian subject, such as a human subject), and the RNA polynucleotides are translated *in vivo* to produce an antigenic polypeptide.

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

An “effective amount” of the RSV RNA vaccine is provided based, at least in part, on the 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 RSV RNA vaccine, and other determinants. In general, an effective amount of the RSV RNA vaccine composition provides an induced or boosted immune response as a function of antigen production in the cell. In general, an effective amount of the RSV RNA vaccine containing RNA polynucleotides having at least one chemical modifications are 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 vaccine), increased protein translation from the polynucleotide, decreased nucleic acid degradation (as demonstrated, for example, by increased duration of protein translation from a modified polynucleotide), or altered antigen specific immune response of the host cell.

The term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*. A "pharmaceutically acceptable carrier," after administered to or upon a subject, does not cause undesirable physiological effects. The carrier in the pharmaceutical composition must be "acceptable" also in the sense that it is compatible with the active ingredient and can be capable of stabilizing it. One or more solubilizing agents can be utilized as pharmaceutical carriers for delivery of an active agent. Examples of a pharmaceutically acceptable carrier include, but are not limited to, biocompatible vehicles, adjuvants, additives, and diluents to achieve a composition usable as a dosage form. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, and sodium lauryl sulfate. Additional suitable pharmaceutical carriers and diluents, as well as pharmaceutical necessities for their use, are described in Remington's Pharmaceutical Sciences.

In some embodiments, RNA vaccines (including polynucleotides and their encoded polypeptides) in accordance with the present disclosure may be used for treatment or prevention of RSV.

RSV RNA 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 vaccines of the present disclosure provided to a cell, a tissue or a subject may be an amount effective for immune prophylaxis.

RSV RNA (*e.g.*, mRNA) vaccines may be administered with other prophylactic or therapeutic compounds. 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 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 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 exemplary embodiments, the time of administration between the initial administration of the prophylactic composition and the booster 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, RSV RNA vaccines may be administered intramuscularly, intranasally or intradermally, similarly to the administration of inactivated vaccines known in the art.

The RSV RNA 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 vaccines may be utilized to treat and/or prevent a variety of infectious disease. RNA vaccines, in many instances, have superior properties in that they produce much larger antibody titers and produce responses early than commercially available anti-virals.

Provided herein are pharmaceutical compositions including RSV RNA vaccines and RNA vaccine compositions and/or complexes optionally in combination with one or more pharmaceutically acceptable excipients.

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

In some embodiments, RSV RNA vaccines do not include an adjuvant (they are adjuvant free).

RSV RNA (*e.g.*, mRNA) vaccines may be formulated or administered in combination with one or more 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 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 & Wilkins, 2005 (incorporated herein by reference in its entirety).

In some embodiments, RSV RNA vaccines are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase “active ingredient” generally refers to the RNA vaccines or the polynucleotides contained therein, for example, RNA polynucleotides (*e.g.*, mRNA polynucleotides) encoding antigenic polypeptides.

Formulations of the vaccine compositions 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.

RSV RNA 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 RSV RNA vaccines (*e.g.*, for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

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 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 pre-mRNA 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 vaccines include a coding region, at least one histone stem-loop, and optionally, a poly(A) sequence or polyadenylation signal. 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 (*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 mechanisms 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 the length of the poly(A) sequence.

In some embodiments, the RNA vaccine does not comprise a histone downstream element (HDE). “Histone downstream element” (HDE) includes a purine-rich polynucleotide stretch of approximately 15 to 20 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. In some embodiments, the nucleic acid does not include an intron.

In some embodiments, the RNA vaccine may or may not contain an 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, and includes an intramolecular base pairing of two neighbored partially or entirely reverse complementary sequences separated by a spacer, consisting of a short sequence, which forms the loop of the structure. The unpaired loop region is typically unable to base pair with 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 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 stem-loop sequence comprises a length of 15 to 45 nucleotides.

In other embodiments the RNA vaccine may have one or more AU-rich sequences removed. These sequences, sometimes referred to as AURES are destabilizing sequences found in the 3'UTR. The AURES may be removed from the RNA vaccines. Alternatively the AURES may remain in the RNA vaccine.

In some embodiments, the RNA polynucleotide does not include a stabilization element.

Nanoparticle Formulations

In some embodiments, RSV RNA (e.g., mRNA) vaccines are formulated in a nanoparticle. In some embodiments, RSV RNA vaccines are formulated in a lipid nanoparticle. In some embodiments, RSV RNA vaccines are formulated in a lipid-polycation complex, referred to as a cationic lipid nanoparticle. The formation of the lipid nanoparticle may be accomplished by methods known in the art and/or as described in U.S. Publication 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, polyornithine and/or polyarginine and the cationic peptides described in International Publication No. WO2012013326 or U.S. Publication No. US20130142818; each of which is herein incorporated by reference in its entirety. In some embodiments, RSV RNA 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; herein incorporated by reference in its entirety), 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 was shown to more effectively deliver siRNA to various antigen presenting cells (Basha *et al.* *Mol Ther.* 2011 19:2186-2200; herein incorporated by reference in its entirety).

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(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 (*see, e.g.*, U.S. Publication No. 20130245107 A1).

In some embodiments, a RSV 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, 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. 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-[(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-9,12-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-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-1-amine (L608), or N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530) 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 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530); (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 PEG-cDMA, 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 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-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), *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, *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%, or 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 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 Da, or around 500 Da. Non-limiting examples of PEG-modified 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 content of which is herein incorporated by reference in its entirety).

In some embodiments, lipid nanoparticle formulations include 25-75% of a cationic 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 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 include 35-65% of a cationic 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319),

(12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 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.

5 In some embodiments, lipid nanoparticle formulations include 45-65% of a cationic 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 5-10% of the neutral lipid, 25-40%
10 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 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)-
15 N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 7.5% of the neutral lipid, 31 % of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

In some embodiments, lipid nanoparticle formulations include 50% of a cationic lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane
20 (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-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 10% of the neutral lipid, 38.5 % of the sterol, and 1.5% of the PEG or PEG-modified lipid on a molar basis.

25 In some embodiments, lipid nanoparticle formulations include 50% of a cationic 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-
30 octylcyclopropyl]heptadecan-8-amine (L530), 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 include 40% of a cationic 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), di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 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 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-1-amine (L608), and N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]heptadecan-8-amine (L530), 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 Reyes et al. (J. Controlled Release, 107, 276-287 (2005), the content of which is herein incorporated by reference in its 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), 57.2/7.1/34.3/1.4 (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/ 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 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 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 reference 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 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 non-limiting 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, L319, L608 and L520.

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 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 non-limiting 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 not limited to, DLin-KC2-DMA, DLin-MC3-DMA, L319, L608 and L520.

In some embodiments, the lipid nanoparticle formulations described herein may comprise a cationic lipid, a non-cationic lipid, a PEG lipid and a structural lipid. As a non-limiting example, the lipid nanoparticle comprise 50% of the cationic lipid DLin-KC2-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 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 DLin-MC3-DMA, 10% of the non-cationic lipid 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, L608 or L520, 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 RNA vaccine composition may comprise the polynucleotide described herein, formulated in a lipid nanoparticle comprising DLin-MC3-DMA, 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 RSV), 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

In some embodiments, the RNA vaccine pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-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).

In some embodiments, the RNA vaccines may be formulated in a lyophilized gel-phase liposomal composition as described in U.S. Publication No. US2012060293, herein incorporated by reference in its entirety.

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. Phosphate conjugates for use with the present invention may be made by the methods described in International Publication No. WO2013033438 or U.S. Publication No. US20130196948, the content of each of which is herein incorporated by reference in its entirety. As a non-limiting example, the phosphate conjugates may include a compound of
5 any one of the formulas described in International Publication No. WO2013033438, 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. Publication No. 20130059360, the content of which is herein incorporated
10 by reference in its entirety. In some aspects, polymer conjugates with the polynucleotides of the present invention may be made using the methods and/or segmented polymeric reagents described in U.S. Publication No. 20130072709, herein incorporated by reference in its entirety. In other aspects, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Publication No.
15 US20130196948, the contents of which is herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present invention in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In some aspects, the conjugate may be a “self” peptide designed from the human membrane protein CD47 (*e.g.*, the “self” particles
20 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 macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In other aspects, 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,
25 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 vaccines of the present invention are formulated in nanoparticles which comprise a conjugate to enhance the delivery of the nanoparticles of the present invention in a subject. The conjugate may be the CD47 membrane or the conjugate may
30 be derived from the CD47 membrane protein, such as the “self” peptide described previously. In other embodiments, the nanoparticle may comprise PEG and a conjugate of CD47 or a derivative thereof. In yet other 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 vaccines of the present invention.

5 In other embodiments, RNA vaccine pharmaceutical compositions comprising the polynucleotides of the present invention and a conjugate, which 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. Publication No.
10 US20130184443, the content of which is herein incorporated by reference in its entirety.

The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a RNA vaccine. As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phytoglycogen octenyl succinate, phytoglycogen beta-dextrin, anhydride-modified
15 phytoglycogen beta-dextrin. (*See e.g.*, International Publication No. WO2012109121, the content of which is herein incorporated by reference in its entirety).

Nanoparticle formulations of the present invention 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
20 and/or coatings that have a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA vaccines within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in U.S. Publication No. US20130183244, the content of which is herein incorporated by reference in its entirety.

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

In other embodiments, the lipid nanoparticles of the present invention may be
30 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 nanoparticle (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 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
5 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.

10 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. Publication No. 20120189700 and International Publication No. WO2012099805, each of which is herein incorporated by reference in its entirety).

The polymer may encapsulate the nanospecies or partially encapsulate the
15 nanospecies. The immunogen may be a recombinant protein, a modified 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 properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such
20 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
25 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 mucosal tissue within seconds or within a few hours. Large polymeric nanoparticles (200 nm to 500 nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-
30 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 its 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. Patent No. 8,241,670 or International Publication No. WO2013110028, the content of each of which is herein incorporated by reference in its entirety.

The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (e.g., 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, polyethyleneimines, 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 Publication No. WO2013116804, the content of which is herein incorporated by reference in its entirety. The polymeric material may additionally be irradiated. As a non-limiting example, the polymeric material may be gamma irradiated (*see e.g.*, International Publication 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 acid-co-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,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, 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), polyvinylpyrrolidone, 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)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), 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 and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a copolymer 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 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, U.S. Publication 20100003337 and U.S. Patent No. 8,263,665, each of which is herein incorporated by reference in its 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 nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang *et al. Angew. Chem. Int. Ed.* 2011 50:25972600, the content of which is herein incorporated by reference in its entirety). A non-limiting scalable method to produce nanoparticles which can penetrate human mucus is described by Xu *et al. (see e.g., J Control Release* 2013, 170(2):279-86, the content of which is herein incorporated by reference in its entirety).

The vitamin of the polymer-vitamin conjugate may be 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 chains and alkylene oxide chains).

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, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-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).

In some embodiments, the RNA vaccines may be formulated in a lyophilized gel- phase liposomal composition as described in U.S. Publication No. US2012060293, herein incorporated by reference in its entirety.

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. Phosphate conjugates for use with the present invention may be made by the methods described in International Publication No. WO2013033438 or U.S. Publication No. 20130196948, the content of each of which is herein incorporated by reference in its entirety. As a non-limiting example, the phosphate conjugates may include a compound of any one of the formulas described in International Publication No. WO2013033438, 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. Application No. 20130059360, the content of which is herein incorporated by reference in its entirety. In some aspects, polymer conjugates with the polynucleotides of the present invention may be made using the methods and/or segmented polymeric reagents described in U.S. Patent Application No. 20130072709, herein incorporated by reference in its entirety. In other aspects, the polymer conjugate may have pendant side groups comprising ring moieties such as, but not limited to, the polymer conjugates described in U.S. Publication No. US20130196948, the content of which is herein incorporated by reference in its entirety.

The nanoparticle formulations may comprise a conjugate to enhance the delivery of nanoparticles of the present invention in a subject. Further, the conjugate may inhibit phagocytic clearance of the nanoparticles in a subject. In some aspects, 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 macrophage-mediated clearance of nanoparticles which enhanced delivery of the nanoparticles. In other aspects, 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 vaccines of the present invention are formulated in nanoparticles that 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 other aspects the nanoparticle may comprise PEG and a conjugate of CD47 or

a derivative thereof. In yet other aspects, the nanoparticle may comprise both the “self” peptide described above and the membrane protein CD47.

In other aspects, 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 vaccines of the present invention.

In other embodiments, RNA vaccine pharmaceutical compositions comprising the polynucleotides of the present invention and a conjugate which 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. Publication No. US20130184443, the content of which is herein incorporated by reference in its 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, phytoglycogen octenyl succinate, phytoglycogen beta-dextrin, anhydride-modified phytoglycogen beta-dextrin. (See *e.g.*, International Publication No. WO2012109121; the content of which is herein incorporated by reference in its entirety).

Nanoparticle formulations of the present invention 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 a neutral surface charge. The hydrophilic coatings may help to deliver nanoparticles with larger payloads such as, but not limited to, RNA vaccines within the central nervous system. As a non-limiting example nanoparticles comprising a hydrophilic coating and methods of making such nanoparticles are described in U.S. Publication No. US20130183244, the content of which is herein incorporated by reference in its entirety.

In some embodiments, the lipid nanoparticles of the present invention may be hydrophilic polymer particles. Non-limiting examples of hydrophilic polymer particles and methods of making hydrophilic polymer particles are described in U.S. Publication No. US20130210991, the content of which is herein incorporated by reference in its entirety.

In other embodiments, the lipid nanoparticles of the present invention 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 nanoparticle (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 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 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 carbo.

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. Publication No. 20120189700 and International Publication No. WO2012099805, each of which is herein incorporated by reference in its entirety).

Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal 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 mucosal tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm 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 its 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. Patent No. 8,241,670 or International Publication No. WO2013110028, the content of each of which is 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, polyethyleneimines, 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 Publication No. WO2013116804, the content of which is herein incorporated by reference in its entirety. The polymeric material may additionally be irradiated. As a non-limiting example, the polymeric material may be gamma irradiated (*see e.g.*, International Publication 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 acid-co-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,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, 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), polyvinylpyrrolidone, 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)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), 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 and trimethylene carbonate, polyvinylpyrrolidone. The lipid nanoparticle may be coated or associated with a copolymer 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 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; each of which is herein incorporated by reference in its 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 nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang *et al. Angew. Chem. Int. Ed.* 2011 50:25972600; the content of which is herein incorporated by reference in its entirety). A non-limiting scalable method to produce nanoparticles which can penetrate human mucus is described by Xu *et al. (see e.g., J Control Release* 2013, 170(2):279-86, the content of which is herein incorporated by reference in its entirety).

The vitamin of the polymer-vitamin conjugate may be 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 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 example dimethyldioctadecylammonium 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, carbocysteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β 4 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 (*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 content of each of which is herein incorporated by reference in its entirety).

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 other embodiments, the mucus penetrating lipid nanoparticles may be a hypotonic formulation comprising a mucosal penetration enhancing coating. The formulation may be hypotonic for the epithelium to which it is being delivered.

Non-limiting examples of hypotonic formulations may be found in International Publication No. WO2013110028, the content of which is herein incorporated by reference in its entirety.

In some embodiments, in order to enhance the delivery through the mucosal barrier the RNA vaccine formulation may comprise or be a hypotonic solution. Hypotonic solutions were found to increase the rate at which muco-inert 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 content of which is herein incorporated by reference in its entirety).

In some embodiments, the RNA vaccine is formulated as a lipoplex, such as, without limitation, the ATUPLEXTM system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECTTM from STEMGENT® (Cambridge, MA), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic 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 U S A.* 2007

6;104:4095-4100; deFougerolles *Hum Gene Ther.* 2008 19:125-132; each of which is incorporated herein by reference in its 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; each of which is incorporated herein by reference in its 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; herein incorporated by reference in its entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified 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 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.* 2012 757:497-507; Peer 2010 *J Control Release.* 20:63-68; Peer *et al.*, *Proc Natl Acad Sci U S A.* 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 319:627-630; Peer and Lieberman, *Gene Ther.* 2011 18:1127-1133; each of which is incorporated herein by reference in its entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccine is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 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 other embodiments, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (*see* Zhang *et al.*, *ACS*

Nano, 2008, 2 (8), pp 1696–1702; the content of which is herein incorporated by reference in its entirety). As a non-limiting example, the SLN may be the SLN described in International Publication No. WO2013105101, the content of which is herein incorporated by reference in its entirety. As another non-limiting example, the SLN may be made by the methods or processes described in International Publication No. WO2013105101, the content of which is herein incorporated by reference in its 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 vaccine; and/or 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; herein incorporated by reference in its entirety). 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 invention can be formulated for controlled release and/or targeted delivery. As used herein, “controlled 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 vaccines may be encapsulated into a delivery agent described herein and/or known in 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 invention, encapsulation may be substantial, complete or partial. The term “substantially encapsulated” 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 invention 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 invention 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 invention 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 present disclosure are encapsulated in the delivery agent.

In some embodiments, the controlled release formulation may include, but is not limited to, tri-block co-polymers. As 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 is herein incorporated by reference in its entirety).

In other embodiments, the RNA 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, FL), HYLENEX® (Halozyne Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, IL).

In other 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 non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In some embodiments, the RNA 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, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® 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. Degradable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In other embodiments, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

In some embodiments, the RNA 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. Patent No. 8,404,222, herein incorporated by reference in its entirety.

In other embodiments, the RNA vaccine controlled release delivery formulation comprising at least one polynucleotide may be the controlled release polymer system described in U.S. Publication No. 20130130348, herein incorporated by reference in its entirety.

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present invention may be encapsulated in a therapeutic nanoparticle, referred to herein as “therapeutic nanoparticle RNA vaccines.” Therapeutic nanoparticles may be formulated by methods described herein and known in the art such as, but not limited to, International Publication Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, U.S. Publication Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286, US20120288541, US20130123351 and US20130230567 and US Patent Nos. 8,206,747, 8,293,276, 8,318,208 and 8,318,211, the content of each of which is herein incorporated by reference in its entirety. In other embodiments, therapeutic polymer nanoparticles may be identified by the methods described in U.S. Publication No. US20120140790, the content of which is herein incorporated by reference in its entirety.

In some embodiments, the therapeutic nanoparticle RNA vaccine may be formulated for sustained release. As used herein, “sustained release” refers to a pharmaceutical composition or compound that conforms to 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 of the present invention (*see* International Publication No. 2010075072 and U.S. Publication Nos. US20100216804, US20110217377 and US20120201859, each of which is herein incorporated by reference in its entirety). In another non-limiting example, the sustained 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. Publication No. US20130150295, the content of which is herein incorporated by reference in its entirety).

In some embodiments, the therapeutic nanoparticle RNA vaccines may be formulated to be target specific. As a non-limiting example, the therapeutic nanoparticles may include a corticosteroid (*see* International Publication No. WO2011084518, herein incorporated by reference in its entirety). As a non-limiting example, the therapeutic nanoparticles may be formulated in nanoparticles described in International Publication Nos. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and U.S. Publication Nos. US20100069426, US20120004293 and US20100104655, each of which is herein incorporated by reference in its entirety.

In some embodiments, the nanoparticles of the present invention may comprise a polymeric matrix. As a non-limiting example, the nanoparticle 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, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester),
5 poly(L-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,
10 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 other embodiments, the diblock copolymer may be a high-X diblock copolymer such as those described in International
15 Publication No. WO2013120052, the content of which is herein incorporated by reference in its entirety.

As a non-limiting example, the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (*see* U.S. Publication No. US20120004293 and U.S. Patent No. 8,236,330, each of which is herein incorporated by reference in its entirety). In another non-limiting
20 example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (*see* U.S. Patent No. 8,246,968 and International Publication No. WO2012166923, the content of each of which is herein incorporated by reference in its 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. Publication No.
25 20130172406, the content of which is herein incorporated by reference in its entirety.

In some embodiments, the therapeutic nanoparticle may comprise a multiblock copolymer (*see e.g.*, U.S. Patent Nos. 8,263,665 and 8,287,910 and U.S. Publication No. 20130195987, the content of each of which is herein incorporated by reference in its
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) used as a TGF-beta1 gene delivery vehicle in Lee *et al.* "Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing." *Pharmaceutical Research*, 2003 20(12): 1995-2000; and used 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; each of which is herein incorporated by reference in its 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 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, herein incorporated by reference in its 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, 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 International Publication No. WO2013032829 or U.S. Publication No. 20130121954, the content of which is herein incorporated by reference in its entirety. In some aspects, the poly(vinyl ester) polymers may be conjugated to the polynucleotides described herein. In other aspects, the poly(vinyl ester) polymer which may be used in the present invention may be those described in.

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 Publication No. WO2013044219; herein incorporated by reference in its entirety). As a non-limiting example, the therapeutic nanoparticle may be used to treat cancer (*see* International publication No. WO2013044219, herein incorporated by reference in its 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 not limited to polylysine, polyethyleneimine, poly(amidoamine) dendrimers, poly(beta-amino esters) (*see e.g.*, U.S. Patent No. 8,287,849, herein incorporated by reference in its entirety) and combinations thereof. In other embodiments,

the nanoparticles described herein may comprise an amine cationic lipid such as those described in International Publication No. WO2013059496, the content of which is herein incorporated by reference in its entirety. In some aspects the cationic lipids may have an amino-amine or an amino-amide moiety.

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

10 In other embodiments, the therapeutic nanoparticle may include a conjugation of at least one targeting ligand. The targeting ligand may be any ligand known in the art such as, but not limited to, a monoclonal antibody (Kirpotin *et al*, *Cancer Res.* 2006 66:6732-6740, herein incorporated by reference in its entirety).

 In some embodiments, the therapeutic nanoparticle may be formulated in an aqueous
15 solution, which may be used to target cancer (*see* International Publication No. WO2011084513 and U.S. Publication No. 20110294717, each of which is herein incorporated by reference in its entirety).

 In some embodiments, the therapeutic nanoparticle RNA vaccines, *e.g.*, therapeutic nanoparticles comprising at least one RNA vaccine may be formulated using the methods
20 described by Podobinski *et al* in U.S. Patent No. 8,404,799, the content of which is herein incorporated by reference in its entirety.

 In some embodiments, the RNA (*e.g.*, mRNA) vaccines may be encapsulated in, linked to and/or associated with synthetic nanocarriers. Synthetic nanocarriers include, but are not limited to, those described in International Publication Nos. WO2010005740,
25 WO2012149454 and WO2013019669, and U.S. Publication Nos. US20110262491, US20100104645, US20100087337 and US20120244222, each of which is herein incorporated by reference in its entirety. The synthetic nanocarriers may be formulated using methods known in the art and/or described herein. As a non-limiting example, the synthetic nanocarriers may be formulated by the methods described in International Publication Nos.
30 WO2010005740, WO2010030763 and WO201213501, and U.S. Publication Nos. US20110262491, US20100104645, US20100087337 and US2012024422, each of which is herein incorporated by reference in its entirety. In other embodiments, the synthetic nanocarrier formulations may be lyophilized by methods described in International Publication No. WO2011072218 and U.S. Patent No. 8,211,473, the content of each of which is herein

incorporated by reference in its entirety. In yet other embodiments, formulations of the present invention, including, but not limited to, synthetic nanocarriers, may be lyophilized or reconstituted by the methods described in U.S. Publication No. 20130230568, the content of which is herein incorporated by reference in its entirety.

5 In some embodiments, the synthetic nanocarriers may contain reactive groups to release the polynucleotides described herein (*see* International Publication No. WO20120952552 and U.S. Publication No. US20120171229, each of which is herein incorporated by reference in its entirety).

10 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 a Th1-based response of the immune system (*see* International Publication No. WO2010123569 and U.S. Publication No. 20110223201, each of which is herein incorporated by reference in its entirety).

15 In some embodiments, the synthetic nanocarriers may be 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 vaccines after 24 hours and/or at a pH of 4.5 (*see* International Publication Nos. WO2010138193 and
20 WO2010138194 and U.S. Publication 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,
25 described herein and/or as described in International Publication No. WO2010138192 and U.S. Publication No. 20100303850, each of which is herein incorporated by reference in its entirety.

 In some embodiments, the RNA vaccine may be formulated for controlled and/or sustained release wherein the formulation comprises at least one polymer that is a crystalline
30 side chain (CYSC) polymer. CYSC polymers are described in U.S. Patent 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 non-limiting 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. 20110293723, each of which is herein incorporated by reference in its 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. 20110293701, each of which is herein incorporated by reference in its entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International Publication No. WO2011150258 and U.S. Publication No. US20120027806, each of which is herein incorporated by reference in its entirety).

In some embodiments, the synthetic nanocarrier may comprise at least one polynucleotide which encodes at least one adjuvant (*e.g.*, a flagellin protein). In some embodiments, the synthetic nanocarrier may comprise 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. Patent No. 8,241,610; herein incorporated by reference in its entirety). In other embodiments, the synthetic nanocarrier may comprise at least one polynucleotide and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising, optionally comprising an adjuvant, may be formulated by the methods described in International Publication No. WO2011150240 and U.S. Publication No. US20110293700, each of which is herein incorporated by reference in its entirety).

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

In some embodiments, the RNA vaccine may be encapsulated in, linked to and/or associated with zwitterionic lipids. Non-limiting examples of zwitterionic lipids and methods of using zwitterionic lipids are described in U.S. Publication No. 20130216607, the content

of which is herein incorporated by reference in its entirety. In some aspects, the zwitterionic lipids may be used in the liposomes and lipid nanoparticles described herein.

In some embodiments, the RNA vaccine may be formulated in colloid nanocarriers as described in U.S. Publication No. 20130197100, the content of which is herein incorporated by reference in its 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, 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; herein incorporated by reference in its entirety.

In some embodiments, LNPs comprise the lipid KL52 (an amino-lipid disclosed in U.S. Application Publication No. 2012/0295832 expressly incorporated herein by reference in its entirety). Activity and/or safety (as measured by examining one or more of ALT/AST, white blood cell count and cytokine induction) 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 equal or improved mRNA and/or protein expression as compared to LNPs comprising MC3.

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

In other embodiments, RNA (*e.g.*, mRNA) vaccines may be delivered using smaller LNPs which may comprise a 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 80 nm, from about 1 nm to about 90 nm, from about 5 nm to about 100 nm, from about 5 nm to about 10 nm, 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. Exemplary 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; each of which is herein incorporated by reference in its entirety).

In some embodiments, methods of LNP generation comprising SHM, further comprise the mixing of at least two input streams wherein mixing occurs by microstructure-induced 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, each of which is expressly incorporated herein by reference in their entirety.

In some embodiments, the RNA vaccine of the present invention 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 für 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* 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: 647651; which is herein incorporated by reference in its entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present invention may be formulated in lipid nanoparticles created using a micromixer chip such as, but not limited to, those from Harvard Apparatus (Holliston, MA) or Dolomite Microfluidics (Royston, UK). A micromixer 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 invention may be formulated for delivery using the drug encapsulating microspheres described in International Publication No. WO2013063468 or U.S. Patent No. 8,440,614, each of which is herein incorporated by reference in its entirety. The microspheres may comprise a compound of the formula (I), (II), (III), (IV), (V) or (VI) as described in International Publication No.

WO2013063468, the content of which is herein incorporated by reference in its entirety. In other aspects, the amino acid, peptide, polypeptide, lipids (APPL) are useful in delivering the RNA vaccines of the invention to cells (*see* International Publication No. WO2013063468, the contents of which is herein incorporated by reference in its entirety).

In some embodiments, the RNA (*e.g.*, mRNA) vaccines of the present disclosure may be formulated in lipid nanoparticles having a diameter from about 10 to about 100 nm such as, 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, 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 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 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, 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 700 nm, greater than 750 nm, greater than 800 nm, greater than 850 nm, greater than 900 nm, greater than 950 nm or greater than 1000 nm.

In some aspects, the lipid nanoparticle may be a limit size lipid nanoparticle described in International Publication No. WO2013059922, the content of which is herein incorporated by reference in its entirety. The limit 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 dihydrosphingomyelin, a cephalin, a cerebroside, a C8-C20 fatty acid diacylphosphatidylcholine, and 1-palmitoyl-2-oleoyl phosphatidylcholine (POPC). In other aspects 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 vaccines may be delivered, localized and/or concentrated in a specific location using the delivery methods described in International Publication No. WO2013063530, the content of which is herein incorporated by reference in its entirety. As a non-limiting example, a subject may be administered an empty polymeric particle prior to, simultaneously with or after delivering the RNA 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 vaccines may be formulated in an active substance release system (*see e.g.*, U.S. Publication No. US20130102545, the contents of which is herein incorporated by reference in its 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 Publication No. WO2013052167, herein incorporated by reference in its entirety. As another non-limiting example, the nanoparticle described in International Publication No. WO2013052167, herein incorporated by reference in its entirety, may be used to deliver the RNA vaccines described herein.

In some embodiments, the RNA vaccines may be formulated in porous nanoparticle-supported lipid bilayers (protocells). Protocells are described in International Publication No. WO2013056132, the content of which is herein incorporated by reference in its entirety.

In some embodiments, the RNA vaccines described herein may be formulated in polymeric nanoparticles as described in or made by the methods described in US Patent 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 or nanoparticles made by the methods described in US Patent No. 8,518,963, the content of which is herein incorporated by reference in its 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 content of which is herein incorporated by reference in its entirety.

In other embodiments, the RNA (*e.g.*, mRNA) vaccines described herein may be formulated in nanoparticles used in imaging. The nanoparticles may be liposome nanoparticles such as those described in U.S. Publication No. 20130129636, 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. Publication No US20130129636, the contents of which is herein incorporated by reference in its entirety).

5 In some embodiments, the nanoparticles which may be used in the present invention are formed by the methods described in U.S. Patent Application No. 20130130348, the contents of which is herein incorporated by reference in its entirety.

10 The nanoparticles of the present invention 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 contents of which is herein incorporated by reference in its 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.

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

20 The RNA (*e.g.*, mRNA) vaccines of the present invention may be formulated in polyanhydride nanoparticles such as, but not limited to, those described in U.S. Patent No. 8,449,916, the contents of which is herein incorporated by reference in its entirety. The nanoparticles and microparticles of the present invention may be geometrically engineered to modulate macrophage and/or the immune response. In some aspects, the geometrically engineered particles may have varied shapes, sizes and/or surface charges in order to incorporated the polynucleotides of the present invention for targeted delivery such as, but not limited to, pulmonary delivery (*see e.g.*, International Publication No. WO2013082111, the content of which is herein incorporated by reference in its entirety). Other physical features the geometrically engineering particles may have include, but are not limited to, 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 invention may be made by the methods described in International Publication No. WO2013082111, the contents of which is herein incorporated by reference in its entirety.

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In some embodiments, the nanoparticles of the present invention may be water soluble nanoparticles such as, but not limited to, those described in International Publication No. WO2013090601, the content of which is herein incorporated by reference in its 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 diameters (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 invention may be developed by the methods described in U.S. Publication No. US20130172406, the content of which is herein incorporated by reference in its entirety.

In some embodiments, the nanoparticles of the present invention are stealth nanoparticles or target-specific stealth nanoparticles such as, but not limited to, those described in U.S. Publication No. 20130172406, the content of which is herein incorporated by reference in its entirety. The nanoparticles of the present invention may be made by the methods described in U.S. Publication No. 20130172406, the content of which is herein incorporated by reference in its entirety.

In other 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, polyureas, polystyrenes, polyamines, polyesters, polyanhydrides, polyethers, polyurethanes, polymethacrylates, polyacrylates, 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 be made by the methods described in U.S. Publication No. 20130171646, the content of which is herein incorporated by reference in its 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 invention may be embedded 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 Publication No. WO2013123523, the content of which is herein incorporated by reference in its entirety.

Modes of Vaccine Administration

5 RSV RNA (*e.g.*, mRNA) vaccines may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited, to intradermal, intramuscular, intranasal, and/or subcutaneous administration. The present disclosure provides methods comprising administering RNA vaccines to a subject in need thereof. The exact amount required will vary from subject to subject, depending on the species, age, and
10 general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. RSV RNA (*e.g.*, 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 RSV RNA (*e.g.*, mRNA) vaccines compositions may be decided by the attending physician within the
15 scope of sound 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 employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of
20 administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

In some embodiments, RSV RNA (*e.g.*, mRNA) vaccines compositions may be administered at dosage levels sufficient to deliver 0.0001 mg/kg to 100 mg/kg, 0.001 mg/kg
25 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 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
30 International Publication No. WO2013078199, herein incorporated by reference in its 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 certain 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, RSV 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, RSV 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, RSV 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 RSV RNA (*e.g.*, mRNA) vaccine composition may be administered three or four times.

In some embodiments, RSV 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 0.010 mg, 0.025 mg, 0.100 mg or 0.400 mg.

In some embodiments the RSV RNA (*e.g.*, mRNA) vaccine for use in a method of vaccinating a subject is administered the subject 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 vaccine for use in a method of vaccinating a subject is administered to the subject a single dosage of between 10 μg and 400 μg of the nucleic acid vaccine in an effective amount to vaccinate the subject. In some embodiments, a RSV 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 an RSV antigen). In some embodiments, a RSV RNA vaccine is administered 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 RSV RNA vaccine may be administered to a subject as a single dose of 25-100, 25-500, 50-100, 50-500, 50-1000, 100-500, 100-1000, 250-500, 250-1000, or 500-1000 μg. In some embodiments, a RSV 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 RSV RNA (*e.g.*, mRNA) vaccine.

A RSV 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, intravitreal, intramuscular, intradermal, intracardiac, intraperitoneal, and subcutaneous).

RSV RNA vaccine formulations and methods of use

Some aspects of the present disclosure provide formulations of the RSV RNA (*e.g.*, mRNA) vaccine, wherein the RSV RNA 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 anti-RSV antigenic polypeptide). “An effective amount” is a dose of an RSV RNA (*e.g.*, mRNA) vaccine effective to produce an antigen-specific immune response. Also provided herein are methods of inducing an antigen-specific immune response in a subject.

In some embodiments, the antigen-specific immune response is characterized by measuring an anti-RSV antigenic polypeptide antibody titer produced in a subject administered a RSV RNA (*e.g.*, mRNA) vaccine as 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-RSV antigenic polypeptide) or epitope of an antigen. Antibody titer is typically expressed as the inverse of the greatest dilution that provides a positive result. Enzyme-linked immunosorbent assay (ELISA) is a common assay for determining antibody titers, for example.

In some embodiments, an antibody titer is used to assess 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 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 RSV RNA (*e.g.*, mRNA) vaccine.

In some embodiments, an anti-RSV antigenic polypeptide antibody titer produced in a subject is increased by at least 1 log relative to a control (*e.g.*, a control vaccine). For example, anti-RSV antigenic polypeptide antibody titer produced 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 (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased by 1, 1.5, 2, 2.5 or 3 log relative to a control (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in the subject is increased by 1-3 log relative to a control (*e.g.*, a control vaccine). For example, the anti-RSV 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 (*e.g.*, a control vaccine).

In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in a subject is increased at least 2 times relative to a control (*e.g.*, a control vaccine). For example, the anti-RSV 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 (*e.g.*, a control vaccine). In some embodiments, the anti-RSV 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 (*e.g.*, a control vaccine). In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in a subject is increased 2-10 times relative to a control (*e.g.*, a control vaccine). For example, the anti-RSV 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 (*e.g.*, a control vaccine).

A control, in some embodiments, is the anti-RSV antigenic polypeptide antibody titer produced in a subject who has not been administered a RSV RNA (*e.g.*, mRNA) vaccine. In some embodiments, a control is an anti-RSV antigenic polypeptide antibody titer produced in

a subject who has been administered a live attenuated RSV 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-RSV antigenic polypeptide antibody titer produced in a subject administered inactivated RSV vaccine. In some embodiments, a control is an anti-RSV antigenic polypeptide antibody titer produced in a subject administered a recombinant or purified RSV 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-RSV antigenic polypeptide antibody titer produced in a subject who has been administered a RSV virus-like particle (VLP) vaccine (*e.g.*, particles that contain viral capsid protein but lack a viral genome and, therefore, cannot replicate/produce progeny virus). In some embodiments, the control is a VLP RSV vaccine that comprises prefusion or postfusion F proteins, or that comprises a combination of the two.

In some embodiments, an effective amount of a RSV RNA (*e.g.*, mRNA) vaccine is a dose that is reduced compared to the standard of care dose of a recombinant RSV protein vaccine. A “standard of care,” as provided herein, refers to 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 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 RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine, that a physician/clinician or other medical professional would administer to a subject to treat or prevent RSV, or a RSV-related condition, while following the standard of care guideline for treating or preventing RSV, or a RSV-related condition.

In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in a subject administered an effective amount of a RSV RNA vaccine is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered a standard of care dose of a recombinant or purified RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine.

In some embodiments, an effective amount of a RSV 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 RSV protein vaccine. For example, an effective amount of a RSV RNA 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 RSV protein vaccine. In some embodiments, an effective amount of a RSV RNA vaccine is a dose equivalent to an 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 RSV protein vaccine. In some embodiments, an effective amount of a RSV RNA 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 purified RSV protein vaccine. In some embodiments, the anti-RSV antigenic polypeptide antibody titer produced in a subject administered an effective amount of a RSV RNA vaccine is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or protein RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine. In some embodiments, an effective amount of a RSV 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 RSV protein vaccine, wherein the anti-RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine.

In some embodiments, the effective amount of a RSV 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 300-, 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 300-, 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 300-, 9 to 200-, 9 to 100-, 9 to 90-, 9 to 80-, 9 to 70-, 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 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 RSV protein vaccine. In some embodiments, such as the foregoing, the anti-RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP 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-, 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-, 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 RSV protein vaccine. In some embodiments, such as the foregoing, an anti-RSV antigenic polypeptide antibody titer produced in the subject is equivalent to an anti-RSV antigenic polypeptide antibody titer produced in a control subject administered the standard of care dose of a recombinant or purified RSV protein vaccine, or a live attenuated or inactivated RSV vaccine, or a RSV VLP vaccine.

In some embodiments, the effective amount of a RSV RNA (*e.g.*, mRNA) vaccine is a total dose of 50-1000 µg. In some embodiments, the effective amount of a RSV 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, 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, 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, 400-900, 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 RSV RNA (*e.g.*, mRNA) vaccine is 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 RSV 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 RSV 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.

5 *Additional Embodiments*

1. A respiratory syncytial virus (RSV) vaccine, comprising:
at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap, an open reading frame encoding at least one RSV antigenic polypeptide, and a 3' polyA tail.
- 10 2. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 257.
3. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 258.
4. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide is
15 encoded by a sequence identified by SEQ ID NO: 259.
5. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 278.
6. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 279.
- 20 7. The vaccine of paragraph 1, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 280.
8. The vaccine of any one of paragraphs 1-7, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp.
9. The vaccine of any one of paragraphs 1-8, wherein 100% of the uracil in the open
25 reading frame is modified to include N1-methyl pseudouridine at the 5-position of the uracil.
10. The vaccine of any one of paragraphs 1-9, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); and polyethylene glycol (PEG)2000-DMG.
11. The vaccine of paragraph 10, wherein the lipid nanoparticle further comprises
30 trisodium citrate buffer, sucrose and water.
12. 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 SEQ ID NO: 278 and a 3' polyA tail, wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 278 are modified to

include N1-methyl pseudouridine at the 5-position of the uracil nucleotide, optionally wherein the vaccine is formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG)2000-DMG.

- 5 13. 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 SEQ ID NO: 279 and a 3' polyA tail, wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 279 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide, optionally
10 wherein the vaccine is formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG)2000-DMG.

14. 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 SEQ ID NO: 280 and a 3' polyA tail, wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 280 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide, optionally
15 wherein the vaccine is formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG)2000-DMG.
20

15. A respiratory syncytial virus (RSV) vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap, an open reading frame encoding at least one RSV antigenic polypeptide, and a 3' polyA tail.

- 25 16. The vaccine of paragraph 15, wherein the at least one mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 5.

17. The vaccine of paragraph 15, wherein the at least one mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 262.

18. The vaccine of paragraph 15, wherein the at least one RSV antigenic polypeptide
30 comprises a sequence identified by SEQ ID NO: 6.

19. The vaccine of paragraph 15, wherein the at least one RSV antigenic polypeptide comprises a sequence identified by SEQ ID NO: 290.

20. The vaccine of paragraph 15, wherein the mRNA polynucleotide is encoded by a sequence identified by SEQ ID NO: 7.

21. The vaccine of paragraph 15, wherein the mRNA polynucleotide comprises a sequence identified by SEQ ID NO: 263.
22. The vaccine of paragraph 15, wherein the at least one RSV antigenic polypeptide comprises a sequence identified by SEQ ID NO: 8.
- 5 23. The vaccine of paragraph 15, wherein the at least one RSV antigenic polypeptide comprises a sequence identified by SEQ ID NO: 291.
24. The vaccine of any one of paragraphs 15-23, wherein the 5' terminal cap is or comprises 7mG(5')ppp(5')NlmpNp.
25. The vaccine of any one of paragraphs 15-24, wherein 100% of the uracil in the open
10 reading frame is modified to include N1-methyl pseudouridine at the 5-position of the uracil.
26. The vaccine of any one of paragraphs 15-25, wherein the vaccine is formulated in a lipid nanoparticle comprising: DLin-MC3-DMA; cholesterol; 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); and polyethylene glycol (PEG)2000-DMG.
27. The vaccine of paragraph 26, wherein the lipid nanoparticle further comprises
15 trisodium citrate buffer, sucrose and water.
28. 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 SEQ ID NO: 262, and a 3' polyA tail, wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 262 are modified to
20 include N1-methyl pseudouridine at the 5-position of the uracil nucleotide, optionally wherein the vaccine is formulated in a lipid nanoparticle comprising DLin-MC3-DMA, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG)2000-DMG.
29. A respiratory syncytial virus (RSV) vaccine, comprising:
25 at least one messenger ribonucleic acid (mRNA) polynucleotide having a 5' terminal cap 7mG(5')ppp(5')NlmpNp, a sequence identified by SEQ ID NO: 263, and a 3' polyA tail, wherein the uracil nucleotides of the sequence identified by SEQ ID NO: 263 are modified to include N1-methyl pseudouridine at the 5-position of the uracil nucleotide, optionally wherein the vaccine is formulated in a lipid nanoparticle comprising DLin-MC3-DMA,
30 cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), and polyethylene glycol (PEG)2000-DMG.

This invention 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 invention is capable of other embodiments 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.

5

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
10 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.

15 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,
20 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
25 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
30 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.

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 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 concatenation.

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 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)
- (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 pyrophosphatase 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 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 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 2x KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, MA). This system includes 2x
 5 KAPA ReadyMix 12.5 µl; Forward Primer (10 µM) 0.75 µl; Reverse Primer (10 µM) 0.75 µl; Template cDNA 100 ng; 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.

The reaction may be cleaned up using Invitrogen's PURELINK™ PCR Micro Kit
 10 (Carlsbad, CA) per manufacturer's instructions (up to 5 µg). Larger reactions may require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA may be quantified using the NANODROP™ 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
 20 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:

25	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 (25mM each)	0.2 µl
30	4)	RNase Inhibitor	20 U
	5)	T7 RNA polymerase	3000 U
	6)	dH ₂ O	up to 20.0 µl. 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 MEGACLEAR™ Kit (Austin, TX) following the manufacturer's instructions. This kit can purify up to 500 µg of RNA. Following the cleanup, the RNA polynucleotide may be quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide 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 µg-180µg and dH₂O up to 72 µl. 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 10x 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, TX) following the manufacturer's instructions. Following the cleanup, the RNA may be quantified using the NANODROP™ (ThermoFisher, Waltham, MA) and analyzed by agarose gel electrophoresis to confirm the RNA polynucleotide is the proper size and that no degradation of the RNA has 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 in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, TX) (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, 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: 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 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 polypeptide, 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 multiple bands or streaking bands. Chemically modified RNA polynucleotides with a single HPLC peak also correspond 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 IFN-beta, 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 nuclease treatment. Nuclease treatment of capped polynucleotides yield a mixture of free nucleotides and the capped 5'-5-triphosphate 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.

10 *Example 8: 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, CA) and run for 12-15 minutes, according to the manufacturer protocol.

15

Example 9: 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.

20

Example 10: Formulation of Modified mRNA Using Lipidoids

RNA (e.g., mRNA) polynucleotides may be formulated 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.

30

Example 11: RSV RNA Vaccine

A RSV RNA (e.g., mRNA) vaccine may comprise, for example, at least one RNA polynucleotide encoded by at least one of the following sequences, or by at least one fragment of the following sequences, or by derivatives and variants thereof. A RSV RNA

vaccine may comprise, for example, at least one RNA (*e.g.*, mRNA) polynucleotide having at least one chemical modification, *e.g.* the RSV vaccine may comprise, for example, at least one chemically modified RNA (*e.g.*, mRNA) polynucleotide encoded by at least one of the following (DNA) sequences or by at least one fragment of the following sequences or by derivatives or variants thereof:

RSV # 1

ATGGAGCTGCTCATCCTCAAAGCAAATGCCATCACCCTATCCTGACCGCCGTCACCTTTCTGCTTC
GCCTCCGGCCAAAATATCACCGAAGAGTTCTATCAGTCCACCTGCTCTGCCGTTTCTAAAGGTTAC
10 CTGTCAGCCCTTAGAACAGGGTGGTATACCTCTGTTATTACCATTGAGTTGTCCAACATTAAGAAG
AACAAAGTGCAATGGCACAGACGCTAAGGTTAAGCTCATCAAGCAGGAGCTCGACAAATATAAAAA
TGCCGTCACGGAGCTGCAGTTATTGATGCAGAGCACCCAGGCGACAAACAACCGTGCACGACGCG
AGCTACCCCGATTTCATGAACTACACCCTCAATAATGCAAAGAAGACAAATGTGACGCTCTCTAAG
AAGCGCAAGCGTCGCTTTCTGGGCTTTCTTCTCGGGGTTGGGAGCGCGATCGCAAGCGGCGTGGCT
15 GTATCAAAAGTGCTTCATCTTGAGGGAGAAGTGAATAAAATCAAAAGTGCTCTGCTATCTACAAA
CAAAGCCGTTGTATCACTGTCCAACGGAGTGTCCGTGCTCACGTCCAAAGTGCTAGATTGAAAGAA
TTACATCGATAAGCAGCTGCTCCCTATTGTGAACAAACAATCATGTTCCATCAGTAACATTGAAAC
AGTCATCGAGTTTCAACAGAAAAACAATAGACTGCTGGAGATTACCAGAGAATTTTCGGTTAACG
CCGGCGTGACTACCCCTGTAAGCACCTACATGTTGACAAACTCCGAACCTTTTGTCAGTGAATAACG
20 ATATGCCTATTACTAATGATCAGAAAAAATTGATGTCCAATAATGTCCAAATCGTCAGGCAACAGT
CCTACAGTATCATGTCTATTATTAAGGAGGAGGTCCTTGCATACGTGGTGCAACTGCCATTATACG
GAGTCATTGATACTCCCTGTTGGAACTCCATACAAGCCCCCTGTGCACTACTAACACTAAAGAGG
GATCAAAATATTTGTCTCACTCGGACAGATAGAGGTTGGTACTGTGATAATGCTGGCTCAGTGTCTAT
TCTTTCCACAGGCTGAAACCTGCAAGGTTCAAGTCAAACAGGGTGTTTTGCGATACCATGAATTCTC
25 TAACCCTCCCCAGTGAGGTGAACCTGTGTAATGTGGATATATTCAACCCCAAGTATGATTGTAAGA
TCATGACCTCCAAGACGGACGTGAGTAGCAGTGTATCACCTCCCTGGGGGCCATTGTATCCTGCT
ACGGAAAAACGAAATGTACTGCCTCGAACAAAAATAGGGGAATCATCAAAACCTTTTAGTAATGGA
TGCGACTACGTATCTAATAAAGGTGTTGACACAGTGTCAAGTGGCAACACACTGTATTACGTGAAT
AAGCAAGAAGGGAAGTCGCTGTATGTCAAAGGGGAGCCTATCATTAATTTTATGACCCACTGGTT
30 TTCCCAGCGATGAGTTTCGACGCCAGCATTAGTCAGGTTAATGAGAAAAATCAACCAGTCCTTGGA
TTTATTCGTAAGAGTGATGAATTGCTCCATAATGTGAACGCTGGTAAATCCACTACCAACATTATG
ATAACTACCATCATCATAGTAATAATAGTAATTTTACTGTCTCTGATCGCTGTGGGCCTGTTACTGT
ATTGCAAAGCCCGCAGTACTCCTGTACCTTATCAAAGGACCAGCTGTCTGGGATAAACAACATCG
CGTTCTCCAAT (SEQ ID NO: 1)

RSV # 2

ATGGAAGTCTCATTTTGAAGGCAAACGCTATCACGACAATACTCACTGCAGTGACCTTCTGTTTT
GCCTCAGGCCAGAACATAACCGAGGAGTTTATCAATCTACATGCAGCGCTGTATCTAAAGGCTAC
40 CTGAGTGCCTCCGCACAGGATGGTACACCTCCGTGATCACCATCGAGCTCAGCAATATTAAAGA
GAACAAGTGCAATGGTACCGACGCTAAAGTCAAACCTTATCAAGCAGGAAGTGCACAAATATAAAA
ACGCTGTGACCGAGCTGCAGTTATTGATGCAGAGTACACCTGCCACCAATAACAGAGCTAGGAGG
GAGTTGCCTAGGTTTATGAACTACACTCTCAACAACGCGAAAAAAACCAATGTGACGCTATCCAA
GAAACGGAAGAGGAGGTTCTTGGGGTTTCTTTTAGGGGTGGGCTCTGCCATTGCTTCCGGCGTGGC
45 TGTATGTAAAGTTCTCCACCTCGAGGGAGAGGTTAATAAGATTAAAGTCGGCCCTGCTGAGTACTAA
CAAAGCAGTGGTGTGCTGAGTAACGGAGTAAGTGTGTTAACATTTAAGGTGCTGGACCTCAAGA
ATTATATTGACAAACAGTTGCTTCTTCTAAACAAACAGAGCTGTTCAATAAGTAATATTGAAA
CTGTTATTGAGTTTCAGCAGAAGAACAACAGGCTTCTTGAGATTACACGCGAGTTCAAGTGTCAATG
CCGGCGTTACAACACCCGTGTCTACCTACATGCTGACGAATTCTGAGCTTCTCTCTCATAAACG
50 ACATGCCCATTACGAATGACCAAAAAAAACCTTATGTCCAACAACGTGCAGATTGTGCGACAGCAA
TCCTATAGCATTATGTGTATCATCAAGGAAGAGGTACTCGCTTATGTTGTGCAGCTACCCTCTAT
GGTGTGATTGACACCCCTGTTGGAAGCTGCATACCGTCCACTCTGCACCACTAACACAAAGGAA
GGGAGCAATATTTGCCCTCACTCGAACCAGCAGGGGGTGGTATTGCGATAATGCGGGCTCCGTGTCC
TTCTTTCCACAGGCTGAAACTTGTAAGGTACAGTCAAACCGCGTGTCTGTGATACTATGAATTCTC
TGACTCTTCCCAGCGAGGTTAATCTCTGCAACGTGCACATTTTCAATCCTAAATATGACTGCAAGA
55 TCATGACCAGCAAGACCGACGTCTCCAGCTCAGTAATCACTAGCCTAGGGGCCATTGTAAGCTGCT
ATGGCAAAACCAAGTGTACTGCCTCTAATAAGAACAGAGGCATAATTAAACCTTTTCAATGGC

TGTGACTATGTGTCGAATAAGGGCGTCGACACGGTCTCAGTAGGGAATACCCTCTACTACGTAAAC
 AAACAGGAAGGCAAATCCCTTTATGTAAAGGGCGAGCCCATCATAAATTTCTACGACCCACTTGTG
 TTCCCCAGTGATGAATTCGATGCATCAATCTCCAGGTGAACGAAAAGATCAATCAATCCCTTGCT
 TTTATACGAAAGTCAGATGAACTCCTGCATAACGTGAATGCTGGGAAATCTACAACCAACATCATG
 5 ATCACTACCATCATTATTGTGATTATCGTAATTCTGCTATCCTTGATTGCTGTCGGGCTGCTTCTGT
 ACTGTAAGGCCAGATCGACGCCTGTGACCCTTTCAAAAGACCAACTTAGCGGTATCAATAATATTG
 CCTTTAGCAAT (SEQ ID NO: 2)

A RSV vaccine may comprise, for example, at least one RNA (*e.g.*, mRNA)

- 10 polynucleotide having an open reading frame that encodes at least one of the following
 antigenic polypeptide sequences or at least one fragment of the following sequences:

RSV # 1

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNG
 15 TDAKVKLIKQELDKYKNAVTELQLLMQSTQATNNRARRELPRFMNYTLNNAKKTNTVLSKKRKRRL
 GFLGVSIAISGVAVSKVLHLEGEVNIKSALLSTNKAVVSLSNGVSVLTISKVLDLKNYIDKQLLPV
 NKQSCSISNIETVIEFQQKNRRLLEITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNN
 VQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGNSICLTRDRGWYCDNA
 GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
 20 YGKTKCTASNKNRGIKTFNSGCDYVSNKGVDTVSVGNTRYVYVKNQEGKSLYVKGEPIINFYDPLVFPS
 DEFDAISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTHIIVILLSLIAVGLLLYCKARSTPVT
 SKDQLSGINNIAFSN (SEQ ID NO: 3)

The underlined region represents a signal peptide sequence. The underlined regions can be
 substituted with alternative sequences that achieve the same or similar functions, or it can be
 25 deleted.

RSV # 2

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKNCNG
 30 TDAKVKLIKQELDKYKNAVTELQLLMQSTPATNNRARRELPRFMNYTLNNAKKTNTVLSKKRKRRL
 GFLGVSIAISGVAVCKVLHLEGEVNIKSALLSTNKAVVSLSNGVSVLTFKVLDLKNYIDKQLLPIL
 NKQSCSISNIETVIEFQQKNRRLLEITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNN
 VQIVRQQSYSIMCIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGNSICLTRDRGWYCDNA
 GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
 35 YGKTKCTASNKNRGIKTFNSGCDYVSNKGVDTVSVGNTRYVYVKNQEGKSLYVKGEPIINFYDPLVFPS
 DEFDAISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTHIIVILLSLIAVGLLLYCKARSTPVT
 SKDQLSGINNIAFSN (SEQ ID NO: 4)

The underlined region represents a signal peptide sequence. The underlined regions can be
 substituted with alternative sequences that achieve the same or similar functions, or it can be
 deleted.

40 *Example 12: Mouse immunogenicity*

In this example, assays were carried out to evaluate the immune response to RSV
 vaccine antigens delivered using an mRNA/LNP platform in comparison to protein antigens.

Female Balb/c (CRL) mice (6-8 weeks old; N= 10 mice per group) were administered
 45 RSV mRNA vaccines or protein vaccines. The mRNA vaccines were generated and
 formulated in MC3 lipid nanoparticles. The mRNA vaccines evaluated in this study
 included:

MRK-1 membrane-bound RSV F protein

MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)

MRK-5 RSV F construct

MRK-6 RSV F construct

MRK-7 RSV F construct

MRK8 RSV F construct

5 MRK9 membrane-bound RSV G protein

MRK11 truncated RSV F protein (ectodomain only); construct modified to include an Ig secretion peptide signal sequence

MRK12 DS-CAV1 (non-membrane bound form); modified to include an Ig secretion peptide signal sequence

10 MRK13: MRK-5 construct modified to include an Ig secretion peptide signal sequence

MRK14: MRK-6 construct modified to include an Ig secretion peptide signal sequence

15 MRK16: MRK-8 construct modified to include an Ig secretion peptide signal sequence

The DNA sequences encoding the above-mentioned 12 mRNAs and related amino acid sequences are listed below.

20 MRK-1 membrane-bound RSV F protein/MRK_01_F (full length, Merck A2 strain)/SQ-030268:

ATGGAGCTGCTCATCCTCAAAGCAAATGCCATCACCCTATCCTGACCGCCGTCACCTTCTGCTTC
 GCCTCCGGCCAAAATATCACCGAAGAGTTCTATCAGTCCACCTGCTCTGCCGTTTCTAAAGTTAC
 CTGTCAGCCCTTAGAACAGGGTGGTATACCTCTGTTATTACCATTGAGTTGTCCAACATTAAGAAG
 25 AACAAGTGCAATGGCACAGACGCTAAGGTTAAGCTCATCAAGCAGGAGCTCGACAAATATAAAAA
 TGCCGTCACGGAGCTGCAGTTATTGATGCAGAGCACCCAGGCGACAAACAACCGTGCACGACGCG
 AGCTACCCCGATTTCATGAACCTACACCTCAATAATGCAAAGAAGACAAATGTGACGCTCTCTAAG
 AAGCGCAAGCGTCGCTTTCTGGGCTTTCTTCTCGGGGTTGGGAGCGCGATCGCAAGCGGCGTGGCT
 GTATCAAAAGTGCTTCATCTTGAGGGAGAAGTGAATAAAATCAAAAGTGCTCTGCTATCTACAAA
 30 CAAAGCCGTTGTATCACTGTCCAACGGAGTGTCCGTGCTCACGTCCAAAGTGCTAGATTTGAAGAA
 TTACATCGATAAGCAGCTGCTCCCTATTGTGAACAAACAATCATGTTCCATCAGTAACATTGAAAC
 AGTCATCGAGTTTCAACAGAAAAACAATAGACTGCTGGAGATTACCAGAGAATTTTCGGTTAACG
 CCGGCGTGACTACCCCTGTAAGCACCTACATGTTGACAAACTCCGAACCTTTTGTCACTGATAAACG
 ATATGCCTATTACTAATGATCAGAAAAAATTGATGTCCAATAATGTCCAAATCGTCAGGCAACAGT
 35 CCTACAGTATCATGTCTATTATTAAGGAGGAGGTCCTTGCATACGTGGTGCAACTGCCATTATACG
 GAGTCATTGATACTCCCTGTTGGAACTCCATACAAGCCCCCTGTGCACTACTAACACTAAAGAGG
 GATCAAAATATTTGTCTCACTCGGACAGATAGAGGTTGGTACTGTGATAATGCTGGCTCAGTGTCAT
 TCTTTCCACAGGCTGAAACCTGCAAGGTTTCAGTCAAACAGGGTGTTTTGCGATACCATGAATTCTC
 TAACCCTCCCCAGTGAGGTGAACCTGTGTAATGTGGATATATTCAACCCCAAGTATGATTGTAAGA
 40 TCATGACCTCCAAGACGGACGTGAGTAGCAGTGTTATCACCTCCCTGGGGGCCATTGTATCCTGCT
 ACGGAAAAACGAAATGTACTGCCTCGAACAAAAATAGGGGAATCATCAAACTTTTAGTAATGGA
 TCGACTACGTATCTAATAAAGGTGTTGACACAGTGTGAGTCGGCAACACACTGTATTACGTGAAT
 AAGCAAGAAGGGAAGTCGCTGTATGTCAAAGGGGAGCCTATCATTAATTTTATGACCCACTGGTT
 TTCCCAGCGATGAGTTTCGACGCCAGCATTAGTCAGGTTAATGAGAAAATCAACCAGTCCTTGGCA
 45 TTTATTCGTAAGAGTGATGAATTGCTCCATAATGTGAACGCTGGTAAATCCACTACCAACATTATG
 ATAACCTACCATCATCATAGTAATAATAGTAATTTTACTGTCTCTGATCGCTGTGGGCCTGTTACTGT

ATTGCAAAGCCCGCAGTACTCCTGTCACCTTATCAAAGGACCAGCTGTCTGGGATAAACAACATCG
CGTTCTCCAAT (SEQ ID NO:5)

5 MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNG
TDAKVKLIKQELDKYKNAVTELQLLMQSTQATNNRARRELPRFMNYTLNNAKKTNTLSKKRKRRL
GFLLGVGSAIASGVA VSKVLHLEGEV NKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIV
NKQSCSISNIETVIEFQQKNRRLLEITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNN
VQIVRQQSYSIMSIIKEEVLAYV VQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNA
10 GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
YGKTKCTASKNRGIKTF SNGCDYVS NKGVDTVSVGNTLYYV NKGEGKSLYVKGEPIINFYDPLVFP
DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTHIIVILLSLIAVG LLLYCKARSTPVT
SKDQLSGINNI AFSN (SEQ ID NO:6)

15 The underlined region represents a signal peptide sequence. The underlined regions can be
substituted with alternative sequences that achieve the same or similar functions, or can be
deleted, as shown below.

20 FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNGTDAKVKLIKQELDKYKNAV
TELQLLMQSTQATNNRARRELPRFMNYTLNNAKKTNTLSKKRKRRLGFLLGVGSAIASGVA VSKV
LHLEGEV NKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIV NKQSCSISNIETVIEFQQKN
NRLLEITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLA
YV VQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVF
CDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSCY GKTKCTASKNRGIKTF S
NGCDYVS NKGVDTVSVGNTLYYV NKGEGKSLYVKGEPIINFYDPLVFP SDEFDASISQVNEKINQSLAFI
25 RKSDHELLHNVNAGKSTTNIMITTHIIVILLSLIAVG LLLYCKARSTPVTLSKDQLSGINNI AFSN (SEQ
ID NO: 290)

MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)/MRK_04_Prefusion
F/DS-CAV1 (Full length, S155C/S290C/S190F/V207L)/SQ-030271:

30 ATGGAAGTGCATTTTGAAGGCAAACGCTATCACGACAATACTCACTGCAGTGACCTTCTGTTTT
GCCTCAGGCCAGAACATAACCGAGGAGTTTTATCAATCTACATGCAGCGCTGTATCTAAAGGCTAC
CTGAGTGCCTCCGCACAGGATGGTACACCTCCGTGATCACCATCGAGCTCAGCAATATTAAAGA
GAACAAGTGCAATGGTACCGACGCTAAAGTCAAACCTTATCAAGCAGGAACCTCGACAAATATAAAA
35 ACGCTGTGACCGAGCTGCAGTTATTGATGCAGAGTACACCTGCCACCAATAACAGAGCTAGGAGG
GAGTTGCCTAGGTTTATGAACTACACTCTCAACAACGCGAAAAAACC AATGTGACGCTATCCAA
GAAACGGAAGAGGAGGTTCTCTGGGGTTTCTTTTAGGGGTGGGCTCTGCCATTGCTTCCGGCGTGGC
TGTATGTAAAGTTCTCCACCTCGAGGGAGAGGTTAATAAGATTAAAGTCGGCCCTGCTGAGTACTAA
CAAAGCAGTGGTGTGCTGAGTAACGGAGTAAGTGTGTTAACATTTAAGGTGCTGGACCTCAAGA
40 ATTATATTGACAAACAGTTGCTTCTTCTTAAACAAACAGAGCTGTTCAATAAGTAATATTGAAA
CTGTTATTGAGTTT CAGCAGAAGAACAACAGGCTTCTTGAGATTACACGCGAGTTCAGTGTCAATG
CCGGCGTTACAACACCCGTGTCTACCTACATGCTGACGAATTCTGAGCTTCTCTCTCATAAACG
ACATGCCCATTACGAATGACCAAAAAAACTTATGTCCAACAACGTGCAGATTGTGCGACAGCAA
TCCTATGAGCATTATGTGTATCATGAAGGAAGAGGTACTGCTTATGTTGTGACGCTACCACCTGAT
45 GGTGTGATTGACACCCCTGTTGGAAGGTGCATACCAGTCCACTCTGCACCACTAACACAAAGGAA
GGGAGCAATATTTGCCCTCACTCGAACCGACAGGGGGTGGTATTGCGATAATGCGGGCTCCGTGTCC
TTCTTTCCACAGGCTGAAACTTGTAAGGTACAGTCAAACCGCGTGTCTGTGATACTATGAATTCTC
TGACTCTTCCCAGCGAGGTTAATCTCTGCAACGTGACATTTTCAATCCTAAATATGACTGCAAGA
TCATGACCAGCAAGACCGACGTCTCCAGCTCAGTAATCACTAGCCTAGGGGCCATTGTAAGCTGCT
50 ATGGCAAAACCAAGTGTACTGCCTCTAATAAGAACAGAGGCATAATTAACCTTTTCAATGGC
TGTGACTATGTGTGCAATAAGGGCGTCGACACGGTCTCAGTAGGGAATACCCTCTACTACGTTAAC
AAACAGGAAGGCAAATCCCTTTATGTAAAGGGCGAGCCCATCATAAATTTCTACGACCCACTTGTG
TTCCCCAGTGATGAATTCGATGCATCAATCTCCAGGTGAACGAAAAGATCAATCAATCCCTTGCT
TTTATACGAAAGTCAGATGAACTCCTGCATAACGTGAATGCTGGGAAATCTACAACCAACATCATG
ATCACTACCATCATTATTGTGATTATCGTAATTCTGCTATCCTTGATTGCTGTGCGGGCTGCTTCTGT
55 ACTGTAAGGCCAGATCGACGCCTGTGACCCTTTCAAAGACCAACTTAGCGGTATCAATAATATTG
CCTTTAGCAAT (SEQ ID NO:7)

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKNCNG
TDAKVKLIKQELDKYKNAVTELQLLMQSTPATNNRARRELPRFMNYTLNNAKKTNTLSKKRKRRL

GFLLGVGSAIASGVA VCKVLHLEGEV NIKSALLSTNKAVVSLN GVS VLT FKVLDLKNYIDKQLLPIL
 NKQSCSISNIETVIEFQ QKNRRLLEITREFSVNAGV TTPVSTYMLTNSELLSLINDMPITNDQKKLMSNN
 VQIVRQQSYSIMCIIKEEV LAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNA
 GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
 5 YGKTKCTASNKNRGIKTF SNGCDYVSNKGVDTVSVGN TLYYV NKQEGKSLYVKGEPIINFYDPLVFPS
 DEFDAISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTHIIVILLSLIAVG LLLYCKARSTPVTLSKDQLSGINNIASFN (SEQ ID NO:8)

The underlined region represents a signal peptide sequence. The underlined regions can be
 substituted with alternative sequences that achieve the same or similar functions, or can be
 10 deleted, as shown below.

FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNGTDAKV KLIKQELDKYKNAV
 TELQLLMQSTPATNNRRELPRFMNYTLNNAKKTNVTL SKKRKRRFLGFLLGVGSAIASGVA VCKVL
 15 HLEGEV NIKSALLSTNKAVVSLN GVS VLT FKVLDLKNYIDKQLLPILNKQSCSISNIETVIEFQ QKNR
 LLEITREFSVNAGV TTPVSTYMLTNSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMCIIKEEV LAY
 VVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVFC
 DTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCY GKTKCTASNKNRGIKTF S
 GCDYVSNKGVDTVSVGN TLYYV NKQEGKSLYVKGEPIINFYDPLVFPSDEFDAISQVNEKINQSLAFIR
 20 KSDHELLHNVNAGKSTTNIMITTHIIVILLSLIAVG LLLYCKARSTPVTLSKDQLSGINNIASFN (SEQ ID
 NO: 291)

MRK-5 RSV F Construct:

ATGGAAC T GCTCATCCTTAAAGCCAACGCGATAACGACCATTCTGACCGCCGTGACCTTCTGCTTC
 25 GCCAGCGGCCAGAACATTACCGAAGAGT TTTACCAGAGCACGTGCTCTGCCGTGAGCAAAGGTTA
 TCTGAGCGCTTTAAGAACTGGCTGGTACACCAGTGTTATTACTATAGAGCTGTCAAATATTA AAAAA
 GAATAAATGCAACGGGACCGATGCCAAAGTAAAATTAATTAAGCAGGAATTGGACAAGTATAAG
 AATGCAGTGACAGAGTTGCAGCTCCTGATGCAGAGCACACAAGCTACAAACAATCGCGCTCGCCA
 GCAGCAACAGCGGTTTTTAGGGTTCCTGCTAGGGGTGGGGTCAGCCATTGCCTCTGGAGTGGCAGT
 30 GTCCAAAGTGCTGCATCTGGAAGGGGAAGTTAACAAGATAAAATCCGCACTCCTCAGCACCAATA
 AAGCCGTGGTCTCCCTGTCCAATGGAGTATCAGTTTGTACAAGCAAGGTGCTGGACCTGAAGAATT
 ATATAGATAAGCAGTTACTGCCAATAGTGAATAAACAGTCATGCTCAATTAGCAACATTGAGACA
 GTTATCGAATTCCAGCAGAAAAATAATAGGCTTCTGGAAATAACTCGGAATTCTCAGTAAATGCC
 GGAGTGACCACACCCGTATCGACTTATATGCTTACAACTCTGAAC TGTGCTTCTGCTGATTACGAT
 35 ATGCCAATAACAAATGACCAGAAAGTAAGTAATGAGCAACAATGTGCAGATTGTAAGACAGCAGTC
 TTA CTCAATAATGTCTATAATAAAGAGGAGGTGTTGGCATATGTGGTGCAACTGCCTCTCTATGG
 CGTGATCGATACTCCTTGCTGGAAGTTACATACATCTCCACTGTGTACA ACTAATACTAAGGAGGG
 TAGCAATATTTGTCTGACACGCACAGATCGGGGTTGGTATTGCGACAACGCGGGCAGTGTGAGCTT
 TTTCCCTCAGGCCGAAACCTGTAAGGTTCAATCTAATCGGGTATTTT GCGACACAATGAACAGCCT
 40 GACCCTTCCGTCCGAAGTTAATTTGTGCAACGTCGACATCTTCAATCCTAAATATGACTGCAAAAT
 CATGACTTCTAAAACCGACGTATCCAGCTCAGTGATAACAAGCCTTGGGGCAATTGTAAGCTGCTA
 TGGCAAGACGAAGTGCACCGCTAGTAACAAGAACCGGGGATTATTAAGACTTTTTTCGAACGGAT
 GCGATTACGTCTCCAACAAAGGCGTCGATACTGTGTCCGTGGGAAACACCCTCTACTATGTGAACA
 AGCAGGAAGGCAAAAGCCTCTACGTCAAAGGAGAGCCTATCATCAATTTCTACGACCCTCTAGTA
 45 TTCCCTTCAGACGAATTTGACGCATCAATTTCCAGGTGAACGAGAAAATAAATCAAAGCTTAGCC
 TTTATCCGCAAGAGTGATGAGTTGCTTCAACAGTCAACGCCGGCAAATCAACCACTAAT (SEQ ID
 NO:9)

MELLILKANAITTILTA VTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNG
 50 TDAKV KLIKQELDKYKNAVTELQLLMQSTQATNNRARQQQRFLGLLGVGSAIASGVA VSKVLHLE
 GEV NIKSALLSTNKAVVSLN GVS VLT SKVLDLKNYIDKQLLP IVNKQSCSISNIETVIEFQ QKNRRLLE
 ITREFSVNAGV TTPVSTYMLTNSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEV LAYVVQ
 LPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTM
 55 NSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCY GKTKCTASNKNRGIKTF SNGCDY
 VSNKGVDTVSVGN TLYYV NKQEGKSLYVKGEPIINFYDPLVFPSDEFDAISQVNEKINQSLAFIRKSDE
 LLHNVNAGKSTTN
 (SEQ ID NO:10)

The underlined region represents a signal peptide sequence. The underlined regions can be substituted with alternative sequences that achieve the same or similar functions, or it can be deleted, as shown below.

5 FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKKNCNGTDAKVKLIKQELDKYKNAV
TELQLLMQSTQATNNRARRQQQRFLGFLGVSIAISGVAVSKVLHLEGEVNIKSALLSTNKAVVSL
SNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNRRLLEITREFSVNAGVTTTPVSTYML
TNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVYVQLPLYGVIDTPCWKLHTSPLC
10 TTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDFNPK
YDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFSTNGCDYVSNKGVDTVSVGNTLYYV
NKQEGKSLYVKGEPIINFYDPLVFPSEFDASISQVNEKINQSLAFIRKSDELLHNVNAGKSTTN (SEQ ID
NO: 292)

MRK-6 RSV F Construct:

15 ATGGAACCTCTTGATCCTGAAGGCTAATGCAATAACAACAATTCTGACAGCAGTCACCTTTTGCTTC
GCCAGCGGACAGAATATTACGGAGGAGTTTATCAATCTACCTGTAGTGCCGTGAGCAAGGGGTG
CCTGTCTGCCCTGAGGACGGGATGGTACACATCCGTGATCACCATCGAGTTGTCTAACATTAATAA
GAACAAGTGCAACGGAAGTACGCCAAGGTGAAGCTCATTAGCAAGAGCTCGACAAATATAAG
20 AATGCGGTTACAGAACTACAGCTACTAATGCAGTCCACACAGGCAACCAATAACCGAGCACGTCA
GCAGCAGCAACGCTTCCTTGGCTTCCTGCTCGGGGTTGGCTCGGCAATTGCATCCGGAGTGGCTGT
TTCCAAGGTTTTGCACCTTGAGGGAGAGGTCAATAAGATCAAGAGCGCCCTCCTGTCAACTAATAA
GGCCGTGGTCAGCCTTTCCAACGGTGTCTGTGTAACTCAAAAGTGCTCGACCTTAAAAACTA
TATCGATAAGCAGCTGCTGCCCATAGTGAACAAACAGTCCTGTTCTATCAGTAATATCGAGACAGT
25 GATCGAATTCCAGCAGAAGAACAATCGTCTGCTGGAAATTACAAGGGAGTTTCAGCGTAAACGCTG
GAGTCACAACCCCCGTGTCCACTTACATGCTGACCAATTCGAGCTGCTGAGTTTGATTAATGATA
TGCCCATTCAGAACGATCAGAAGAACTGATGTCGAATAATGTTTCAGATCGTTAGGCAGCAGTCTT
ATAGCATCATGAGTATTATCAAAGAGGAGGTCTCTGCCTATGTGGTTTCAGCTGCCTCTCTACGGCG
30 TTATAGACACCCCATGCTGGAAGCTTCACACCTCTCTCTGTGTACGACCAATACAAAGGAGGGCT
CAACATTTGCCTTACCCGCACAGATAGAGGATGGTACTGCGATAATGCTGGCTCTGTGTCTTTCT
TTCTCAGGCCGAAACATGTAAGGTACAGTCCAATAGGGTATTTTGCACACCATGAACTCCCTAA
CCTTACCAAGTGAAGTGAACCTCTGCAATGTGGACATCTTTAACCCGAAGTATGACTGCAAAATCA
TGACTTTCAAAGACAGACGTGTCCAGTAGTGTGATTACCTCACTGGGCGCAATCGTTTCATGCTATG
35 GGAAGACAAAGTGCACCGCAAGCAAGAATCGGGGCATCATCAAAACCTTCAGTAACGGTTGT
GACTATGTTTCAAACAAGGGAGTCGATACCGTGTCTGGTGGGCAATACTTTACTACGTGAATAAA
CAGGAGGGGAAATCACTGTATGTGAAAGGTGAGCCGATCATTAACTTTTACGACCCTCTCGTGT
CCCTCCGATGAGTTCGACGCATCCATCAGTCAGGTCAATGAGAAAATCAACCAATCTCTCGCCTTC
ATTAGAAAATCTGACGAATTACTGAGTGCCATTGGAGGATATATTCGGGAGGCTCCAGGGACGG
40 GCAGGCTTACGTCCGAAAGGATGGAGAATGGGTCCTACTGAGCACATTTCTA (SEQ ID NO:11)

The underlined region represents a sequence coding for foldon. The underlined region can be substituted with alternative sequences which achieve a same or similar function, or can be deleted.

45 MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKKNCNG
TDAKVKLIKQELDKYKNAVTELQLLMQSTQATNNRARRQQQRFLGFLGVSIAISGVAVSKVLHLE
GEVNIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNRRLLE
ITREFSVNAGVTTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVYVQ
LPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTM
NSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFSTNGCDY
50 VSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSEFDASISQVNEKINQSLAFIRKSDE
LLSAIGGYIPEAPRDGQAYVRKDGWVLLSTFL (SEQ ID NO:12)

The first underlined region represents a signal peptide sequence. The first underlined regions can be substituted with alternative sequences that achieve the same or similar functions, or it can be deleted, as shown below. The second underlined region represents a foldon. The
55 second underlined region can be substituted with alternative sequences which achieve a same or similar function.

FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNGTDAKVKLIKQELDKYKNAV
 TELQLLMQSTPATNNRARRQQQRFLGFLGVSIAISGVAVSKVLHLEGEVNIKSALLSTNKAVVSL
 SNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNNRLLLEITREFSVNAGVTPVSTYML
 TNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIKEEVLAYVYVQLPLYGVIDTPCWKLHTSPLC
 5 TTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPK
 YDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNNGCDYVSNKGVDTVSVGNTLYYV
 NKQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDELL (SEQ ID NO: 293)

MRK-7 RSV F Construct:

ATGGAGCTCCTGATCTTGAAGGCGAATGCCATTACCACCATCCTCACC GCAGTAAC TTTCTGTTTC
 GCAAGTGGCCAGAATATAACAGAAGAGTTCTATCAGTCAACCTGTAGCGCAGTCTCAAAGGGGTA
 TTTATCAGCACTGAGAACCGGTTGGTATACCAAGTGTATTACAATAGAGCTGAGTAACATAAAGGA
 GAATAAGTGCAACGGCACTGACGCCAAGGTCAAGTCTATCAAACAGGAACTCGATAAATACAAGA
 15 ACGTGTCTACTGAACTGCAGCTGCTGATGCAAAGCACCCCGCCACCAACAATAGGGCCCCGCAGA
 GAGCTTCCTAGATTTATGAACTACACTCTGAACAACGCCAAAAAGACCAATGTAACACTGTCAA
 GAAACAGAAACAGCAGGCTATTGCAAGCGGTGTGGCTGTGTCTAAAGTGCTGCATCTCGAGGGGG
 AGGTCAACAAGATCAAATCCGCATTGCTCAGCACCAACAAGGCTGTGGTGAGCCTGTCCAATGGT
 GTCTCAGTGCTCACCAGCAAAGTGCTGGACCTGAAGAATTATATTGATAAGCAGCTGCTACCCATA
 20 GTCAACAAACAGTCATGCTCCATATCTAATATTGAGACTGTCTCGAGTTCCAACAGAAGAACAAT
 CGCCTGCTGGAGATTACCAGGGAGTTCTCAGTCAATGCCGGGGTCACGACACCCGTTAGTACTTAT
 ATGCTTACCAACTCCGAGCTTCTCTCTTTGATCAATGACATGCCAATTACTAACGACCAGAAGAAG
 TTGATGTCTAACAATGTACAGATCGTTCGCCAGCAGTCTTATCCATTATGTGATTATTAAAGAG
 GAGGTTCTTGCATACGTCGTGCAGTTGCCATTATATGGAGTCATCGACACCCCTGCTGGAACTG
 25 CATACGTCACCATTATGCACCACGAATACAAAGGAGGGCAGTAATATTTGTCTTACACGGACTGAT
 CGAGGCTGGTATTGTGATAACGCAGGCTCGGTGTCTTCTTCCACAGGCTGAAACCTGTAAGGTG
 CAATCTAATAGGGTGTTTTTGCATACCATGAATTCTCTGACTCTGCCCAGTGAGGTCAATTTGTGTA
 ACGTGGACATCTTCAACCCAAAGTACGACTGCAAGATCATGACATCTAAGACAGATGTGTCTATCC
 AGCGTTATCACGAGCCTCGGCGCTATAGTCTCCTGTTACGGCAAGACCAAGTGCACCGCTAGCAAC
 30 AAGAATCGGGGAATCATCAAAACCTTTTCTAACGGTTGTGACTACGTGAGCAACAAGGGGGTGGGA
 TACCGTCTCAGTCGGTAACACCCTGTACTACGTGAATAAACAGGAGGGGAAGTCATTGTACGTGA
 AGGGTGAACCTATCATCAACTTTTATGACCCCTCGTCTTCCCATCAGACGAGTTTGACGCGTCCAT
 CTCTCAGGTGAATGAGAAGATTAACCAGAGCCTGGCTTTTATCCGCAAATCAGACGAACTACTGCA
 CAATGTCAACGCTGGCAAGAGCACAACAAATATAATGATAACAACCATCATCATCGTCATTATTGT
 35 GATCTTGTTATCACTGATCGCTGTGGGGCTCCTCCTTTATTGCAAGGCTCGTAGCACCCCTGTCACC
 CTCAGTAAAGATCAGCTGTGAGGGATCAATAATATCGCGTTTAGCAAC (SEQ ID NO:13)

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKNCNG
 TDAKVKLIKQELDKYKNAVTELQLLMQSTPATNNRARRRELPRFMNYTLNNAKKTNTVLSKKQKQQA
 40 ASGVAVSKVLHLEGEVNIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIE
 TVIEFQQKNNRLLLEITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSY
 MSIIKEEVLAYVYVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAET
 CKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASN
 45 KNRGIKTFNNGCDYVSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQV
 NEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTHIIVILLSLIAVGLLLYCKARSTPVTLSKDQLSGIN
 NIAFSN (SEQ ID NO:14)

The underlined region represents a signal peptide sequence. The underlined regions can be substituted with alternative sequences that achieve the same or similar functions, or it can be deleted, as shown below.

FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKNCNGTDAKVKLIKQELDKYKNAV
 TELQLLMQSTPATNNRARRRELPRFMNYTLNNAKKTNTVLSKKQKQQAISGVAVSKVLHLEGEVNI
 KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNNRLLLEITREFS
 VNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIKEEVLAYVYVQLPLYG
 50 VIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLP
 SEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNNGCDYVSNKG
 55 VDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDELLHN
 VNAGKSTTNIMITTHIIVILLSLIAVGLLLYCKARSTPVTLSKDQLSGIN NIAFSN (SEQ ID NO: 294)

MRK8 RSV F Construct:

ATGGAATTATTAATTTTGAAGACAAATGCTATAACCGCGATACTAGCGGCTGTGACTCTTTGTTTC
 GCATCAAGCCAGAATATTACAGAAGAATTTTATCAATCCACCTGCAGCGCTGTATCGAAAGGTTAC
 5 CTCAGCGCGCTTAGGACAGGATGGTATACCTCCGTTATCACGATTGAACTGAGTAATATCAAGGAA
 AACAAGTGTAACGGAACAGACGCCAAGGTCAAACCTATTAAACAAGAAGTGGACAAGTATAAGTC
 TGCAGTGACCGAATTGCAGCTCCTGATGCAGAGTACCCCTGCAACTAACAACAAGTTTTTGGGCTT
 TCTGCAAGGCGTGGGTAGCGCGATCGCCTCCGGAATCGCGGTCTCCAAAGTGTTCACCTGGAGG
 GAGAAGTTAACAAGATCAAATCGGCTCTGTTGAGTACCAACAAGGCAGTGGTGTCACTGAGCAAC
 10 GGTGTAAGCGTGTTAACAAGCAAGGTATTGGACTTAAAGAACTATATTGACAAACAGCTGCTCCC
 CATCGTGAACAAACAGAGCTGCTCAATCTCCAATATAGAGACGGTGATAGAGTTCAGCAAAAAA
 ATAATCGGCTCCTTGAGATCACCCGCGAATTCTCAGTTAATGCCGGCGTCACAACCTCCGGTGTCTA
 CATACATGCTGACCAACTCGGAGCTGTTATCCTTAATAAATGACATGCCCATCACCAATGATCAAA
 AAAAAGTATGTCAAATAACGTCCAGATAGTAAGACAGCAGAGCTACAGCATCATGTCGATTATC
 15 AAAGAGGAGGTGCTGGCGTACGTGGTGCAGCTGCCCTGTATGGGGTGATTGACACCCCTTGTGG
 AAGCTGCACACCTCCCCACTATGTACTACCAATACCAAAGAAGGATCCAACATCTGCCTTACCCGC
 ACCGATAGGGGATGGTATTGCGACAACGCCGGATCCGTCAGCTTCTTTCCACTTGCCGAACTTGC
 AAGGTTCAAGTCAAACCGGGTGTCTGCGATACAATGAATTCCTTACCTTGCCAGCGAAGTTAAT
 CTCTGTAATATTGACATCTTTAACCCCAAATACGATTGCAAAATTATGACGTCAAAAACCGATGTC
 20 AGTTCAAGCGTTATCACCAGCTTGGGTGCTATCGTTTCATGCTATGGCAAACCAAGTGTACGGCT
 AGTAACAAAAACCGCGGAATAATTAAGACATTCAGCAATGGTTGCGACTACGTATCAATAAGGG
 TGTCGACACCGTTTCCGTGGGCAATACGCTGTACTATGTTAATAAACAGGAAGGCAAGTCACTGTA
 TGTTAAAGGTGAACCCATCATCAACTTCTACGACCCCTGGTTTTCCCTCCGACGAGTTTGATGCC
 AGCATATCACAGGTTAATGAAAAAATAAACGGCACATTGGCGTTTATCAGAAAGTCTGACGAGAA
 25 ACTTCATAACGTGGAAGACAAGATAGAAGAGATATTGAGCAAAATCTATCATATTGAGAACGAGA
TCGCCAGGATCAAAAAGCTTATTGGGGAG (SEQ ID NO:15)

The underlined region represents a region coding for GCN4. The underlined region can be substituted with alternative sequences which achieve a same or similar function.

30 MELLILKTNAITAILAAVTLCFASSQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNG
 TDAKVLIKQELDKYKSAVTELQLLMQSTPATNNKFLGFLQGVGSAIASGIAVSKVLHLEGEVNIKISA
 LLSTNKAVVSLNNGVSVLTSKVLDLKNYIDKQLLPIVNBKQSCSISNIETVIEFQQKNNRLEITREFSVNA
 GVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDT
 PCWKLHTSPLCTTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPLAETCKVQSNRVFCDTMNSLTLPSEV
 35 NLCNIDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDYVSNKGVD
 VSVGNTLYYVNBKQEGKSLYVKGEPIINFYDPLVFPSPDEFDASISQVNEKINGTLAFIRKSDEKLHNVEDK
IEILSKIYHIENEIARIKKLIGE (SEQ ID NO:16)

The first underlined region represents a signal peptide sequence. The underlined region can
 be substituted with alternative sequences that achieve the same or similar functions, or it can
 40 be deleted, as shown below. The second underlined region represents GCN4. The underlined
 region can be substituted with alternative sequences which achieve a same or similar
 function, or can be deleted.

FASSQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNGTDAKVLIKQELDKYKSAV
 45 ELQLLMQSTPATNNKFLGFLQGVGSAIASGIAVSKVLHLEGEVNIKISALLSTNKAVVSLNNGVSVLTS
 KVLDLKNYIDKQLLPIVNBKQSCSISNIETVIEFQQKNNRLEITREFSVNAGVTPVSTYMLTNSSELLSLIN
 DMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNI
 CLTRTRDRGWYCDNAGSVSFFPLAETCKVQSNRVFCDTMNSLTLPSEVNLCNIDIFNPKYDCKIMTSKTD
 VSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDYVSNKGVDTVSVGNTLYYVNBKQEGKSLYVK
 50 GEPIINFYDPLVFPSPDEFDASISQVNEKINGTLAFIRKSDEKLHN (SEQ ID NO: 295)

MRK9 membrane-bound RSV G protein:

ATGTCTAAAAACAAGGACCAGCGCACTGCTAAGACGCTGGAACGCACATGGGATACCCTGAACCA
 TCTGTTATTCATTTCCAGCTGCCTCTACAAGCTAAACCTTAAAAGTGTTGCACAAATCACACTCAGC
 55 ATCCTGGCAATGATTATTTCAACATCCCTGATCATAGCCGCAATCATATTTATCGCCTCAGCAAATC
ACAAAGTTACCCCGACCACAGCCATTATCCAGGACGCTACATCCCAAATCAAAAACACCACACCT
 ACATATCTCACTCAGAACCCGACGCTGGGCATTTACCATCCAACCCTTCCGAGATCACCTCTCAAAT
 CACCACCATTCTCGCCTCTACTACCCCGGGAGTAAAGAGCACTCTTCAGAGCACAAACCGTTAAAC

TAAAAATACCACCACCACTCAGACTCAGCCTTCGAAACCAACGACTAAACAGCGGCAAAATAAGC
CTCCATCCAAACCGAATAACGACTTTCATTTTCGAAGTCTTTAACTTTGTGCCATGCAGTATTTGCTC
CAATAATCTTACTTGTGTTGGCTATCTGCAAGAGAATCCCTAACAAGAAGCCTGGAAAGAAGACAA
CGACAAAGCCAACTAAGAAGCCGACACTTAAGACTACCAAAAAAGACCCTAAGCCGCAGACTACC
5 AAGAGCAAGGAGGTTCCCAACAACCAAGCCTACAGAGGAGCCGACTATTAACACAACAAAGACCA
ACATCATCACCACCCTGCTTACTTCTAATACTACCGGAAACCCAGAGCTGACGTCCAGATGGAGA
CGTTCCATTCCACATCTTCCGAAGGGAATCCTAGTCCCAGCCAGGTGAGCACAAACCTCAGAATACC
CGTCCCAGCCCTCATCACCTCCTAATACCCCCCGGCAG (SEQ ID NO:17)

The underlined region represents a region coding for transmembrane domain. The underlined
10 region can be substituted with alternative sequences which achieve a same or similar
function, or can be deleted.

MSKNKDQRTAKTLERTWDTLNLHLLFISSCLYKLNLSVAQITLSILAMIISTSLIIAIIIFIASANHKVTPT
15 TAIHQDATSQIKNTTPTLYLTQNPQLGISPSNPSEITSQITTLASTTPGVKSTLQSTTVKTKNTTTTQTQPSK
PTTKQRQNKPPSKPNNDFFHEVFNFPVPCISCSNNPTCWAICKRIPNKKPGKKTITTKPTKKPTLKTTKKDP
KPQTTKSKEVPTTKPTEEPTINTTKTNIITLLTSNTTGNPELTSQMETFHSTSSSEGNPSPSQVSTTSEYPS
QPSSPNTPRQ (SEQ ID NO:18)

The underlined region represents a transmembrane domain. The underlined region can be
substituted with alternative sequences which achieve a same or similar function.

20 MRK11 truncated RSV F protein (ectodomain only); construct modified to include an Ig
secretion peptide signal sequence:

ATGGAGACGCCTGCCAGCTGCTGTTCTGCTGTTGTTGTGGCTGCCAGATACTACTGGGTTTGCA
25 AGCGGACAAAACATTACCGAAGAGTTCTATCAATCCACATGCTCTGCAGTGTCTAAGGGCTACCTT
AGTGCATTACGAACCGGGTGGTATACGAGTGTAATCACCATTGAGCTGTCCAACATCAAGAAGAA
CAAGTGCAATGGGACTGATGCCAAGGTGAAACTTATCAAAACAAGAGCTCGACAAGTATAAGAAGC
CCGTGACCGAACTACAACCTCTGATGCAATCGACTCAGGCTACTAACAACAGAGCTCGGAGGGAG
CTGCCCAGATTTCATGAATTATACCTTAAACAACGCTAAAAAACAATGTGACCCTGAGTAAGAA
30 GCGGAAACGAAGGTTCTTGGGCTTCTGCTCGGTGTGGGGTCTGCAATAGCAAGCGGCGTCTGCTGT
GTCCAAGGTCCTTCACTTAGAAGGTGAGGTCAATAAGATCAAGTCCGCTCTCCTCTCTACCAACAA
GGCAGTGGTGAGCCTGTCTAACGGTGTGTCCGTGCTGACATCGAAGGTACTGGACCTGAAAAACT
ACATCGACAAGCAGCTGCTGCCTATTGTGAATAAGCAATCCTGCAGTATCTCCAACATTGAGACAG
TGATTGAATTTTCAGCAAAAGAACAATCGTTTGTGGAGATAACAAGAGAATTCAGTGTTAATGCCG
35 GCGTTACCACTCCCGTGTGACATACATGCTAACAATAGCGAGCTGCTATCTCTCATTAAATGATA
TGCCTATCACCAATGACCAGAAAAAACTTATGTCCAATAACGTGCAGATAGTCAGGCAGCAGTCC
TACAGCATTATGAGCATAATTAAAGAGGAAGTGTGGCTTACGTTCGTCCAGCTTCCACTGTATGGC
GTGATCGATACCCCTTGTGGAAGCTGCATACTTCCCCCTTTGTACAACATAACCAAAGAAGGG
AGTAATATATGCCTCACAAGGACTGACAGAGGCTGGTACTGCGACAACGCCGGGAGCGTCAGCTT
40 TTTCCCGCAGGCCGAGACATGTAAGGTGCAGAGCAACCGTGTCTTTTGCGACACCATGAATAGCCT
GACTTTGCCAAGTGAGGTCAACCTTTGCAACGTGGATATTTTAAACCTAAGTACGATTGTAAGAT
AATGACATCCAAAACCGATGTTAGTAGCTCCGTGATCACTTCGCTGGGTGCGATAGTTAGCTGCTA
TGGAAAGACAAAGTGTACCGCAAGTAACAAGAACCGCGGGATTATTAACATTTAGCAATGGGT
GCGACTACGTATCAACAAGGGGGTGGATACAGTCAGCGTGGGAAACACACTTTACTACGTTAAC
45 AAGCAGGAAGGGAAATCCCTTTATGTGAAGGGAGAACCAATTATCAACTTTTATGATCCCCCTCGT
TTTCCAAGTGATGAATTCGACGCAAGCATCTCGCAGGTGAACGAGAAAAATCAATCAGAGTCTAGC
TTTCATAAGGAAGTCTGATGAAGTCTTAGTGCCATTGGCGGGTACATACCGGAAGCCCCACGCGA
CGGTCAGGCTTACGTGAGGAAGGACGGCGAGTGGGTTCTGCTGTCCACTTTCCTT (SEQ ID NO:19)

The first underlined region represents region coding for human Igk signal peptide, second
50 underlined region represents region coding for foldon. The underlined regions can be
substituted with alternative sequences which achieves same or similar functions, or can be
deleted.

METPAQLLFLLLLWLPDITGFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKKNCNG
55 TDKVKLIKQELDKYKNAVTELQLLMQSTQATNNRRELPRFMNYTLNNAKKTNTLSKKRKRRL
GFLLVGSAIASGVAVSKVLHLEGEVNIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPV
NKQSCSISNIETVIEFQKNNRLLITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNN
VQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNA

GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
YGKTKCTASNKNRGIKTFNSNGCDYVSNKGVDTVSVGNTRYVVKQEGKSLYVKGEPIINFYDPLVFPS
DEFDASISQVNEKINQSLAFIRKSDELLSAIGGYIPEAPRDGOAYVRKDGEWVLLSTFL (SEQ ID NO:20)

The first underlined region represents human Igk signal peptide, second underlined region
represents foldon. The underlined regions can be substituted with alternative sequences which
achieves same or similar functions, or can be deleted, as shown below.

FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNCNGTDAKVKKLIKQELDKYKNAV
TELQLLMQSTQATNNRRELPRFMNYTLNNAKKTNTVLSKKRKRRLGFLGVSAGVAVSKV
LHLEGEVNIKSALLSTNKAVVSLNNGVSVLTISKVLDLKNYIDKQLLPIVVKQSCSISNIETVIEFQQKN
NRLLEITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQSYSIMSIKEEVLA
YVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVF
CDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTF
NGCDYVSNKGVDTVSVGNTRYVVKQEGKSLYVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSLAFI
RKSDLELL (SEQ ID NO: 296)

MRK12 DS-CAV1 (non-membrane bound form); modified to include an Ig secretion peptide
signal sequence:

ATGGAGACTCCCGCTCAGCTGCTGTTTTTGGCTCCTCCTATGGCTGCCGGATACCACCGGCTTTGCCT
CTGGACAGAACATTACCGAGGAATTCTATCAGTCGACTTGTTCGCAGTCTCGAAGGGGTACCTGA
GTGCCCTGCGCACCGGGTGGTACACCAGTGTTATCACTATTGAGCTGTCCAACATTAAAGAAAATA
AGTGTAATGGAAGTACGCGAAGGTGAAGTTGATAAAACAGGAGCTGGATAAATAACAAGAAATGC
AGTGACCGAAGTGCAGCTCCTGATGCAGTCCACTCCAGCAACAAATAATCGCGCGAGACGCGAAC
TCCCCCGCTTTATGAACTACACTCTGAATAATGCGAAGAAAACGAATGTGACACTAAGTAAGAAA
AGAAAACGGCGATTTCTTGGGTTCCTGCTCGGGGTGGGATCTGCCATAGCAAGCGGGGTGGCGGT
ATGTAAAGTCCTTACCTAGAAAGGGGAGGTGAACAAAATTAAGAGTGCCCTGCTGAGCACCAACA
AGGCTGTGGTTTCACTGTCAAACGGAGTAAGCGTGCTAACATTTAAAGTCTTGGACCTGAAGAATT
ATATTGACAAGCAGCTCCTGCCCATTTCTCAACAAACAGTCATGTTCCATTAGCAACATCGAAACAG
TCATTGAGTTTCAGCAAAAAAACAACCGCTCCTTGAGATTACGCGTGAGTTTCCGTCAATGCTG
GAGTCACGACACCGGTGTCCACTTACATGCTGACTAACAGCGAACTCCTGAGCCTAATCAATGACA
TGCCCATTAATAACGACCAGAAAAAATTGATGTCCAATAACGTGCAGATAGTGCGCCAGCAATCTT
ACTCCATAATGTGCATTATCAAGGAGGAAGTCCTGGCGTACGTTGTTTCAGCTGCCGCTGTATGGTG
TGATAGATACGCCATGCTGGAACTGCACACATCCCCCTTTGCACAACGAATACTAAAGAGGGA
AGTAACATTTGCTTGACCAGAACAGATCGGGGCTGGTACTGCGACAACGCTGGTAGTGTGTCATTT
TTCCCCCAGGCAGAAACGTGTAAAGTCCAGAGCAATCGCGTGTCTGCGACACAATGAAGTCACTT
ACTTTGCCCTCAGAGGTCAATTTGTGTAATGTGGATATCTTCAACCCGAAATACGATTGTAAGATT
ATGACGAGCAAAACAGACGTGTCTTCATCAGTGATAACAAGTCTGGGCGCAATAGTGTGTCATGCTA
TGGTAAGACTAAGTGCACTGCCTCCAATAAAACCGCGGCATCATCAAGACATTTTCAAATGGAT
GCGACTACGTGTCAAACAAGGCGCTGACACAGTAAGCGTTGGGAACACCCATATACTACGTCAAC
AAGCAGGAGGGGAAAAGCCTATACGTGAAAGGCGAGCCAATCATCAATTTCTACGATCCACTGGT
CTTTCCAAGTGACGAATTTGATGCCAGCATATCGCAGGTGAACGAGAAAAATAAATCAGTCACTCG
CCTTCATCAGGAAGTCAGATGAGCTGCTGTCCGCCATCGGAGGATACATTCAGAAAGCCCCACGC
GACGGCCAGGCATACGTGCGGAAGGACGGCGAATGGGTCTTTTGGAGCACTTTTCTA (SEQ ID
NO:21)

The first underlined region represents a region coding for human Igk signal peptide, the
second underlined region represents a region coding for a foldon. The underlined regions can
be substituted with alternative sequences which achieves same or similar functions, or can be
deleted.

METPAQLLFLLLLWLPDTFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNG
TDAKVKKLIKQELDKYKNAVTELQLLMQSTPATNNRRELPRFMNYTLNNAKKTNTVLSKKRKRRL
GFLGVSAGVAVCKVLHLEGEVNIKSALLSTNKAVVSLNNGVSVLTFKVLDLKNYIDKQLLPIL
NKQSCSISNIETVIEFQQKNNRLLEITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNN
VQIVRQSYSIMCIIKEEVLA YVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNA
GSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSSVITSLGAIVSC
YGKTKCTASNKNRGIKTFNSNGCDYVSNKGVDTVSVGNTRYVVKQEGKSLYVKGEPIINFYDPLVFPS
DEFDASISQVNEKINQSLAFIRKSDELLSAIGGYIPEAPRDGOAYVRKDGEWVLLSTFL (SEQ ID NO:22)

The first underlined region represents human Igk signal peptide, the second underlined region represents foldon. The underlined regions can be substituted with alternative sequences which achieves same or similar functions, or can be deleted, as shown below.

5 FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV
TELQLLMQSTPATNNRARRLPRFMNYTLNNAKKTNTLSKKRKRRFLGFLGVSIAISGVAVCKVL
HLEGEVNKIKSALLSTNKAVVSLNNGVSVLTFKVLDLKNYIDKQLLPILNKQSCSISNIETVIEFQQKNNR
LLEITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMCIIKEEVLAY
10 VVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFC
DTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSN
GCDYVSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSPDEFDASISQVNEKINQSLAFIR
KSDELL (SEQ ID NO: 297)

MRK13 MRK-5 construct modified to include an Ig secretion peptide signal sequence:

15 ATGGAGACTCCAGCCCAATTACTGTTCTGCTACTCCTTTGGCTGCCCGATACTACTGGATTTCGCTT
CGGGTCAGAATATTACAGAGGAGTTCTACCAAAGTACTTGCTCTGCAGTCTCCAAGGGATACCTGT
CCGCTCTGCGGACGGGATGGTATACCAAGTGTATAACGATCGAGTTGAGCAACATCAAGAAGAAC
AAATGTAATGGAACAGATGCCAAGGTGAACTGATCAAACAGGAGTTGGATAAATATAAGAATGC
20 TGTCACCGAACTGCAGCTATTGATGCAGTCCACCCAGGCTACCAACAACCGGGCCAGGCAGCAAC
AACAGAGATTTTTGGGTTTCTTGCTGGGCGTGGGGTCTGCCATCGCTTCAGGGGTGGCCGTGAGTA
AAGTCTGCACCTGGAAGGCGAAGTCAACAAGATCAAGTCTGCATTACTAAGTACCAATAAGGCT
GTAGTTAGCCTGTCCAATGGCGTGAGTGTGCTTACTTCTAAGGTACTGGACCTGAAGAACTACATC
GACAAGCAACTACTACCCATTGTAAATAAGCAGTCATGTAGCATATCAAACATCGAGACAGTGAT
25 CGAATTTCAACAGAAGAATAACCGGCTGTTGGAGATAACACGGGAGTTCTCTGTAAATGCCGGCG
TGACGACCCCTGTCAGCACCTACATGCTCACGAATAGCGAGTTGCTTTCCCTGATTAAATGATATGC
CGATTACAAATGACCAGAAGAAGCTGATGAGTAATAATGTCCAAATTGTCCGTCAGCAGAGCTAT
TCGATTATGTCCATCATCAAGGAGGAAGTCTTAGCCTATGTGGTGACAGTCCCCCTCTACGGAGTGA
TTGACACACCGTGCTGGAAGCTGCACACCTCCCCTTTGTGTACAACCAATACCAAGGAGGGCTCCA
30 ACATCTGCCTTACTAGGACCGACAGGGGATGGTATTGCGACAACGCCGGGTCCGTCTCATTTTTTC
CTCAGGCGGAAACCTGTAAGGTACAGTCGAATCGAGTGTTTTGTGACACTATGAACAGCCTGACCT
TGCTTAGCGAGGTGAATCTGTGTAACGTTGATATCTTCAACCCTAAGTATGACTGTAAAGATCATGA
CTTCAAAAATGATGTCTCTCAAGCGTGATCACCTCTTTGGGCGCCATCGTGTGATGCTACGGAA
AGACGAAGTGCACCGCCTCTAACAAGAACCGAGGGATCATAAAACATTCTCCAATTGGCTGTGAT
35 TACGTAGTAACAAGGTGTGGACACAGTCTCCGTGGGCAATACGTTATATTATGTGAATAAGCA
GGAGGGAAAAAGTCTCTATGTGAAGGGTGAACCGATAATCAATTTCTACGATCCCTTGGTGTTC
AAGCGACGAGTTCGACGCTCGATCAGCCAGGTGAACGAGAAAAATCAACCAGTCTTTGGCATTCA
TCCGCAAGAGCGACGAGCTACTGCATAACGTGAACGCAGGCAAGAGTACTACCAAT (SEQ ID
NO:23)

40 The underlined region represents a region coding for human Igk signal peptide. The
underlined region can be substituted with alternative sequences which achieve a same or
similar function, or can be deleted.

45 METPAQLLFLLLLWLPDITGFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNKCNG
TDAKVKLIKQELDKYKNAVTELQLLMQSTQATNNRARRQQQRFLGFLGVSIAISGVAVSKVLHLE
GEVNKIKSALLSTNKAVVSLNNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNNRLL
ITREFSVNAGVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQ
LPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTM
NSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDY
50 VSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSPDEFDASISQVNEKINQSLAFIRKSDE
LLHNVNAGKSTTN (SEQ ID NO:24)

The underlined region represents human Igk signal peptide. The underlined region can be
substituted with alternative sequences which achieve a same or similar function, or can be
deleted, as shown below.

55 FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNKCNGTDAKVKLIKQELDKYKNAV
TELQLLMQSTQATNNRARRQQQRFLGFLGVSIAISGVAVSKVLHLEGEVNKIKSALLSTNKAVVSL
SNGVSVLTSKVLDLKNYIDKQLLPVINKQSCSISNIETVIEFQQKNNRLLLEITREFSVNAGVTTPVSTYML
TNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLC

TTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPK
YDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNNGCDYVSNKGVDTVSVGNTLYYV
NKQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDELLHNVNAGKSTTN (SEQ ID
NO: 298)

MRK14 MRK-6 construct modified to include an Ig secretion peptide signal sequence:

ATGGAGACTCCCGCTCAGTTGTTGTTCCCTGCTACTGCTGTGGCTGCCTGATACAACCGGATTTGCTA
GTGGGCAGAATATCACCGAAGAATTCTATCAGAGCACTTGCAGTGCAGTGTCCAAAGGATATTTG
AGCGCCCTGCGCACTGGGTGGTACACAAGTGTCAACATCGAGCTAAGTAACATTAACAAAAA
CAAATGCAACGGGACTGACGCAAAGGTCAAACCTATTAAGCAAGAACTTGACAAATATAAGAACG
CTGTTACAGAGTTGCAGCTGCTAATGCAAAGCACTCAGGCTACCAATAACCGAGCGAGACAGCAG
CAGCAACGTTTCCTGGGTTTCCTGTTAGGTGTGGGTAGCGCAATTGCCAGTGGTGTAGCCGTGTCC
AAGGTGCTGCACCTGGAAGGGGAAGTGAATAAGATCAAGTCTGCACTGCTGTCCACCAATAAGGC
GGTCGTTTCGCTGTCTAACGGCGTCTCGGTCTCAACAAGTAAAGTTCTGGATTTAAAGAACTATAT
TGATAAGCAATTGCTGCCTATCGTAAATAAGCAGAGTTGCAGCATTAGCAATATCGAGACAGTGA
TAGAATTTTCAGCAAAAGAACAATCGATTACTCGAAATCACACGCGAATTCAGTGTCAATGCCGGG
GTTACAACCCCTGTGTCGACCTACATGCTTACCAATTCCGAGCTTCTGTCTCTTATTAACGATATGC
CCATCACGAACGATCAGAAGAACTGATGTCAAATAACGTCCAAATTGTGCGGCAGCAAAGCTAC
AGTATCATGAGCATCATCAAAGAGGAGGTGCTCGCCTATGTGGTCCAATTGCCGCTATACGGGGTCT
ATTGATACACCCTGTTGGAAGCTCCATACATCCCCACTTTGTACAACGAATACCAAGGAGGGGTCT
AACATTTGTCTGACCCGGACCGACAGAGGCTGGTATTGCGATAATGCTGGAAGCGTTAGTTTCTTT
CCTCAGGCAGAAACATGCAAGGTGCAGTCAAACAGAGTTTTCTGTGACACCATGAATTCCTTGACG
CTGCCTTCAGAAGTGAATCTGTGTAACGTGGATATCTTTAATCCGAAGTACGATTGTAAAATTATG
ACTAGCAAGACAGATGTCTCGTCCTCTGTGATCACTAGCCTGGGAGCGATTGTGAGCTGTTATGGT
AAAACAAAGTGTACTGCTAGCAATAAGAACAGGGGGATTATCAAAACGTTACGTAACGGCTGTGA
TTACGTATCCAACAAGGGGGTGGACACCGTGTGAGTCGGGAACACGCTCTACTACGTGAACAAGC
AGGAAGGTAAGTCGCTATACGTGAAGGGGGGAACCCATAATCAATTTCTACGATCCGCTCGTGTTC
CTAGCGACGAATTCGACGCATCTATCAGCCAGGTGAACGAGAAGATCAATCAGAGTCTGGCCTTC
ATCCGCAAGTCCGACGAGCTGCTTAGTGCTATCGGAGGTTATATCCCTGAGGCCCGGAGGGACGG
CCAAGCGTATGTGAGAAAGGACGGGGAATGGGTACTGTTGTCAACTTTCCTA (SEQ ID NO:25)

The first underlined region represents a region coding for human Igk signal peptide, the
second underlined region represents a region coding for a foldon. The underlined regions can
be substituted with alternative sequences which achieves same or similar functions, or can be
deleted.

METPAQLLFLLLLWLPDTTGFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNKCN
TDAKVKLIKQELDKYKNAVTELQLLMQSTQATNNRARQQQQRFLGLLGVSIAISGVAVSKVLHLE
GEVNKIKSALLSTNKAVVSLNNGVSVLTSKVLDLKNYIDKQLLPVNVKQSCSISNIETVIEFQKNNRLL
ITREFSVNAGVTTVPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYV
VQPLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTM
NSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNNGCDY
VSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDE
LLSAIGGYIPEAPRDGOAYVRKDGEWVLLSTFL (SEQ ID NO:26)

The first underlined region represents human Igk signal peptide, second underlined region
represents a foldon. The underlined regions can be substituted with alternative sequences
which achieves same or similar functions, or can be deleted, as shown below.

FASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKKNKCN TDAKVKLIKQELDKYKNAV
TELQLLMQSTQATNNRARQQQQRFLGLLGVSIAISGVAVSKVLHLEGEVNKIKSALLSTNKAVVSL
NNGVSVLTSKVLDLKNYIDKQLLPVNVKQSCSISNIETVIEFQKNNRLLITREFSVNAGVTTVPVSTYML
TNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYV VQPLPLYGVIDTPCWKLHTSPLC
TTNTKEGSNICLTRTRDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPK
YDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNNGCDYVSNKGVDTVSVGNTLYYV
NKQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDELL (SEQ ID NO: 299)

MRK16 MRK-8 construct modified to include an Ig secretion peptide signal sequence:

ATGGAGACACCTGCCCAACTTCTGTTCCCTTCTTTTGCTCTGGCTGCCTGACACAACCGGCTTCGCAT
 CTTACAAAAACATCACGGAAGAGTTTTACCAGAGCACATGCTCCGCGGTCTCTAAAGGCTATCTTT
 CTGCCCTGCGGACTGGCTGGTATACCAGCGTCATCACCATAGAGCTGTCAAACATCAAGGAGAAC
 AAGTGTAACGGCACTGACGCCAAGGTCAAGCTTATAAAGCAGGAAGTGGACAAGTATAAGAGTGC
 5 TGTACCGAGCTCCAGTTGCTTATGCAGTCCACCCCCGCAACAAACAATAAATTTCTGGGCTTTCT
 ACAGGGCGTCGGAAGCGCCATCGCAAGCGGCATCGCTGTGAGCAAGGTGTTGCATCTGGAGGGAG
 AGGTGAATAAGATAAAGAGTGTCTGCTTTCCACTAACAAAGCCGTGGTGAGCTGAGCAATGGC
 GTATCTGTTCTGACTTCTAAAGTCTGGATCTCAAGAACTATATCGACAAGCAGCTCTTGCCCATTTG
 TCAACAAACAGTCTGCTCCATTTCCAATATTGAGACCGTCATTGAGTTCCAACAGAAGAATAACC
 10 GTTTGCTGGAAATTACAAGGGAATTCAGTGTTAATGCCGGTGTAACCAACCCCTGTGAGCACCTATA
 TGCTACCAACTCTGAACTGCTGAGTCTGATTAACGATATGCCCATTTACTAATGATCAGAAGAAAC
 TAATGAGTAACAATGTCCAGATAGTTCGGCAGCAGTCATATTCCATTATGAGTATAATCAAGGAGG
 AAGTGCTAGCCTACGTAGTTCAGCTCCCCCTCTACGGCGTTATAGACACGCCATGTTGGAAGCTGCA
 TACGAGTCTCTGTGCACTACAAATACCAAGGAGGGCAGTAACATATGCTTGACTAGAACTGATA
 15 GAGGCTGGTACTGCGACAATGCAGGCTCCGTGTCAATCTTTCTCTCGCCGAGACGTGTAAAGTGC
 AGAGTAACAGAGTGTTTTGTGACACAATGAACTCATTGACCCTGCCTAGCGAAGTGAAGTTATGCA
 ACATCGACATTTTTAAACCAAAATACGATTGCAAGATTATGACCTCTAAGACTGACGTATCTTCAT
 CCGTCATAACTTCTCTAGGAGCGATCGTGAGCTGCTACGGTAAGACTAAATGCACGGCTAGTAATA
 AAAATAGAGGTATCATTAAGACTTTTAGTAACGGTTGCGATTATGTGTCAAACAAGGGAGTCGAC
 20 ACTGTTTCAGTGGGCAATACTCTCTACTACGTTAACAAACAGGAGGGTAAATCCCTTTATGTGAAA
 GGGGAACCCATCATTAATTTTTATGACCCACTTGTGTTTCCTAGTGACGAGTTTGACGCTTCAATCA
 GTCAAGTGAACGAAAAAATTAATGGCACGCTCGCGTTTATCAGGAAAAGCGACGAGAAGCTGCAT
 AACGTGGAAGATAAGATCGAGGAGATTCTCTCGAAAATTTATCATATAGAGAATGAAATCGCAAG
 AATCAAAAAGCTTATTGGGGAG (SEQ ID NO:27)

25 The first underlined region represents a region coding for human Igk signal peptide, the
 second underlined region represents a region coding for GCN4. The underlined regions can
 be substituted with alternative sequences which achieves same or similar functions, or can be
 deleted.

30 METPAQLLFLLLLWLPDITGFASSQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNG
TDKVKLIKQELDKYKSAVTELQLLMQSTPATNNKFLGFLQGVGSAIASGIAVSKVLHLEGEVNIKIS
LLSTNKAVVSLNSGVSVLTSKVLDLKNYIDKQLLPIVNBKQSCSISNIETVIEFQKNNRLEITREFSVNA
GVTTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDT
PCWKLHTSPLCTTNTKEGSNICLTRDRGWYCDNAGSVSFFPLAETCKVQSNRVFCDTMNSLTLPSEV
 35 NLCNIDIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDYVSNKGVD
VSVGNTLYYVNBKQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINGTLAFIRKSDEKLHN
VEDEKIEILSKIYHIENEIARIKKLIGE (SEQ ID NO:28)

The first underlined region represents human Igk signal peptide, second underlined region
 represents GCN4. The underlined regions can be substituted with alternative sequences which
 40 achieves same or similar functions, or can be deleted, as shown below.

FASSQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQELDKYKSAVT
 ELQLLMQSTPATNNKFLGFLQGVGSAIASGIAVSKVLHLEGEVNIKISALLSTNKAVVSLNSGVSVLTS
 KVLDLKNYIDKQLLPIVNBKQSCSISNIETVIEFQKNNRLEITREFSVNAGVTTPVSTYMLTNSSELLSLIN
 45 DMPITNDQKKLMSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNI
 CLTRDRGWYCDNAGSVSFFPLAETCKVQSNRVFCDTMNSLTLPSEVNLCNIDIFNPKYDCKIMTSKTD
 VSSSVITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDYVSNKGVDTVSVGNTLYYVNBKQEGKSLYVK
 GEPIINFYDPLVFPSEDFDASISQVNEKINGTLAFIRKSDEKLHN (SEQ ID NO: 300).

50 The protein vaccine evaluated in this study was DS-CAV1 stabilized prefusion F
 protein (1 mg/mL), as described in McLellan *et al. Science* 342, 592 (2013). The protein was
 buffered in 50 mM Hepes, 300 mM NaCl and was formulated with Adju-phos.

Briefly, groups of 10 mice were immunized intramuscularly with the following
 vaccines:

55

Group	N	Vaccine	Concentration (ug/ml)	Total dose /mouse (ug)
1	10	mF (MRK01)	100	10
3	"	mDS-CAV1 (MRK04)	100	10
4	"	MRK05	100	10
5	"	MRK06	100	10
6	"	MRK07	100	10
7	"	MRK08	100	10
8	"	mG (MRK09)	100	10
9	"	IgSP_sF (MRK11)	100	10
10	"	IgSP_sDS-CAV1 (MRK12)	100	10
11	"	MRK13	100	10
12	"	MRK14	100	10
14	"	MRK16	100	10
15	"	DS-CAV1 protein/adju phos	100	10
16	10	mF (MRK01)	20	2
18	"	mDS-CAV1 (MRK04)	20	2
19	"	MRK05	20	2
20	"	MRK06	20	2
21	"	MRK07	20	2
22	"	MRK08	20	2
23	"	mG (MRK09)	20	2
24	"	IgSP_sF (MRK11)	20	2
25	"	IgSP_sDS-CAV1 (MRK12)	20	2
26	"	MRK13	20	2
27	"	MRK14	20	2
29	"	MRK16	20	2
30	"	DS-CAV1 protein/adju phos	20	2
31	"	naive		

The animals were immunized on day 0 and day 21 of the experiment. On days 14 and 35, blood was drawn from each animal and used for serological assays. On days 42 and 49, a subset of the animals were sacrificed and spleens were harvested to support ELISPOT and intracellular cytokine staining studies.

A. RSV Neutralization Assay:

Mouse sera from each group were pooled and evaluated for neutralization of RSV-A (Long strain) using the following procedures:

1. All sera samples were heat inactivated by placing in dry bath incubator set at 56°C for 30 minutes. Samples and control sera were then diluted 1:3 in virus diluent

(2% FBS in EMEM) and duplicate samples were added to an assay plate and serially diluted.

2. RSV-Long stock virus was removed from the freezer and quickly thawed in 37°C water bath. Viruses were diluted to 2000 pfu/mL in virus diluent
3. Diluted virus was added to each well of the 96-well plate, with the exception of one column of cells.
4. HEp-2 cells were trypsinized, washed, resuspended at 1.5×10^5 cells/ml in virus diluent, and 100 mL of the suspended cells were added to each well of the 96-well plate. The plates were then incubated for 72 hours at 37°C, 5% CO₂.
5. Following the 72 hour incubation, the cells were washed with PBS, and fixed using 80% acetone dissolved in PBS for 10-20 minutes at 16-24°C. The fixative was removed and the plates were allowed to air-dry.
6. Plates were then washed thoroughly with PBS + 0.05% Tween. The detections monoclonal antibodies, 143-F3-1B8 and 34C9 were diluted to 2.5 plates were then washed thoroughly with PBS + 0.05% 50 plates were then washed thoroughly with PBS + 0.05% Tween. The plates were then incubated in a humid chamber at 16-24°C for 60-75 minutes on rocker
7. Following the incubation, the plates were thoroughly washed.
8. Biotinylated horse anti-mouse IgG was diluted 1:200 in assay diluent and added to each well of the 96-well plate. Plates were incubated as above and washed.
9. A cocktail of IRDye 800CW Streptavidin (1:1000 final dilution), Sapphire 700 (1:1000 dilution) and 5mM DRAQ5 solution (1:10,000 dilution) was prepared in assay diluent and 50 mL of the cocktail was added to each well of the 96-well plate. Plates were incubated as above in the dark, washed, and allowed to air dry.
10. Plates were then read using an Aeries Imager. Serum neutralizing titers were then calculated using a 4 parameter curve fit in Graphpad Prism.

The serum neutralizing antibody titers for the mouse immunogenicity study measured post dose 1 (PD1) and post dose 2 (PD2) are shown in Fig. 1. The PD2 serum neutralizing antibody titers are also provided in tabular form below:

Description	10ug dose	2 ug dose
mF (MRK01)	4075	1391
mDS-CAV1 (MRK04)	3160	846
MRK05	600	331
MRK06	465	178
MRK07	2259	2168

MRK08	2318	656
mG (MRK09)	86	39
IgSP_sF (MRK11)	4559	3597
IgSP_sDS-CAV1 (MRK12)	3458	2007
MRK13	750	269
MRK14	471	116
MRK16	1077	1088
DS-CAV1 protein/adju phos	692	1166
Naive		<4

The results indicated that the neutralizing antibody titers are robust and several of the mRNA vaccines, including the RSV mF vaccine and the RSVmDS-CAV1 mRNA vaccine elicited neutralizing antibody titers higher than DS-CAV1 protein/adjuv-phos vaccine.

5

B. Assays for Cellular Immune Response:

Mouse IFN- γ ELISPOT Assay Procedures

I. Preparation of Splenocytes:

10 Spleens were placed in a 60-mm tissue culture dish and palpated up and down with a syringe handle to remove the cells. Minced spleens were then transferred to 15-mL tubes, centrifuged at 1200 rpm for 10 min, resuspended in an Ammonium-Chloride-Potassium (ACK) Lysing Buffer and incubated at room temperature for 5 minutes. R10 media was added to the tubes and cells were centrifuged at 1200 rpm for 10 minutes, and then washed
15 once more with R10 media. Following a second centrifugation, the cells were resuspended in 10 mL of R10 media and filtered through a 70 μ m nylon cell strainer into a 50 mL centrifuge tube. The strainer was rinsed with an additional 10 mL of media and this was added to the cells. The cells were counted on a hemocytometer and the cell concentration was normalized across the groups.

20 II. ELISPOT ASSAY:

- 1) 96-well MultiScreen-IP sterile white filtration plates were coated with MABTECH purified anti-mouse IFN- γ , clone AN18 at 10 μ g/ml PBS in Bio-Hood (1:100 dilution) and incubated at 4 °C overnight
- 2) The following morning, the plates were washed with sterile PBS and blocked with
25 R10 medium at 37 °C for 4 hrs.

- 3) Splenocytes were added to the plate at 4×10^5 cells/well, and the cells were stimulated with peptide pools for RSV-F and RSV-G. The peptide pools were as follows.

For RSV-F:

Sequence = sequence in FM	peptide ID	SEQ ID No:
MELPILKANAITTIL	RSV_F_1 – 15	29
ILKANAITTILTAVT	RSV_F_5 – 19	30
NAITTILTAVTFCFA	RSV_F_9 – 23	31
TILTAVTFCFASSQN	RSV_F_13 – 27	32
AVTFCFASSQNITEE	RSV_F_17 – 31	33
CFASSQNITEEFYQS	RSV_F_21 – 35	34
SQNITEEFYQSTCSA	RSV_F_25 – 39	35
TEEFYQSTCSAVSKG	RSV_F_29 – 43	36
YQSTCSAVSKGYLSA	RSV_F_33 – 47	37
CSAVSKGYLSALRTG	RSV_F_37 – 51	38
SKGYLSALRTGWYTS	RSV_F_41 – 55	39
LSALRTGWYTSVITI	RSV_F_45 – 59	40
RTGWYTSVITIELSN	RSV_F_49 – 63	41
YTSVITIELSNIKEN	RSV_F_53 – 67	42
ITIELSNIKENKCNG	RSV_F_57 – 71	43
LSNIKENKCNGTDAK	RSV_F_61 – 75	44
KENKCNGTDAKVCLI	RSV_F_65 – 79	45
CNGTDAKVCLIQEL	RSV_F_69 – 83	46
DAKVCLIQELDKYK	RSV_F_73 – 87	47
KLIKQELDKYKNAVT	RSV_F_77 – 91	48
QELDKYKNAVTELQL	RSV_F_81 – 95	49
KYKNAVTELQLMQS	RSV_F_85 – 99	50
AVTELQLMQSTPAA	RSV_F_89 – 103	51
LQLMQSTPAANNRA	RSV_F_93 – 107	52
MQSTPAANNRARREL	RSV_F_97 – 111	53
PAANNRARRELPRFM	RSV_F_101 – 115	54
NRARRELPRFMNYTL	RSV_F_105 – 119	55
RELPRFMNYTLNNAK	RSV_F_109 – 123	56
RFMNYTLNNAKKTNV	RSV_F_113 – 127	57
YTLNNAKKTNVTLISK	RSV_F_117 – 131	58
NAKKTNVTLSKKRKR	RSV_F_121 – 135	59
TNVTLSKKRKRRLG	RSV_F_125 – 139	60
LSKKRKRRLGFLG	RSV_F_129 – 143	61
RKRRLGFLGVGSA	RSV_F_133 – 147	62
FLGFLGVGSAIASG	RSV_F_137 – 151	63
LLGVGSAIASGIAVS	RSV_F_141 – 155	64
GSAIASGIAVSKVLH	RSV_F_145 – 159	65
ASGIAVSKVLHLEGE	RSV_F_149 – 163	66
AVSKVLHLEGEVNKI	RSV_F_153 – 167	67
VLHLEGEVNKIKSAL	RSV_F_157 – 171	68
EGEVNLIKSAALLSTN	RSV_F_161 – 175	69

Sequence = sequence in FM	peptide ID	SEQ ID No:
NKIKSALLSTNKAVV	RSV_F_165 - 179	70
SALLSTNKAVVSLSN	RSV_F_169 - 183	71
STNKAVVSLSNGVSV	RSV_F_173 - 187	72
AVVSLSNGVSVLTSK	RSV_F_177 - 191	73
LSNGVSVLTSKVLDL	RSV_F_181 - 195	74
VSVLTSKVLDLKNYI	RSV_F_185 - 199	75
TSKVLDLKNYIDKQL	RSV_F_189 - 203	76
LDLKNYIDKQLPIV	RSV_F_193 - 207	77
NYIDKQLPIVNKQS	RSV_F_197 - 211	78
KQLLPIVNKQSCSIS	RSV_F_201 - 215	79
PIVNKQSCSISNIET	RSV_F_205 - 219	80
KQSCSISNIETVIEF	RSV_F_209 - 223	81
SISNIETVIEFQQKN	RSV_F_213 - 227	82
IETVIEFQQKNRLL	RSV_F_217 - 231	83
IEFQQKNRLLLEITR	RSV_F_221 - 235	84
QKNNRLLLEITREFSV	RSV_F_225 - 239	85
RLLLEITREFSVNAGV	RSV_F_229 - 243	86
ITREFSVNAGVTPV	RSV_F_233 - 247	87
FSVNAGVTPVSTYM	RSV_F_237 - 251	88
AGVTPVSTYMLTNS	RSV_F_241 - 255	89
TPVSTYMLTNSSELLS	RSV_F_245 - 259	90
TYMLTNSSELLSLIND	RSV_F_249 - 263	91
TNSSELLSLINDMPIT	RSV_F_253 - 267	92
LLSLINDMPITNDQK	RSV_F_257 - 271	93
INDMPITNDQKKLMS	RSV_F_261 - 275	94
PITNDQKKLMSNNVQ	RSV_F_265 - 279	95
DQKKLMSNNVQIVRQ	RSV_F_269 - 283	96
LMSNNVQIVRQQSYS	RSV_F_273 - 287	97
NVQIVRQQSYSIMSI	RSV_F_277 - 291	98
VRQQSYSIMSIKKE	RSV_F_281 - 295	99
SYSIMSIKKEVLAY	RSV_F_285 - 299	100
MSIIKKEVLAYVVQL	RSV_F_289 - 303	101
KKEVLAYVVQLPLYG	RSV_F_293 - 307	102
LAYVVQLPLYGVIDT	RSV_F_297 - 311	103
VQLPLYGVIDTPCWK	RSV_F_301 - 315	104
LYGVIDTPCWKLHTS	RSV_F_305 - 319	105
IDTPCWKLHTSPLCT	RSV_F_309 - 323	106
CWKLHTSPLCTTNTK	RSV_F_313 - 327	107
HTSPLCTTNTKEGSN	RSV_F_317 - 331	108
LCTTNTKEGSNICLT	RSV_F_321 - 335	109
NTKEGSNICLTRTDR	RSV_F_325 - 339	110
GSNICLTRTDRGWYC	RSV_F_329 - 343	111
CLTRTDRGWYCDNAG	RSV_F_333 - 347	112
TDRGWYCDNAGSVSF	RSV_F_337 - 351	113
WYCDNAGSVSFFPQA	RSV_F_341 - 355	114
NAGSVSFFPQAETCK	RSV_F_345 - 359	115
VSFFPQAETCKVQSN	RSV_F_349 - 363	116

Sequence = sequence in FM	peptide ID	SEQ ID No:
PQAETCKVQSNRVFC	RSV_F_353 - 367	117
TCKVQSNRVFCDTMN	RSV_F_357 - 371	118
QSNRVFCDTMNSLTL	RSV_F_361 - 375	119
VFCDTMNSLTLPSEV	RSV_F_365 - 379	120
TMNSLTLPSEVNLCN	RSV_F_369 - 383	121
LTLPSEVNLCNVDIF	RSV_F_373 - 387	122
SEVNLCNVDIFNPKY	RSV_F_377 - 391	123
LCNVDIFNPKYDCKI	RSV_F_381 - 395	124
DIFNPKYDCKIMTSK	RSV_F_385 - 399	125
PKYDCKIMTSKTDVS	RSV_F_389 - 403	126
CKIMTSKTDVSSSVI	RSV_F_393 - 407	127
TSKTDVSSSVITSLG	RSV_F_397 - 411	128
DVSSSVITSLGAIVS	RSV_F_401 - 415	129
SVITSLGAIVSCYGK	RSV_F_405 - 419	130
SLGAIVSCYGKTKCT	RSV_F_409 - 423	131
IVSCYGKTKCTASNK	RSV_F_413 - 427	132
YGKTKCTASNKNRGI	RSV_F_417 - 431	133
KCTASNKNRGIIKTF	RSV_F_421 - 435	134
SNKNRGIIKTFSNGC	RSV_F_425 - 439	135
RGIKTFSNGCYVS	RSV_F_429 - 443	136
KTFSNGCYVSNKGV	RSV_F_433 - 447	137
NGCDYVSNKGVDTVS	RSV_F_437 - 451	138
YVSNKGVDTVSVGNT	RSV_F_441 - 455	139
KGVDTVSVGNTLYYV	RSV_F_445 - 459	140
TVSVGNTLYYV NKQE	RSV_F_449 - 463	141
GNTLYYV NKQEGKSL	RSV_F_453 - 467	142
YYV NKQEGKSLYVKG	RSV_F_457 - 471	143
KQEGKSLYVKGEPPII	RSV_F_461 - 475	144
KSLYVKGEPPIINFYD	RSV_F_465 - 479	145
VKGEPPIINFYDPLVF	RSV_F_469 - 483	146
PIINFYDPLVFPSGE	RSV_F_473 - 487	147
FYDPLVFPSGEFDAS	RSV_F_477 - 491	148
LVFPSGEFDASISQV	RSV_F_481 - 495	149
SGEFDASISQVNEKI	RSV_F_485 - 499	150
DASISQVNEKINQSL	RSV_F_489 - 503	151
SQVNEKINQSLAFIR	RSV_F_493 - 507	152
EKINQSLAFIRKSDE	RSV_F_497 - 511	153
QSLAFIRKSDELLHN	RSV_F_501 - 515	154
FIRKSDELLHNVNAG	RSV_F_505 - 519	155
SDELLHNVNAGKSTT	RSV_F_509 - 523	156
LHNVNAGKSTTNIMI	RSV_F_513 - 527	157
NAGKSTTNIMITAI	RSV_F_517 - 531	158
STTNIMITAIIVIV	RSV_F_521 - 535	159
IMITAIIVIVVILL	RSV_F_525 - 539	160
AIIIVIVVILLSLIA	RSV_F_529 - 543	161
VIVVILLSLIAVGLL	RSV_F_533 - 547	162
ILLSLIAVGLLLYCK	RSV_F_537 - 551	163

Sequence = sequence in FM	peptide ID	SEQ ID No:
LIAVGLLLYCKARST	RSV_F_541 - 555	164
GLLLYCKARSTPVT	RSV_F_545 - 559	165
YCKARSTPVTLSKDQ	RSV_G_549 - 563	166
RSTPVTLSKDQLSGI	RSV_F_553 - 567	167
VTLSKDQLSGINIA	RSV_F_557 - 571	168
KDQLSGINIAFSN	RSV_F_561 - 574	169

For RSV-G:

Sequence	peptide ID	SEQ ID No:
MSKNKDQRTAKTLER	RSV_G_1 - 15	170
KDQRTAKTLERTWDT	RSV_G_5 - 19	171
TAKTLERTWDTLNHL	RSV_G_9 - 23	172
LERTWDTLNHLLFIS	RSV_G_13 - 27	173
WDTLNHLLFISSCLY	RSV_G_17 - 31	174
NHLLFISSCLYKLN	RSV_G_21 - 35	175
FISSCLYKLNLSVA	RSV_G_25 - 39	176
CLYKLNLSVAQITL	RSV_G_29 - 43	177
LNLSVAQITLSILA	RSV_G_33 - 47	178
SVAQITLSILAMIIS	RSV_G_37 - 51	179
ITLSILAMIISTSLI	RSV_G_41 - 55	180
ILAMIISTSLIIAAI	RSV_G_45 - 59	181
IISTSLIIAAIIFIA	RSV_G_49 - 63	182
SLIIAAIIFIASANH	RSV_G_53 - 67	183
AAIIFIASANHKVTS	RSV_G_57 - 71	184
FIASANHKVTSTTTI	RSV_G_61 - 75	185
ANHKVTSTTTIIQDA	RSV_G_65 - 79	186
VTSTTTIIQDATSQI	RSV_G_69 - 83	187
TTHIQDATSQIKNTT	RSV_G_73 - 87	188
QDATSQIKNTTPTYL	RSV_G_77 - 91	189
SQIKNTTPTYLTQSP	RSV_G_81 - 95	190
NTTPTYLTQSPQLGI	RSV_G_85 - 99	191
TYLTQSPQLGISPSN	RSV_G_89 - 103	192
QSPQLGISPSNPSEI	RSV_G_93 - 107	193
LGISPSNPSEITSQI	RSV_G_97 - 111	194
PSNPSEITSQITIL	RSV_G_101 - 115	195
SEITSQITILASTT	RSV_G_105 - 119	196
SQITILASTTPGVK	RSV_G_109 - 123	197
TILASTTPGVKSTLQ	RSV_G_113 - 127	198
STTPGVKSTLQSTTV	RSV_G_117 - 131	199
GVKSTLQSTTVGTKN	RSV_G_121 - 135	200
TLQSTTVGTKNTTTT	RSV_G_125 - 139	201
TTVGTKNTTTTQAQP	RSV_G_129 - 143	202
TKNTTTTQAQPSKPT	RSV_G_133 - 147	203
TTTQAQPSKPTTKQR	RSV_G_137 - 151	204
AQPSKPTTKQRQNK	RSV_G_141 - 155	205
KPTTKQRQNKPPSKP	RSV_G_145 - 159	206

Sequence	peptide ID	SEQ ID No:
KQRQNKPPSKPNNDNF	RSV_G_149 - 163	207
NKPPSKPNNDFHFEV	RSV_G_153 - 167	208
SKPNNDFHFEVFNFV	RSV_G_157 - 171	209
NDFHFEVFNFVPCSI	RSV_G_161 - 175	210
FEVFNFVPCSICSNN	RSV_G_165 - 179	211
NFVPCSICSNNPTCW	RSV_G_169 - 183	212
CSICSNNPTCWAICK	RSV_G_173 - 187	213
SNNPTCWAICKRIPN	RSV_G_177 - 191	214
TCWAICKRIPNKKPG	RSV_G_181 - 195	215
ICKRIPNKKPGKKT	RSV_G_185 - 199	216
IPNKKPGKKTTKPT	RSV_G_189 - 203	217
KPGKKTTKPTEEPT	RSV_G_193 - 207	218
KTTTKPTEEPTFKTA	RSV_G_197 - 211	219
KPTEEPTFKTAKEDP	RSV_G_201 - 215	220
EPTFKTAKEDPKPQT	RSV_G_205 - 219	221
KTAKEDPKPQTGSG	RSV_G_209 - 223	222
EDPKPQTGSGEVPT	RSV_G_213 - 227	223
PQTGSGEVPTTKPT	RSV_G_217 - 231	224
GSGEVPTTKPTGEPT	RSV_G_221 - 235	225
VPTTKPTGEPTINTT	RSV_G_225 - 239	226
KPTGEPTINTTKTNI	RSV_G_229 - 243	227
EPTINTTKTNITTLL	RSV_G_233 - 247	228
NTTKTNITTLLTSN	RSV_G_237 - 251	229
TNITTLLTSNTRN	RSV_G_241 - 255	230
TLLTSNTRNPELT	RSV_G_245 - 259	231
TSNTRNPELTSQME	RSV_G_249 - 263	232
TRNPELTSQMETFHS	RSV_G_253 - 267	233
ELTSQMETFHSTSSE	RSV_G_257 - 271	234
QMETFHSTSSEGNPS	RSV_G_261 - 275	235
FHSTSSEGNPSQV	RSV_G_265 - 279	236
SSEGNPSQVSITS	RSV_G_269 - 283	237
NPSQVSITSEYLS	RSV_G_273 - 287	238
SQVSITSEYLSQPSS	RSV_G_277 - 291	239
ITSEYLSQPSSPNT	RSV_G_281 - 295	240
YLSQPSSPNTPR	RSV_G_285 - 297	241

- 4) Plates were incubated at 37°C, 5% CO₂ for 20-24 hrs.
- 5) The following day, the plates were thoroughly washed and 100 µL/well MABTECH detection antibody, clone R4-6A2 was added to 0.25µg/ml in PSB/1%FBS (1:4000 dilution) in each well. Plates were incubated for 2 hrs and then washed thoroughly with PBS/0.05% Tween 20
- 6) Streptavidin-AP was diluted 1:3000 in PSB/1% FBS and 100 µL was added to each well.

- 7) Plates were incubated for 60 min at room temperature and washed thoroughly with PBS/Tween 20 (0.05%).
- 8) 100µl of 1-STEP NBT/BCIP was added to each well, plates were held at room temperature for several minutes, washed with tap water, and allowed to dry overnight.
- 5 9) Plates were imaged using AID imager system and data were processed to calculate the number of IFN-γ secreting cells per million splenocytes.

The data showed that RNA/LNP vaccines gave much higher cellular immune responses than the protein antigen formulated with alum, which elicited little to no detectable cellular immune responses. See Fig. 2, where columns with a * indicate that the number of spots of interferon gamma were too high to count accurately.

III. Intracellular cytokine staining:

15 Splenocytes were harvested as described above. Freshly harvested splenocytes were rested overnight in R10 media at 1×10^7 cells per mL. The following morning, 100 µL of cells were added to each well according to plate template for a final number of 1×10^6 cells/ well. Pooled RSV-F or RSV-G peptides were used to stimulate the cells. The RSV-F peptide pools were as described above. The RSV-G peptide pools were either as described above or
20 purchased from JPT (catalog PM-RSV-MSG). Cells were incubated for 1 hr at 37 °C, and BFA and monensin were added to each well to a final concentration of 5 µg each.

To stain the cells, 20 µL of 20 mM EDTA was added to each cell well, and the cells were incubated for 15 minutes at Room Temperature (RT). The plates were centrifuged at 500xg for 5 minutes and the supernatant was aspirated. The plates were then washed with
25 PBS and centrifuged again. ViVidye was reconstituted with DMSO and diluted in PBS. 125 µL diluted Vividye was added to each well and incubated at room temperature for 15 minutes. The plates were centrifuged, the supernatant was removed and the plates were washed again with 175 µL FACSWash. A BD cytofix/cytoperm solution was added to each well, and the plates were incubated for 20-25 minutes at 2-8 °C. The plates were then
30 centrifuged and washed twice with a BD perm wash buffer. Finally, FC block was added to a final concentration of 0.01 mg/mL in a volume of 125 mL per well in the BD perm wash buffer. The cells were stained with an intracellular antibody cocktail made as follows:

- a) IL-10 FITC:
- b) IL-17A PE:
- 35 c) IL-2 PCF594:

- d) CD4 PerCPcy5.5:
- e) TNF PE Cy7:
- f) IFN γ APC:
- g) CD8a BV510:
- h) CD3 APC Cy7:
- i) Perm Wash:

The cells were incubated with the antibody cocktail (20 μ L per test well) at 2-8 °C for 35 minutes, washed twice with the BD perm wash buffer, and resuspended in 200 μ L per well of BD stabilizing fixative. Samples were acquired on an LSRII and data were analyzed using Flojo software. The percentage of CD4+ splenocytes that respond to the peptide pools and produced Ifn- γ , IL-2, or TNF α are shown in FIGs. 3A, 3B, and 3C and the percentage of CD8+ splenocytes that respond to the peptide pools and produce Ifn- γ , IL-2 or TNF α are shown in FIGs. 4A, 4B, and 4C. The data were a that RSV-F mRNA/LNP vaccines and RSV-G mRNA/LNP vaccines but not DS-CAV1 protein antigens elicit robust Th1 biased CD4+ immune responses in mice. In addition, RSV-F mRNA/LNP vaccines but not RSV-G mRNA/LNP vaccines or DS-CAV1 protein antigens elicit robust Th1 biased CD8+ immune responses in mice.

Example 13: Mouse immunogenicity

In this example, additional assays were carried out to evaluate the immune response to RSV vaccine antigens delivered using an mRNA/LNP platform in comparison to protein antigens.

Again, female Balb/c (CRL) mice (6-8 weeks old; N= 10 mice per group) were administered mRNA vaccines or protein vaccines. The mRNA vaccines were generated and formulated in MC3 lipid nanoparticles. The mRNA vaccines evaluated in this study included the followings:

- MRK-1 membrane-bound RSV F protein
- MRK-2 secreted RSV F protein
- MRK-3 secreted DS-CAV1
- MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)
- MRK-5 RSV F construct
- MRK-7 RSV F construct
- MRK8 RSV F construct
- MRK9 membrane-bound RSV G protein

Influenza M1

Listed below are the DNA sequences encoding the mRNA sequences for MRK-2, MRK-3 and Influenza M1. Also shown are the corresponding amino acid sequences. All other sequences are provided elsewhere herein.

MRK-2 non-membrane bound form RSV F protein/MRK_02_F (soluble, Merck A2 strain)/

ATGGAGCTGTTGATCCTTAAGGCCAACGCCATCACTACTATTCTCACCGCGGTAA
 10 CATTCTGCTTCGCCTCCGGGCAGAACATCACCGAGGAGTTCTACCAGTCTACGTG
 CTCCGCCGTCTCCAAAGGTTACCTGTCCGCATTAAGGACGGGGTGGTACACTTCC
 GTCATAACTATTGAACTGAGTAACATAAAAAAGAACAAGTGTAATGGGACGGAT
 GCCAAGGTGAAGCTCATCAAGCAAGAGCTTGACAAATACAAGAATGCAGTGACA
 GAGCTCCAACCTTCTCATGCAGTCTACACAGGCCACGAATAACCGTGCCCGAAGA
 15 GAACTGCCTAGATTTATGAATTACACTTTGAACAACGCCAAAAAGACCAACGTG
 ACTCTAAGCAAAAAAAGGAAACGGCGTTTTCTGGGCTTTCTGCTGGGGGTGGTA
 GCGCCATCGCATCTGGCGTGGCAGTCAGTAAAGTTTTGCACCTTGAGGGGGAGGT
 CAACAAAATCAAGAGCGCGCTGTTATCAACAAACAAGGCAGTCGTGTCCCTCTC
 CAATGGCGTGTCTGTCCTGACCTCTAAAGTACTGGATCTCAAGAACTATATCGAC
 20 AAACAACCTGCTACCAATCGTCAATAAGCAGAGTTGCTCTATTTCCAATATTGAGA
 CCGTGATCGAGTTTCAACAGAAGAATAACAGATTGTTGGAGATCACCAGGGAAT
 TCAGCGTCAATGCAGGGGTGACCACACCCGTATCTACCTACATGCTGACCAACTC
 GGAACCTCCTCTCCTTAATAAACGACATGCCTATTACTAACGACCAAAAAAAGTTG
 ATGTCCAACAATGTCCAGATCGTGCGACAGCAATCTTATTCAATTATGTCCATTA
 25 TAAAAGAGGAGGTGCTGGCGTACGTAGTGCAGCTGCCCCCTTTACGGAGTGATCG
 ACACCCCATGCTGGAAGCTCCACACCTCCCCCCTGTGCACCACTAATACCAAAGA
 AGGCAGCAACATCTGTCTGACCCGTACCGACCGCGGATGGTACTGCGATAATGC
 AGGTAGCGTCTCTTTTTTTTCCCCAGGCTGAAACTTGCAAGGTTCAGTCCAACCGG
 GTATTCTGTGACACGATGAACAGTCTCACCCCTACCATCAGAGGTGAACCTGTGCA
 30 ATGTGGACATATTTAACCCTAAATATGACTGTAAGATCATGACCTCCAAAACCTGA
 CGTTTCCAGCAGTGTCTAACCTCACTGGGCGCAATAGTTTCATGCTATGGAAAG
 ACTAAGTGCAGTGCCTCTAACAAAAATCGAGGTATTATTAAGACCTTTAGCAATG
 GCTGCGATTATGTCAGTAACAAAGGTGTTGATACAGTGAGTGTGGGCAACACATT
 ATACTATGTTAACAAGCAAGAAGGCAAGAGCCTCTATGTGAAGGGAGAACCAAT
 35 CATTAATTTTTACGATCCGCTGGTCTTTCCAGCGATGAGTTCGATGCATCCATCT
 CTCAGGTGAATGAAAAAATTAACCAATCACTGGCTTTCATACGGAAGAGCGATG
 AACTGCTGAGCGCCATCGGGGGATACATCCCTGAAGCTCCGAGGGACGGCCAAG
CTTATGTCCGCAAAGACGGAGAGTGGGTGTTGCTCAGTACCTTCCTC (SEQ ID NO:
 242) The underlined region represents a region coding for a foldon. The underlined region
 40 can be substituted with alternative sequences which achieve a same or similar function.

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIE
 LSNIKKNKCNGTDAKVLIKQELDKYKNAVTELQLLMQSTQATNNRARRELPRFMN
 YTLNNAKKTNVTLSKKRKRRLGFLGVSIAISGVAVSKVLHLEGEVNIKISALLS
 45 TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNBKQSCSISNIETVIEFQQKNNRLL
 ITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMSI
 IKEEVLAYVYVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRDRGWYCDNAGS
 VSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSV

ITSLGAIVSCYGKTKCTASNKNRGIKTFNSNGCDYVSNKGVDTVSVGNTRYVYVKNQEGKSLYVKGEPIINFYDPLVFPSEDFDASISQVNEKINQSLAFIRKSDELLSAIGGYIPEAPRDGQAYVRKDGWVLLSTFL(SEQ ID NO: 243)

The first underlined region represents a signal peptide sequence. The first underlined regions can be substituted with alternative sequences that achieve the same or similar functions, or it can be deleted. The second underlined region represents a foldon. The second underlined region can be substituted with alternative sequences which achieve a same or similar function.

10 MRK-3 non-membrane bound form DS-CAV1 (stabilized prefusion F protein)//MRK_03_DS-CAV1 (soluble, S155C/S290C/S190F/V207L)/SQ-030271:

ATGGAAGTCTGCTGATTCTTAAGGCGAATGCCATAACCACTATCTTGACCGCAGTTA
CTTTTGGCTTCGCCTCTGGGCAGAATATTACCGAAGAGTTCTACCAGTCCACGTG
15 CAGTGCCGTGTCTAAGGGCTACCTTTCCGCGCTTCGCACTGGCTGGTACACGTCA
GTCATAACGATCGAACTCTCTAATAAAGGAAAATAAGTGTAACGGAACAGAC
GCTAAGGTCAAGTTAATCAAGCAGGAGCTGGACAAATATAAGAATGCCGTAACG
GAGCTCCAGCTGCTCATGCAGAGCACGCCAGCTACAAACAACAGGGGCACGCCGT
GAGCTCCCCCGATTTATGAACTACACATTGAACAACGCCAAGAAAATAACGTG
20 ACTTTGTCCAAGAAGAGGAAGCGGCGATTCTTAGGGTTCCTTTTGGGGGTAGGCT
CGGCGATTGCCAGTGGGGTTGCCGTATGCAAGGTGCTCCACCTGGAAGGGGAGG
TGAACAAGATTAAGTCGGCTCTGCTCAGTACAAACAAAGCTGTCGCTCTCATTGTC
AAACGGAGTCAGTGTATTGACATTTAAAGTCCTCGACCTGAAGAATAATATAGAT
AAACAGTTACTCCCAATCTTGAATAAGCAGTCCTGTAGCATCAGCAACATTGAGA
25 CAGTGATCGAGTTCCAGCAGAAGAATAATCGCCTACTCGAGATCACCAGAGAAT
TCTCAGTCAATGCCGGAGTAACCACTCCTGTCAGCACATACATGCTCACAACTC
TGAACCTCTAAGCCTGATTAATGATATGCCTATCACAAATGATCAGAAGAACTC
ATGAGCAATAATGTGCAGATTGTAAGACAGCAGAGTTATTCTATAATGTGTATTA
TTAAGGAGGAGGTACTGGCCTATGTGGTTCAACTTCCTCTGTATGGGGTGATAGA
30 TACACCATGCTGGAAGCTGCACACCAGCCCACTGTGTACGACCAATACAAAGGA
GGGCTCCAATATTTGCTTAACACGGACTGACCGGGGGTGGTATTGCGACAATGCC
GGATCAGTCTCCTTCTTCCCCCAAGCAGAGACCTGCAAGGTGCAGTCCAATAGAG
TTTTCTGCGACACAATGAACTCGCTGACCCTACCTAGCGAAGTTAACTTATGCAA
CGTGGATATTTTTAATCCGAAGTATGATTGTAAATCATGACTAGCAAAACGGAT
35 GTTAGCTCCAGCGTAATCACCTCCCTAGGCGCTATCGTGAGCTGTTATGGCAAGA
CGAAGTGCAGTGCATCTAATAAAAATAGGGGTATTATTAACCTTCAGCAATG
GCTGCGACTATGTGAGCAATAAGGGCGTGGACACCGTGTGAGTGGGAAACACCC
TCTATTATGTGAACAAGCAGGAGGGGAAAATCCCTTTATGTAAAGGGCGAACCCA
TTATCAATTTCTATGACCCCTGGTTTTCCCAAGCGACGAGTTCGACGCATCTATC
40 TCTCAAGTGAACGAGAAAATCAATCAGAGTCTTGCCTTTATCAGAAAATCCGATG
AGCTGCTTTCCGCCATCGGTGGCTATATCCCAAGAGAGACGGACAAG
CGTACGTCGGAAAGATGGTGAGTGGGTCTCCTCTCTACCTTTCTT (SEQ ID NO:
244)

The underlined region represents a region coding for a foldon. The underlined region can be substituted with alternative sequences which achieve a same or similar function.

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIE
LSNIKENKCNGTDAKVLIKQELDKYKNAVTELQLLMQSTPATNNRRELPRFMN
YTLNNAKKTNTLSKKRKRRLGFLGVSASVAVCKVLHLEGEVNIKISALLS
50 TNKAVVSLSNGVSVLTFKVLDLKNYIDKQLLPILNKQSCSISNIETVIEFQQKNNRLE
ITREFSVNAGVTPVSTYMLTNSSELLSLINDMPITNDQKKLMSNNVQIVRQQSYSIMC

IIKEEVLAYVVLPLYGVIDTPCWKLHTSPLCTTNTKEGSNICLTRTDRGWYCDNAG
SVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDFNPKYDCKIMTSKTDVSSS
VITSLGAIVSCYGKTKCTASNKNRGIKTFSNGCDYVSNKGVDTVSVGNTLYYVNKQ
EGKSLYVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELLSAIGGYIPEA
5 PRDGQAYVRKDGGEWVLLSTFL (SEQ ID NO: 245)

The first underlined region represents a signal peptide sequence. The first underlined regions
can be substituted with alternative sequences that achieve the same or similar functions, or it
can be deleted. The second underlined region represents a foldon. The second underlined
region can be substituted with alternative sequences which achieve a same or similar
10 function.

Influenza M-1 (A/California/04/2009(H1N1), ACP44152)+hIgκ

ATGGAGACTCCTGCACAGCTGCTGTTTCTGCTATTGTTGTGGCTTCCGGACACTAC
15 TGGGTCCCTCCTCACCAGAGGTGGAACATACGTGCTGTCCATCATACCATCCGGG
CCCTTGAAAGCCGAGATCGCCCAGAGACTCGAATCTGTATTTCGCAGGAAAGAAC
ACGGATTTGGAGGCACTAATGGAATGGCTGAAGACCCGTCCGATCCTGTCTCCTC
TCACAAAGGGGATTCTTGGATTTGTCTTTACCTCACC GTCCCGAGCGAGCGCGG
TCTCCAGCGCAGACGTTTTGTACAGAATGCACTGAATGGCAACGGCGATCCCAAT
20 AACATGGATCGTGCGGTAAAGCTTTATAAAAAGCTGAAGAGAGAAATCACTTTC
CATGGGGCTAAAGAGGTGAGTCTCTCCTATTCAACCGGGGCATTGGCCTCTTGCA
TGGGTCTTATATACAATCGAATGGGCACCGTTACCACCGAGGCCGCATTTGGTCT
GGTTTGTGCTACGTGCGAGCAAATCGCAGATAGCCAGCATCGGTCCCATCGGCA
GATGGCCACCACTACGAACCCTCTAATTCGACATGAAAATCGCATGGTCCTGGCT
25 AGCACCACCGCAAAGGCAATGGAGCAGATGGCGGGCTCTAGTGAACAGGCAGC
CGAGGCAATGGAAGTGGCCAATCAGACCAGGCAGATGGTCCATGCTATGCGGAC
TATTGGTACCCACCCGTCCAGCAGTGCTGGACTGAAGGATGACCTCCTTGAGAAC
CTGCAGGCATACCAGAAACGAATGGGGGTGCAAATGCAGAGATTCAAG (SEQ ID
NO: 246)

30 The underlined region represents a region coding for human Igκ signal peptide. The
underlined region can be substituted with alternative sequences which achieve a same or
similar function.

METPAQLLFLLLLWLPD TTGSLLTEVETYVLSIIPSGPLKAEIAQRLESVFAGKNTDLE
35 ALMEWLKTRPILSPLTKGILGFVFTLTVPSEGLQRRRFVQNALNGNGDPNNMDRAV
KLYKKLKREITFHGAKEVSLSYSTGALASCMGLIYNRMGTVTTEAAFGLVCA TCEQI
ADSQHRSHRQMATTNPLIRHENRMVLASTTAKAMEQMAGSSEQAAEAMEVANQT
RQMVHAMRTIGTHPSSSAGLKDDLLENLQAYQKRMGVQMQRFK (SEQ ID NO: 247)

40 The underlined region represents human Igκ signal peptide. The underlined region can be
substituted with alternative sequences which achieve a same or similar function.

The influenza M1 mRNA was combined with MRK-1, MRK-4 or MRK-9 in an effort
to increase the immune response by having the cells that take up the mRNAs make virus like
45 particles (VLPs).

Protein vaccine evaluated in this study was DS-CAV1 stabilized prefusion F protein
as described in McLellan et al. *Science* 342, 592 (2013); 1 mg/mL. The protein was buffered
in 50 mM Hepes, 300 mM NaCl and was formulated with Adju-phos.

Groups of 10 mice were immunized intramuscularly with 100 groups of 10 mice were immunized intramuscularly with 100 μ L of vaccine, delivered with 50 μ L injections into each quadriceps. The groups were vaccinated with the following vaccines:

5 Table 1. Vaccines

Group	Vaccine	Concentration	Total dose /mouse
		(ug/ml)	(ug)
1	mF (MRK01)	100	10
2	sF (MRK02)	100	10
3	mDS-CAV1 (MRK04)	100	10
4	sDS-CAV1 (MRK03)	100	10
5	mG (MRK09)	100	10
6	mF (MRK01) + Influenza M1 (1:1 mixture)	100	10
7	mDS-CAV1 (MRK04) + Influenza M1 (1:1 mixture)	100	10
8	mG (MRK09) + Influenza M1 (1:1 mixture)	100	10
9	MRK05	100	10
10	MRK07	100	10
11	MRK08	100	10
12	DS-CAV1 protein/adju phos	100	10
13	mF (MRK01)	20	2
14	sF (MRK02)	20	2
15	mDS-CAV1 (MRK04)	20	2
16	sDS-CAV1 (MRK03)	20	2
17	mG (MRK09)	20	2
18	VLP/mF (MRK01)	20	2
19	VLP/mDS-CAV1 (MRK04)	20	2
20	VLP/G (MRK09)	20	2
21	MRK05	20	2
22	MRK07	20	2
23	MRK08	20	2
24	DS-CAV1 protein/adju phos	20	2
25	naïve	N/A	N/A

The animals were immunized on day 0 and day 21 of the experiment. On days 14 and 35, blood was drawn from each animal and used for serological assays. On day 42, a subset of the animals were sacrificed and spleens were harvested to support ELISPOT and intracellular cytokine staining studies.

On day 27, the mice were challenged intranasally with 1×10^6 PFU RSV A2. Four days post inoculation, the animals were sacrificed by CO₂ inhalation and lung and nasal turbinates were removed and homogenized in 10 volumes of Hanks Balanced Salt Solution

(Lonza) containing SPG on wet ice. The samples were clarified by centrifugation at 2000 rpm for 10 minutes, aliquotted, flash frozen, and immediately stored frozen at -70°C.

A. RSV Neutralization Assay:

Neutralizing antibody titers were determined as described above. The titers are shown in Fig. 5 (PD1= samples taken post-dose 1, PD2= samples taken post-dose2). The results showed that mRNA/LNP vaccines were strongly immunogenic and elicited high neutralizing antibody titers, as was demonstrated in the previous experiment. Attempts to generate a significantly higher neutralizing antibody by co-delivering mRNAs expressing influenza M1 with mRNAs expressing membrane-bound protein antigen were not successful.

B. Intracellular Cytokine Staining.

Intracellular cytokine staining was conducted in the same manner described above in Examples 13. The CD4 ICS responses to RSV-F and G peptide pools are shown in Figs. 6A, 6B, and 6C. As in the previous study, the ICS results showed that mRNA vaccines expressing RSV-F and RSV-G elicited robust Th1-biased CD4 immune responses.

The CD8 ICS responses are shown in Figs. 7A, 7B, and 7C. The data confirm the previous observation that mRNAs expressing RSV-F antigens but not mRNAs expressing RSV-G or DS-CAV1 protein/adju phos elicited robust Th1 biased CD8 responses.

C. Mouse Challenge Results

The procedure for measuring viral titers is outlined below. Briefly, samples were diluted and added in duplicate to 24- well plates containing confluent HEp-2 cell monolayers. The plates were incubated at 37°C for one hour. Following the one hour incubation, sample inoculum was aspirated and 1ml of overlay containing 0.75% methylcellulose was added. The plates were incubated at 37°C for 5 days. Following the 5 day incubation, the cells were fixed and stained with crystal violet/ glutaraldehyde solution. Plaques were counted and titers were expressed as pfu/gram of tissue. As shown in Fig. 8, no virus was recovered from the lungs of any of the mice immunized with the mRNA vaccines formulated with MC3 LNP and only one animal at the lower dose of DS-CAV1 protein /adju phos vaccine had any virus detectable in the nose.

Example 14: Cotton Rat Immunogenicity and Efficacy

In this example, assays were carried out to test the immunogenicity and efficacy of mRNA/LNP vaccines in the cotton rat RSV challenge model.

More specifically, female cotton rats (SAGE) were used and immunizations began at 3-7 weeks of age. The mRNA vaccines used were generated and formulated in MC3 lipid nanoparticles. The mRNA vaccines evaluated in this study included:

MRK-1 membrane-bound RSV F protein

5 MRK-2 secreted RSV F protein (truncated ectodomain)

MRK-3 secreted DS-CAV1 (trimeric ectodomain)

MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)

MRK9 membrane-bound RSV G protein

Influenza M1 protein

10 Protein vaccine evaluated in this study was DS-CAV1 stabilized prefusion F protein as described in McLellan et al. *Science* 342, 592 (2013); 1 mg/mL. The protein was buffered in 50 mM Hepes, 300 mM NaCl and was formulated with Adju-phos.

Groups of 10 cotton rats were immunized intramuscularly with 120 μ L of vaccine, delivered with 60 μ L injections into each quadricep. The groups were vaccinated with the
15 the following vaccines as set out in Table 2:

Table 2. Vaccine Formulations Tested for Immunogenicity in Cotton Rats

Group	Vaccine	Conc (μ g/ml)	Dose (μ g)
1	mF (MRK01), I.M.	250	30
2	sF (MRK02) I.M.	250	30
3	mDS-CAV1 (MRK04), I.M.	250	30
4	sDS-CAV1 (MRK03), I.M.	250	30
5	mG (MRK09), I.M.	250	30
6	VLP/mF (MRK10 + MRK01), I.M.	250	30
7	VLP/mG (MRK10 + MRK09), I.M.	250	30
8	VLP/mDS-CAV1 (MRK10 + MRK04), I.M.	250	30
9	DS-CAV1 protein/adju phos, I.M.	250	30
10	RSV A2 5.5log10pfu, I.N.	NA	NA
11	None	NA	NA

The animals were immunized on day 0 and day 28 of the experiment. On days 28 and
20 56, blood was drawn from each animal and used for serological assays. On day 56, the cotton rats were challenged intranasally with $1 \times 10^{5.5}$ PFU RSV A2. Four days post inoculation, animals were sacrificed by CO₂ inhalation and lung (left lobes) and nasal turbinates were removed and homogenized in 10 volumes of Hanks Balanced Salt Solution (Lonza) containing SPG on wet ice. The samples were clarified by centrifugation at 2000 rpm for 10
25 minutes, aliquoted, flash frozen, and immediately stored frozen at -70 °C.

A. RSV Neutralization Assay

Neutralizing antibody titers were determined as described above.

The titers determined post dose 1 and post dose 2 are shown in Fig. 9. The neutralizing titers were robust in cotton rats following a single immunization and overall were several fold higher than those elicited by the DS-CAV1 protein antigen formulated with adju-phos or with infection with RSV A2 virus. The highest neutralizing antibody titers were elicited by RNA vaccines expressing full length RSV-F protein, truncated F-protein (ectodomain), mDS-CAV1 (stabilized prefusion F protein containing the RSV F transmembrane domain), and sDS-CAV1 (a truncated form of the stabilized prefusion F protein) as well as mRNA combination, including full length F protein and influenza M1 (termed "VLP/mF" in the graph above).

Titers determined post-dose two indicate that overall, neutralizing antibody titers were quite high for both mRNA vaccines and for the DS-CAV1 protein comparator. Surprisingly, in this study, as in the two mouse immunogenicity studies, relatively high neutralizing antibody titers were observed for the mG and mG+influenza M1 mRNA vaccine groups after the second dose of vaccine. With other vaccine modalities used to delivery RSV-G antigens, it was reported that neutralizing antibody activity is not observed *in vitro* unless complement is included in the assay.

B. Competition ELISA

The immune response to specific epitopes on RSV F-protein for neutralizing antibodies was characterized. The antigenic site II is the binding site for palivizumab, a monoclonal antibody developed for the prevention of lower respiratory infection with RSV in at risk infants and toddlers. Antigenic site Ø is a binding site for more potent neutralizing antibodies that are elicited by natural infection with RSV. A competition ELISA was developed to characterize the antigenic site Ø and antigenic site II response to the various mRNA-based vaccines.

Methods

ELISA plates were coated with either prefusion F protein or postfusion F protein (McLellan *et al.*, 2013). After coating, the plates were washed and blocked with blocking buffer (PBST/3% nonfat dried milk). Test sera from the cotton rat challenge study was then diluted with blocking buffer and titrated in the ELISA plate. Biotinylated D25 (a monoclonal antibody that binds to antigenic site Ø) or biotinylated palivizumab (a monoclonal antibody that binds to antigenic site II) were diluted in blocking buffer and added to each well of the ELISA plate (biotinylated D25 is only used with plates coated with prefusion F protein;

biotinylated palivizumab may be used with plates coated with prefusion or postfusion F protein as antigenic site II is present on both forms of the antigen). Following incubation, plates were washed and streptavidin-tagged horse radish peroxidase was added to each well of the ELISA plate. Plates were incubated at room temperature for 1 hr, washed, and incubated with TMB substrate (ThermoScientific). The color was allowed to develop for 10 minutes and then quenched with 100 μ L of 2N sulfuric acid and the plates were read at 450 nM on a microplate reader. The results are shown in Fig. 10. Fig. 10 illustrates the ability of cotton rat sera to compete with either D25 binding to prefusion F protein or palivizumab binding to postfusion F protein.

Background binding titers were seen in both the naïve mice and in those immunized with mG or with VLP/mG (neither of which will express the epitopes bound by D25 or palivizumab). The unlabeled monoclonal antibodies were included in the experiment as positive controls and those data are shown in the right-hand column of Fig. 10. No D25 competing titers were evident in cotton rats immunized with MRK01, MRK02, MRK09, MRK10+MRK01, or MRK10+MRK9. Only immunization with a mRNA encoding the DS-CAV1 sequence (MRK04, MRK03, and MRK10+MRK04) elicited D25-competing antibody titers, illustrating that these mRNAs produce a form of RSV F protein that is primarily in the prefusion conformation. In contrast, palivizumab competing titers were far higher in animals immunized with MRK01 or MKR02 mRNAs, illustrating that these mRNAs were produced as postfusion RSV F protein in cotton rats.

C. Cotton Rat Challenge Results

Procedures for measuring RSV titers in the cotton rat nose were followed as described above for mice. Nasal titers are shown in Fig. 11. In this assay, the limit of detection was 40 pfu/g of tissue. It was found that only one vaccinated animal (one mouse vaccinated with mDS-CAV1 (MRK4) mRNA encapsulated with MC3 LNP) had any detectable virus presence in the nose. In contrast, the geometric mean titer of RSV A2 virus in animals that were not vaccinated but were challenged in the same study was >10,000 pfu/g tissue.

Example 15: African Green Monkey Immunogenicity and Efficacy

In this example, assays were carried out to test the immunogenicity and efficacy of mRNA/LNP vaccines in the African Green Monkey RSV challenge model.

More specifically, male and female adult African Green Monkeys with body weights ranging from 1.3 to 3.75 kg, which were confirmed to be RSV-negative by neutralizing

antibody titer, were used. The mRNA vaccines used were generated and formulated in MC3 lipid nanoparticles. The mRNA vaccines evaluated in this study included:

MRK01 membrane-bound RSV F protein

MRK04 membrane-bound DS-Cav1 (stabilized prefusion F protein)

5 Groups of four African Green Monkeys were immunized intramuscularly with 1000 μ L of vaccine, delivered with 500 μ L injections into each deltoid. The groups were vaccinated with the following vaccines as set out in Table 3.

Table 3. Vaccine Formulations Tested for Immunogenicity in African Green Monkeys

Group	Vaccine	Conc (μ g/ml)	Dose (μ g)
1	mF (MRK01), I.M.	125	125
2	mDS-Cav1 (MRK04), I.M.	125	125
3	mF (MRK01) + mDS-Cav1 (MRK04), I.M.	125	125 (62.5 μ g each mRNA)
4	RSV A2 5.5log10pfu, I.N.	NA	NA
5	None	NA	NA

10

The animals were immunized on day 0, day 28, and day 56 of the experiment. On days 0, 14, 28, 42, 56 and 70, blood was drawn from each animal and used for serological assays. On day 70, the African Green Monkeys were challenged intranasally with $1 \times 10^{5.5}$ PFU RSV A2. Nasopharyngeal swabs were collected on days 1-12, 14, and on day 18 post challenge, and lung lavage samples were collected on days 3, 5, 7, 9, 12, 14, and 18 post challenge to test for viral replication.

15

A. RSV Neutralization Assay

Neutralizing antibody titers (NT_{50}) were determined as described above.

The NT_{50} titers determined post dose 1 and post dose 2 are shown in Fig. 12. Titers were seen to increase after each dose for both groups receiving mRNA vaccines as well as the group receiving RSV A2. The GMTs obtained with mRNA vaccines at week 10 (2 weeks post-dose 3) were more than 2 orders of magnitude higher than in the animals that received RSV A2.

20

B. Competition ELISA

The immune response to specific epitopes on RSV F-protein for neutralizing antibodies was characterized using the competition assays described above.

25

The palivizumab and D25 competing antibody titers measured at week 10 (2 weeks PD3) are presented in Figs. 13A-13B. The GMT palivizumab competing titers were 5 fold higher in the groups that received mF or the combination of mF+mDS-Cav1 compared to the group that received mDS-Cav1. While the GMT D25 competing antibody titers were 2 fold

higher in the groups that received mDS-Cav1 or the combination of mF+ mDS-Cav1 than in the group that received mF mRNA. The prefusion F stabilized antigen (mDS-Cav1), was able to elicit prefusion specific responses.

C. African Green Monkey Challenge Results

5 As mentioned above, in order to evaluate vaccine efficacy African Green Monkeys were challenged intranasally with $1 \times 10^{5.5}$ PFU RSV A2 on day 70 post vaccination and nasopharyngeal swabs and lung lavage samples were collected post challenge to test for the presence of virus.

10 In order to measure RSV titers in the African Green Monkey nasopharyngeal swabs and lung lavage samples an RSV RT-qPCR assay to detect RSV A was carried out as follows:

1) Equipment and Materials:

A. Equipment

- 15
1. Stratagene Mx3005P Real Time PCR system and MxPro Software
 2. Jouan GR422 centrifuge or equivalent
 3. Jouan Plate carriers or equivalent

B. Reagents

- 20
1. Quantitect® Probe Rt-PCR kit (1000) catalog # 204445
 2. Water, Molecular Biology Grade DNAase-free and Protease free, 5 Prime, catalog # 2900136
 3. TE buffer, 10mM Tris 1mM EDTA ph 8.0, Fisher Bioreagents, catalog # BP2473-100
 4. Viral primers: RSV A Forward and Reverse primers, Sigma custom, HPLC
 - 25 purified. Primer stocks are reconstituted to 100 μ M in Molecular grade water and stored at -20 °C.
 5. RSV dual labeled probe, Sigma custom, HPLC purified. Probe stocks are reconstituted to 100 μ M in TE buffer and stored at -20 °C protected from light.
 6. RSV A standard were generated in-house and stored at -20 °C. Standards for the
 - 30 assay were generated by designing primer pairs to the N gene of RSV A. The product length for the RSV A standard is 885 bp. QIAGEN OneStep RT-PCR was used to generate this standard.

Table 4. Primers

Primers	Sequences
RSV A F N gene	5' CTC AAT TTC CTC ACT TCT CCA GTG T (SEQ ID NO: 248)
RSV A R N gene	5' CTT GAT TCC TCG GTG TAC CTC TGT (SEQ ID NO: 249)
RSV A FAM N gene	5'FAM-TCC CAT TAT GCC TAG GCC AGC AGC A (BHQ1) (SEQ ID NO: 250)

7. Promega, Maxwell® 16 Viral Total Nucleic Acid Purification Kit (Product #AS1150

5 C. Supplies

1. Stratagene Optical cap 8x strip, catalog # 401425
2. Stratagene Mx3000P 96 well plates, skirted, catalog # 401334
3. ART filtered pipet tips

10 2) *RT-PCR Reactions and set up*

A. Preparation of Complete Master Mix

1. Prepare complete Master Mix following the set up below for a final reaction volume of 50 μ L. The following table is volume per well. Final primer concentration is 300 nM and final probe concentration is 200 nM.

15

Table 5. Reagents

Reagent	mL
2X Master Mix	25
RSV A F 100uM	0.2
RSV A R 100uM	0.2
RSV A FAM 100uM	0.1
RT enzyme mix	0.5
Water	19

2. Add 45 μ L of complete master mix to each well. Cover plate with plate cover and wrap in aluminum foil to protect from light.

20 B. Preparation of Standard curve

1. Remove standard from -20 °C.
2. Dilute standards to final concentrations of 1×10^6 copy/5 μ L to 1 copy/5 μ L using 10-fold dilutions.

C. Sample preparation

1. Nasopharyngeal swab and lung lavage samples are prepared for the RT-PCR reaction using the Maxwell® 16 Viral Total Nucleic Acid Purification Kit (Promega, product #AS1150)
2. 200 µL of sample is extracted following the manufactures protocol and eluted into 50 µL to be used in PCR reactions.

D. Additions of samples

1. Add 5 µL of extracted samples to appropriate wells. After addition of samples, carefully cap sample wells before adding standard curves.
2. Add 5 µL of diluted standard to appropriate wells and cap.
3. Add 5 µL of molecular grade water to No Template Control (NTC) wells.
4. Wrap plates in aluminum foil and transfer plates to centrifuge.
5. Spin plates for 2 mins at 100 rpm to pull down any samples or master mix that may be on the sides of well.
6. Wrap plates in aluminum foil and transfer to Stratagene instrument.

E. Thermo cycler: Stratagene MX 3005P

1. Place plates in Stratagene Mx3005P and set thermal profile conditions to:

Table 6. Thermocycler Steps

Step	Time	Temperature
Reverse Transcription	30 min	50
PCR intial activation step	15 min	95
2-step cycling:		
Denaturation	16 sec	94
Combined annealing/extension	60 sec	62
Number of cycles	40	

2. Analyze results using the Stratagene Mx3005p software

The mean RNA copy number detected in the lung and nose samples are presented in Figs. 14A-14B. The animals that received mRNA encoding mF, mDS-Cav1 or mF + mDS-Cav1 formulated in MC3 showed complete protection (no virus detected) in lungs similar to the control group immunized with RSV A2. The animals that received mRNA vaccines also showed a greater than 2 log reduction in virus detected in the nose on the majority of the assay days compared to the no vaccine control group.

Example 16: Immunogenicity in RSV-Experienced African Green Monkeys

The immunogenicity of mRNA vaccines formulated in MC3 LNP was tested in RSV-experienced African Green Monkeys.

Healthy adult, African Green Monkeys of either sex (n=5/group), weighing more than 1.3 kg, that were confirmed to be RSV seropositive by ELISA and neutralizing antibody titers, were selected for the study. The pool of animals selected for this study had been experimentally infected with RSV in previous vaccine studies and were distributed across study groups based on their pre-study RSV neutralization titers so that all groups would have similar group GMTs at study start. RSV-experienced animals provide a model of immune memory recall response to vaccination that may reflect the responses that can be anticipated in seropositive human adults.

A single vaccine dose was administered to each animal at week 0 by the intramuscular (IM) route. A control group receiving only the MC3 LNP was also included in the study design. Vaccines were administered as described in Table 7. After vaccination, the animals were observed daily for any changes at the inoculation site or other changes in activity or feeding habits that might indicate an adverse reaction to the vaccine, but none were noted. Serum samples were collected for assessment of RSV neutralizing antibody titers, as well as palivizumab (site II) and D25 (site Ø) competing antibody titers. PBMC samples were collected to assess cell-mediated immune responses.

Table 7. Vaccine Formulations Tested for Immunogenicity in RSV Seropositive African Green Monkeys

Group	Vaccine	Conc (µg/ml)	Dose (µg)
1	mF (MRK01), I.M.	125	125
2	mDS-Cav1 (MRK04), I.M.	125	125
3	mF (MRK01) + mDS-Cav1 (MRK04), I.M.	125	125 (62.5 µg each mRNA)
4	RSV A2 5.5 _{log10} pfu, I.N.	NA	NA
5	None	NA	NA

Individual animal NT₅₀ titers were measured in serum samples collected at baseline and 2 weeks post vaccination using methods described above, and the results are shown in Fig. 15. Vaccination with the mRNA vaccines resulted in, on average, a 150-fold increase in serum neutralization titers. The fold increase was comparable for all mRNA vaccines. No increase in titers was observed in the LNP only vaccine control group. The durability of the serum neutralization titers was assessed by measuring the titers every 2 to 4 weeks post

vaccination. The GMTs for each group measured out to week 24 post vaccination are presented in Fig. 16. The titers remain about 50 fold higher than baseline at week 24.

To evaluate the quality of the boosted responses in the vaccinated animals, both palivizumab (site II) and D25 (site Ø) competing antibody titers were determined. As described above, antigenic site II is a neutralization epitope found on both the prefusion and the postfusion conformation of the F protein, while site Ø is a prefusion specific neutralization epitope. The palivizumab (site II) and D25 (site Ø) competing antibody titers measured 4 weeks post vaccination using the methods described above are summarized in Figs. 17A-17B. All of the mRNA vaccines resulted in a boost in palivizumab competing titers of approximately 7 fold from baseline. Although D25 competing antibody titers were below the limit of detection of the assay before immunization in all but one animal in the MC3 LNP only control group, D25 competing antibody titers were elicited in all animals receiving an mRNA based vaccine. The GMTs were highest in the groups receiving mDS-Cav1 or the combination of mF + mDS-Cav1. No increase in palivizumab or D25 (site Ø) competing antibody titers were seen in the LNP only control group.

The mRNA vaccines were also found to boost T cell responses in the RSV-experienced African green monkeys as determined by ICS assay at week 6 post vaccination (Figs. 18A-18B).

ICS assays for African Green Monkeys were conducted as follows:

A. Day 1: Thawing PBMCs

1. PBMC vials were removed from liquid nitrogen and placed on dry ice until ready to thaw.
2. Cells were thawed quickly with gentle agitation in 37 °C set point water bath.
3. For each subject, cell suspension was transferred to an appropriately labeled 15 mL or 50 mL tube, using a serologic pipette.
4. Approximately 0.5 mL R10 medium was slowly added to the cells, which were then swirled gently to mix the media and cell suspension.
5. Three times the frozen cell volume of R10 media was then added drop wise to each tube, swirling each after 0.5 mL to 1.0 mL of R10 media were added.
6. R10 Media was then added at a rate of 1.0 mL to 2.0 mL at a time until approximately 10 to 15 mL was added to each tube.
7. The tubes were swirled to mix the media and cell suspension, and then centrifuged at 250xg (setpoint) for 8 to 10 minutes at room temperature.

8. The supernatant was removed and the cells were gently resuspended in 5 mL of R10 medium.
9. The cell suspensions were then transferred into a 12 well tissue culture plate.
10. The tissue culture plates were placed in a 37 °C +/- 2 °C, 4% to 6% CO₂ incubator overnight.

B. Day 2: Counting and Stimulation Procedure for PBMC

PBMC counting

1. PBMCs from each well of the 12-well tissue culture plate were placed into labeled 50mL conical tubes.
2. Cells were then counted by trypan blue exclusion on a hemacytometer or by Guava PC and resuspended to 1 x 10⁷ cells per mL.

Stimulation Set-up

1. 100 µL of the resuspended PBMCs were then added to each well of a 96-well sterile U bottom tissue culture plate for a final number of 1 x 10⁶ cells/ well.
2. Peptide pools corresponding to the RSV F protein sequence were generated as follows. For optimal results the peptides were combined into two pools, RSV F1 and RSV F2. RSVF1 includes the first 71 peptides in the following list, and RSV F2 includes the following 70 peptides:

Table 8. Peptides

First aa number	15-mer	aa #		SEQ ID NO:
1	MELPILKANAITTIL	1 - 15	start F protein pool 1	29
5	ILKANAITTILTAVT	5 - 19		30
9	NAITTILTAVTFCFA	9 - 23		31
13	TILTAVTFCFASSQN	13 - 27		32
17	AVTFCFASSQNITEE	17 - 31		33
21	CFASSQNITEEFYQS	21 - 35		34
25	SQNITEEFYQSTCSA	25 - 39		35
29	TEEFYQSTCSAVSKG	29 - 43		36
33	YQSTCSAVSKGYLSA	33 - 47		37
37	CSAVSKGYLSALRTG	37 - 51		38
41	SKGYLSALRTGWYTS	41 - 55		39
45	LSALRTGWYTSVITI	45 - 59		40
49	RTGWYTSVITIELSN	49 - 63		41
53	YTSVITIELSNIKEN	53 - 67		42
57	ITIELSNIKENKCNG	57 - 71		43
61	LSNIKENKCNGTDAK	61 - 75		44
65	KENKCNGTDAKVCLI	65 - 79		45
69	CNGTDAKVCLIQEL	69 - 83		46

First aa number	15-mer	aa #		SEQ ID NO:
73	DAKVKLIKQELDKYK	73 - 87		47
77	KLIKQELDKYKNAVT	77 - 91		48
81	QELDKYKNAVTELQL	81 - 95		49
85	KYKNAVTELQLLMQS	85 - 99		50
89	AVTELQLLMQSTPAA	89 - 103		51
93	LQLLMQSTPAANNRA	93 - 107		52
97	MQSTPAANNRARREL	97 - 111		53
101	PAANNRARRELPRFM	101 - 115		54
105	NRARRELPRFMNYTL	105 - 119		55
109	RELPRFMNYTLNNAK	109 - 123		56
113	RFMNYTLNNAKKTNV	113 - 127		57
117	YTLNNAKKTNVTL SK	117 - 131		58
121	NAKKTNVTL SKKRKR	121 - 135		59
125	TNVTL SKKRKR RFLG	125 - 139		60
129	LSKKRKR RFLG FLLG	129 - 143		61
133	RKKR RFLG FLLG VGSA	133 - 147		62
137	FLG FLLG VGS AIASG	137 - 151		63
141	LLGVGS AIASG IAVS	141 - 155		64
145	GSAIASG IAVS KVLH	145 - 159		65
149	ASG IAVS KVLH LEGE	149 - 163		66
153	AVS KVLH LEGE VNKI	153 - 167		67
157	V LHLEGE VNKI KSAL	157 - 171		68
161	EGEVN KI SALLSTN	161 - 175		69
165	NKI SALLSTN KAVV	165 - 179		70
169	SALLSTN KAVV SLSN	169 - 183		71
173	STN KAVV SLSN GVS	173 - 187		72
177	AVV SLSN GVS VLT SK	177 - 191		73
181	LSN GVS VLT SK VLDL	181 - 195		74
185	VSVLT SK VLDL KNYI	185 - 199		75
189	TSKVLDL KNYI DKQL	189 - 203		76
193	LDL KNYI DKQL LPIV	193 - 207		77
197	NYI DKQL LPIV NKQS	197 - 211		78
201	KQL LPIV NKQSCSIS	201 - 215		79
205	PIV NKQSCSIS NIET	205 - 219		80
209	KQSCSIS NIET VIEF	209 - 223		81
213	SIS NIET VIEF QQKN	213 - 227		82
217	IET VIEF QQKN NRLL	217 - 231		83
221	IEF QQKN NRLL EITR	221 - 235		84
225	QKNNRLL EITREFSV	225 - 239		85
229	RLLEITREFSVNAGV	229 - 243		86
233	ITREFSVNAGV TTPV	233 - 247		87
237	FSVNAGV TTPV STYM	237 - 251		88
241	AGV TTPV STYM LTNS	241 - 255		89
245	TPV STYM LTNS ELLS	245 - 259		90
249	TYMLTNS ELLS LIND	249 - 263		91
253	TNSELLS LIND MPIT	253 - 267		92
257	LLSLIND MPIT NDQK	257 - 271		93
261	IND MPIT NDQK KLMS	261 - 275		94
265	PIT NDQK KLMS NN VQ	265 - 279		95

First aa number	15-mer	aa #		SEQ ID NO:
269	DQKKLMSNNVQIVRQ	269 - 283		96
273	LMSNNVQIVRQQSYS	273 - 287		97
277	NVQIVRQQSYSIMSI	277 - 291		98
281	VRQQSYSIMSIHKKE	281 - 295		99
285	SYSIMSIHKKEVLAY	285 - 299	start F protein pool 2	100
289	MSIHKKEVLAYVVQL	289 - 303		101
293	KKEVLAYVVQLPLYG	293 - 307		102
297	LAYVVQLPLYGVIDT	297 - 311		103
301	VQLPLYGVIDTPCWK	301 - 315		104
305	LYGVIDTPCWKLHTS	305 - 319		105
309	IDTPCWKLHTSPLCT	309 - 323		106
313	CWKLHTSPLCTTNTK	313 - 327		107
317	HTSPLCTTNTKEGSN	317 - 331		108
321	LCTTNTKEGSNICLT	321 - 335		109
325	NTKEGSNICLTRTDR	325 - 339		110
329	GSNICLTRTDRGWYC	329 - 343		111
333	CLTRTDRGWYCDNAG	333 - 347		112
337	TDRGWYCDNAGSVSF	337 - 351		113
341	WYCDNAGSVSFFPQA	341 - 355		114
345	NAGSVSFFPQAETCK	345 - 359		115
349	VSFFPQAETCKVQSN	349 - 363		116
353	PQAETCKVQSNRVFC	353 - 367		117
357	TCKVQSNRVFCDTMN	357 - 371		118
361	QSNRVFCDTMNSLTL	361 - 375		119
365	VFCDTMNSLTLPSEV	365 - 379		120
369	TMNSLTLPSEVNLCN	369 - 383		121
373	LTLPSEVNLCNVDIF	373 - 387		122
377	SEVNLCNVDIFNPKY	377 - 391		123
381	LCNVDIFNPKYDCKI	381 - 395		124
385	DIFNPKYDCKIMTSK	385 - 399		125
389	PKYDCKIMTSKTDVS	389 - 403		126
393	CKIMTSKTDVSSSVI	393 - 407		127
397	TSKTDVSSSVITSLG	397 - 411		128
401	DVSSSVITSLGAIVS	401 - 415		129
405	SVITSLGAIVSCYGK	405 - 419		130
409	SLGAIVSCYGKTKCT	409 - 423		131
413	IVSCYGKTKCTASNK	413 - 427		132
417	YGKTKCTASNKNRGI	417 - 431		133
421	KCTASNKNRGIKTF	421 - 435		134
425	SNKNRGIKTFSGNC	425 - 439		135
429	RGIKTFSGNCDYVS	429 - 443		136
433	KTFSNGCDYVSNKGV	433 - 447		137
437	NGCDYVSNKGVDTVS	437 - 451		138
441	YVSNKGVDTVSVGNT	441 - 455		139
445	KGVDTVSVGNTLYYV	445 - 459		140
449	TVSVGNTLYYVKNQE	449 - 463		141
453	GNTLYYVKNQEGKSL	453 - 467		142
457	YYVKNQEGKSLYVKG	457 - 471		143

First aa number	15-mer	aa #		SEQ ID NO:
461	KQEGKSLYVKGEPII	461 - 475		144
465	KSLYVKGEPIINFYD	465 - 479		145
469	VKGEPIINFYDPLVF	469 - 483		146
473	PIINFYDPLVFPSGE	473 - 487		147
477	FYDPLVFPSGEFDAS	477 - 491		148
481	LVFPSGEFDASISQV	481 - 495		149
485	SGEFDASISQVNEKI	485 - 499		150
489	DASISQVNEKINQSL	489 - 503		151
493	SQVNEKINQSLAFIR	493 - 507		152
497	EKINQSLAFIRKSDE	497 - 511		153
501	QSLAFIRKSDELLHN	501 - 515		154
505	FIRKSDELLHNVNAG	505 - 519		155
509	SDELLHNVNAGKSTT	509 - 523		156
513	LHNVNAGKSTTNIMI	513 - 527		157
517	NAGKSTTNIMITAI	517 - 531		158
521	STTNIMITAIIVIV	521 - 535		159
525	IMITAIIVIVVILL	525 - 539		160
529	AIIIVIVVILLSLIA	529 - 543		161
533	VIVVILLSLIAVGLL	533 - 547		162
537	ILLSLIAVGLLLYCK	537 - 551		163
541	LIAVGLLLYCKARST	541 - 555		164
545	GLLLYCKARSTPVTL	545 - 559		165
549	YCKARSTPVTLSKDQ	549 - 563		166
553	RSTPVTLSKDQLSGI	553 - 567		167
557	VTLSKDQLSGINNIA	557 - 571		168
561	KDQLSGINNIAFSN	561 - 575 561-574	14mer	169 -

3. Peptide pools (either RSV F1 or RSV F2 pool) were added to the cells to a final concentration of 2.5 µg/mL.
4. One mock well was prepared for each subject. The volume of DMSO corresponding to the volume of the peptide pool was added to the mock well.
5. Positive control wells were stimulated with a solution of PMA (20 ng/mL)/Ionomycin (1.25 µg/mL).
6. CD28/ CD49d cocktail was added to each well at a final concentration of 2 µg/mL.
7. Following the addition of peptides and the CD28/CD49d cocktail, the plates were incubated 30-60 minutes in 37 degree incubator.
8. 5 mL of Brefeldin A (0.5 mg/mL) was then added to each well, and the plates were then incubated for an additional 4-5 hours in 37 °C 5%CO₂ incubator.
9. Plates were then removed and 20 µL of 20 mM EDTA (dissolved in 1X PBS) was added to each cell well.

10. The plates were then held at 4 °C overnight.

C. Day 3: Staining

1. Plates were centrifuged at 500xg for 5 min, and the supernatant was removed.
- 5 2. Each well was washed with 175 mL of FACS Wash, and the plate was centrifuged again at 500xg for 5 min, and the supernatant was removed.
3. The PBMCs were stained with the extracellular antibodies as follows according to manufacturer recommended volume:
 - i. CD8 APCH7 : 5 µL per test
 - 10 ii. CD3 PE: 20 µL per test
 - iii. CD4 PCF594: 5 µL per test
 - iv. ViViDye: 3 µL per test
4. After the cocktail was added to all wells, 120 µL of FACS wash was added to each well and mixed. The plates were incubated in the dark at room temperature for 25-30
15 minutes.
5. Plates were then centrifuged plate at 500xg for 5 minutes and washed with 175 µL per well of FACS wash.
6. 200 µL of BD Cytofix/cytoperm solution was added to each well and the plates were incubated 20 to 25 minutes 4 °C.
- 20 7. Plates were then centrifuged plate at 500xg for 5 minutes and washed twice with 175 µL per well of PD perm wash buffer.
8. The PBMCs were then stained with the intracellular antibodies as follows:
 - i. IFN-g FITC 20 µL per test
 - ii. TNF PEcy7 5 µL per test
 - 25 iii. IL-2 APC 20 µL per test
9. After the cocktail was added to all wells, 120 µL of BD PermWash was added to each well, and the plates were incubated in the dark at room temperature for 25 minutes.
10. Following the incubation, the plates were centrifuged at 500xg for 5 minutes, washed with 175 µL BD perm wash buffer and the cells were then resuspended in 200 µL per
30 well of BD stabilizing fixative. Samples were then stored overnight at 4°C and acquired on an LSRII within 24 hrs of fixing.

As shown in Figs. 18A-18B, mRNA vaccines (mF, mDS-Cav1 or mF+ mDS-Cav1) resulted in increases in RSV F specific CD4+ and CD8+ T cell responses that were positive for IFN- γ , IL-2, and TNF- α . Overall the responses were comparable across all mRNA vaccine groups. T cell responses were not boosted in the MC3 LNP only control group.

5

Example 17: Immunogenicity and Efficacy Against RSV-B in Cotton Rat; Effectiveness of mRNA vaccine encapsulated with MC3

The immunogenicity and efficacy of experimental mRNA RSV vaccine formulations against challenge with RSV-B was tested in cotton rats. The study compared mRNAs encoding different forms of RSV-F protein encapsulated in MC3 lipid nanoparticle.

10

More specifically, female cotton rats (SAGE) were used and immunizations began at 3-7 weeks of age. The mRNA vaccines evaluated in this study included:

MRK01 membrane-bound RSV F protein

MRK04 membrane-bound DS-Cav1 (stabilized prefusion F protein)

15

The groups included in the study are as summarized in Table 9. The study evaluated all mRNA vaccines at a single dose of 25 mg. Control groups included in the study received either RSV A2 ($1 \times 10^{5.5}$ pfu) or no vaccine. Two doses of vaccine were administered to each animal (at week 0 and 4) except for the group receiving RSV A2 which received a single intranasal inoculum at week 0. Serum samples were collected for assessment of RSV neutralizing antibody titers. At week 8 cotton rats were challenged intranasally with RSV B strain RSV 18537. Four days post challenge the animals were euthanized and nose and lung tissue were collected to assess vaccine efficacy by measuring RSV levels in the tissue.

20

Table 9. Vaccine Formulations Tested for Immunogenicity and Efficacy in Cotton Rats

Group	No. of Cotton Rats	Vaccine Formulation (mRNA/ LNP)	Concentration ($\mu\text{g/mL}$)	Final mRNA Dose (μg)
1	6	mF (MRK01) mRNA/ MC3, I.M.	250	25
2	6	mDS-Cav1 (MRK04) mRNA/ MC3, I.M.	250	25
3	6	RSV A2 (intranasal)	NA	5.5 log 10 pfu
4	6	No Vaccine	NA	NA

25

Individual animal neutralizing antibody (NT_{50}) titers were measured in serum samples collected at week 4 (4 weeks post-dose 1) and week 8 (4 weeks post-dose 2; day of challenge). At week 4 all of the animals responded to vaccination with mRNA vaccines as

well as with the RSV A2 challenge. Titers increased in both mRNA vaccine groups following the second immunization. Both the mRNA vaccines and the RSV A2 infection resulted in roughly equivalent neutralizing antibody titers against RSV A and RSV B. The individual animal and group geometric mean NT₅₀ titers measured at weeks 4 and 8 (4 weeks post-dose 1 (PD1) and 4 weeks post-dose 2 (PD2; day of challenge)) are presented in Fig. 19.

The *in vivo* efficacy of the various vaccine formulations was evaluated by measuring inhibition of viral replication in the lungs and nasal passages of the immunized cotton rats after challenge with RSV B strain 18537 using the methods described above. The data are shown in Fig. 20. Complete inhibition of virus replication was observed in the lungs and the nose of cotton rats immunized with wt RSV A2. Both mF and mDS-Cav1 mRNAs completely protected both the lung and the nose from challenge with RSV B 18537, despite being designed based on sequences from RSV A. Both mF and mDS-Cav1 mRNA vaccines were equally effective against RSV B challenge when formulated with MC3 lipid nanoparticles.

Each of the sequences described herein encompasses a chemically modified sequence or an unmodified sequence which includes no nucleotide modifications.

Example 18: Mouse immunogenicity

In this example, assays are carried out to evaluate the immune response to RSV vaccine antigens delivered using an chemically unmodified mRNA/LNP platform in comparison to protein antigens.

Female Balb/c (CRL) mice (6-8 weeks old; N= 10 mice per group) are administered RSV mRNA vaccines or protein vaccines. The mRNA vaccines are generated and formulated in MC3 lipid nanoparticles. The mRNA vaccines to be evaluated in this study include (each in a chemically unmodified form):

MRK-1 membrane-bound RSV F protein

MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)

MRK-5 RSV F construct

MRK-6 RSV F construct

MRK-7 RSV F construct

MRK8 RSV F construct

MRK9 membrane-bound RSV G protein

MRK11 truncated RSV F protein (ectodomain only); construct modified to include an Ig secretion peptide signal sequence

MRK12 DS-CAV1 (non-membrane bound form); modified to include an Ig secretion peptide signal sequence

MRK13: MRK-5 construct modified to include an Ig secretion peptide signal sequence

5 MRK14: MRK-6 construct modified to include an Ig secretion peptide signal sequence

MRK16: MRK-8 construct modified to include an Ig secretion peptide signal sequence

10 The animals are immunized on day 0 and day 21 of the experiment. On days 14 and 35, blood is drawn from each animal and used for serological assays. On days 42 and 49, a subset of the animals are sacrificed and spleens are harvested to support ELISPOT and intracellular cytokine staining studies.

A. RSV Neutralization Assay:

15 Mouse sera from each group are pooled and evaluated for neutralization of RSV-A (Long strain) using the following procedures:

11. All sera samples are heat inactivated by placing in dry bath incubator set at 56°C for 30 minutes. Samples and control sera are then diluted 1:3 in virus diluent (2% FBS in EMEM) and duplicate samples are added to an assay plate and serially diluted.
- 20 12. RSV-Long stock virus is removed from the freezer and quickly thawed in 37°C water bath. Viruses are diluted to 2000 pfu/mL in virus diluent
13. Diluted virus is added to each well of the 96-well plate, with the exception of one column of cells.
- 25 14. HEp-2 cells are trypsinized, washed, resuspended at 1.5×10^5 cells/ml in virus diluent, and 100 μ L of the suspended cells are added to each well of the 96-well plate. The plates are then incubated for 72 hours at 37°C, 5% CO₂.
15. Following the 72 hour incubation, the cells are washed with PBS, and fixed using 80% acetone dissolved in PBS for 10-20 minutes at 16-24°C. The fixative is removed and the plates are allowed to air-dry.
- 30 16. Plates are then washed thoroughly with PBS + 0.05% Tween. The detections monoclonal antibodies, 143-F3-1B8 and 34C9 are diluted to 2.5 plates are then washed thoroughly with PBS + 0.05% 50 plates are then washed thoroughly with PBS + 0.05% Tween. The plates are then incubated in a humid chamber at 16-24°C for 60-75 minutes on rocker

17. Following the incubation, the plates are thoroughly washed.
18. Biotinylated horse anti-mouse IgG is diluted 1:200 in assay diluent and added to each well of the 96-well plate. Plates are incubated as above and washed.
19. A cocktail of IRDye 800CW Streptavidin (1:1000 final dilution), Sapphire 700 (1:1000 dilution) and 5mM DRAQ5 solution (1:10,000 dilution) is prepared in assay diluent and 50 mL of the cocktail is added to each well of the 96-well plate. Plates are incubated as above in the dark, washed, and allowed to air dry.
20. Plates are then read using an Aeries Imager. Serum neutralizing titers are then calculated using a 4 parameter curve fit in Graphpad Prism.

The serum neutralizing antibody titers for the mouse immunogenicity study are measured post dose 1 (PD1) and post dose 2 (PD2).

Table 10. Flagellin Nucleic Acid Sequences

Name	Sequence	SEQ ID NO:
NT (5' UTR, ORF, 3' UTR)	TCAAGCTTTTGGACCCTCGTACAGAAGCTAATACGACTCACTAT AGGGAAATAAGAGAGAAAAAGAAGAGTAAGAAGAAATATAAG AGCCACCATGGCACAAGTCATTAATACAAACAGCCTGTCGCTG TTGACCCAGAATAACCTGAACAAATCCCAGTCCGCACTGGGCA CTGCTATCGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCG AAAGACGATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCG CGAACATCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGA CGGTATCTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAA ATCAACAACAACCTGCAGCGTGTGCGTGAAGTGGCGGTTTCACT CTGCGAATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAG GCTGAAATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCG GCCAGACTCAGTTCAACGCGGTGAAAGTCCTGGCGCAGGACAA CACCTGACCATCCAGGTTGGTGCCAACGACGGTGAAACTATC GATATTGATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTG ATAAGCTTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGC TGTAACCGTTGATAAAACTACCTATAAAAATGGTACAGATCCT ATTACAGCCCAGAGCAATACTGATATCCAAACTGCAATTGGCG GTGGTGCAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGA TGGTCAATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTG TTTATAAAGCCACTTATGATGAAACTACAAAGAAAGTTAATAT TGATACGACTGATAAACTCCGTTGGCAACTGCGGAAGCTACA GCTATTCGGGGAACGGCCACTATAACCCACAACCAAATTGCTG AAGTAACAAAAGAGGGTGTGATACGACCACAGTTGCGGCTCA ACTTGCTGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACT AGCCTTGTAATACTATCGTTTGAGGATAAAAACGGTAAGGTTA TTGATGGTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGC CGCTACATATGATGAGAAAACAGGTGCAATTACTGCTAAAACC ACTACTTATACAGATGGTACTGGCGTTGCTCAAACTGGAGCTGT GAAATTTGGTGGCGCAAAATGGTAAATCTGAAGTTGTTACTGCT ACCGATGGTAAGACTTACTTAGCAAGCGACCTTGACAAACATA ACTTCAGAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAA GACTGAAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAG GTTGATACACTTCGTTCTGACCTGGGTGCGGTTTCAAGACCGTTT CAACTCCGCTATCACCACCTGGGCAATACCGTAAATAACCTG TCTTCTGCCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGA	251

Name	Sequence	SEQ ID NO:
	AGTCTCCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGT ACCTCCGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCC TCTCTTTACTGCGTTGATAATAGGCTGGAGCCTCGGTGGCCATG CTTCTTGGCCCTTGGGCCTCCCCCAGCCCTCCTCCCCTTCCTG CACCCGTACCCCGTGGTCTTTGAATAAAGTCTGAGTGGGCGG C	
ORF Sequence, NT	ATGGCACAAAGTCATTAATACAAACAGCCTGTCGCTGTTGACCC AGAATAACCTGAACAAATCCCAGTCCGCACTGGGCACTGCTAT CGAGCGTTTGTCTTCCGGTCTGCGTATCAACAGCGCGAAAGAC GATGCGGCAGGACAGGCGATTGCTAACCGTTTTACCGCAACA TCAAAGGTCTGACTCAGGCTTCCCGTAACGCTAACGACGGTAT CTCCATTGCGCAGACCACTGAAGGCGCGCTGAACGAAATCAAC AACAACCTGCAGCGTGTGCGTGAACCTGGCGGTTTCAGTCTGCGA ATGGTACTAACTCCCAGTCTGACCTCGACTCCATCCAGGCTGAA ATCACCCAGCGCCTGAACGAAATCGACCGTGTATCCGGCCAGA CTCAGTTCAACGGCGTGAAAGTCTTGCGCAGGACAACACCCCT GACCATCCAGGTTGGTGCCAACGACGGTGAAACTATCGATATT GATTTAAAAGAAATCAGCTCTAAAACACTGGGACTTGATAAGC TTAATGTCCAAGATGCCTACACCCCGAAAGAAACTGCTGTAAC CGTTGATAAAACTACCTATAAAAATGGTACAGATCCTATTACA GCCCAGAGCAATACTGATATCCAACTGCAATTGGCGGTGGTG CAACGGGGGTTACTGGGGCTGATATCAAATTTAAAGATGGTCA ATACTATTTAGATGTTAAAGGCGGTGCTTCTGCTGGTGTTTATA AAGCCACTTATGATGAAACTACAAAGAAAGTTAATATTGATAC GACTGATAAAACTCCGTTGGCAACTGCGGAAGCTACAGCTATT CGGGGAACGGCCACTATAACCCACAACCAAATTGCTGAAGTAA CAAAAGAGGGTGTTGATACGACCACAGTTGCGGCTCAACTGC TGCAGCAGGGGTTACTGGCGCCGATAAGGACAATACTAGCCTT GTAAAACTATCGTTTGAGGATAAAAACGGTAAGGTTATTGATG GTGGCTATGCAGTGAAAATGGGCGACGATTTCTATGCCGCTAC ATATGATGAGAAAACAGGTGCAATTACTGCTAAAACCACTACT TATACAGATGGTACTGGCGTTGCTCAAACCTGGAGCTGTGAAAT TTGGTGGCGCAAATGGTAAATCTGAAGTTGTTACTGCTACCGAT GGTAAGACTTACTTAGCAAGCGACCTTGACAAACATAACTTCA GAACAGGCGGTGAGCTTAAAGAGGTTAATACAGATAAGACTG AAAACCCACTGCAGAAAATTGATGCTGCCTTGGCACAGGTTGA TACACTTCGTTCTGACCTGGGTGCGGTTCAGAACCGTTTCAACT CCGCTATCACCAACCTGGGCAATACCGTAAATAACCTGTCTTCT GCCCCGTAGCCGTATCGAAGATTCCGACTACGCAACCGAAGTCT CCAACATGTCTCGCGCGCAGATTCTGCAGCAGGCCGGTACCTC CGTTCTGGCGCAGGCGAACCAGGTTCCGCAAAACGTCCTCTCTT TACTGCGT	252
mRNA Sequence (assumes T100 tail)	G*GGGAAAUAGAGAGAGAAAAGAAGAGUAAGAAGAAAUUAUA GAGCCACCAUGGCACAAGUCAUUAUACAAACAGCCUGUCGC UGUUGACCCAGAAUAACCUGAACAAAUCCAGUCCGCACUGG GCACUGCUAUCGAGCGUUUGUCUUCGCGUCUGCGUAUCAACA GCGCGAAAGACGAUGCGGCAGGACAGGCGAUUGCUAACCGUU UUACCGCGAACAUCAAAGGUCUGACUCAGGCUUCCCGUAACG CUAACGACGGUAUCUCCAUUGCGCAGACCACUGAAGGCGCGC UGAACGAAAUCAACAACAACCUGCAGCGUGUGCGUGAACUGG CGGUUCAGUCUGCGAAUGGUACUAAACUCCAGUCUGACCUCG ACUCCAUCCAGGCGAAAUACCCAGCGCCUGAACGAAUACG ACCGUGUAUCCGGCCAGACUCAGUUAACGGCGUGAAAGUCC UGGCGCAGGACAACACCCUGACCAUCCAGGUUGGUGCCAACG ACGGUGAAACUAUCGAUAUUGAUUUAAAAGAAAUCAGCUCU AAAACACUGGGACUUGAUUAAGCUUAAUGUCCAAGAUGCCUAC ACCCCGAAAGAAACUGCUGUAACCGUUGAUAAAACUACCUAU AAAAAUGGUACAGAUCCUAUUACAGCCCAGAGCAAUACUGAU AUCCAAACUGCAAUUGGCGGUGGUGCAACGGGGGUACUGG	253

[illegible]

Table 11. Flagellin Amino Acid Sequences

[illegible]

CTGAGTGCCTCCGCACAGGATGGTACACCTCCGTGATCACCATCGAGCTCAGCAATATTAAGA
GAACAAGTGCAATGGTACCGACGCTAAAGTCAAACCTTATCAAGCAGGAACCTCGACAAATATAAGA
ACGCTGTGACCGAGCTGCAGTTATTGATGCAGAGTACACCTGCCACCAATAACAGAGCTAGGAGG
GAGTTGCCTAGGTTTATGAACTACACTCTCAACAACGCGAAGAAGACCAATGTGACGCTATCCAA
5 GAAACGGAAGAGGAGGTTCCCTGGGGTTTCTTTTAGGGGTGGGCTCTGCCATTGCTTCCGGCGTGGC
TGTATGTAAAGTTCTCCACCTCGAGGGAGAGGTTAATAAGATTAAGTCGGCCCTGCTGAGTACTAA
CAAAGCAGTGGTGTGCTGAGTAACGGAGTAAGTGTGTTAACATTTAAGGTGCTGGACCTCAAGA
ATTATATTGACAAACAGTTGCTTCTATTCTAAACAAACAGAGCTGTTCAATAAGTAATATTGAAA
CTGTTATTGAGTTTCAGCAGAAGAACAACAGGCTTCTTGAGATTACACGCGAGTTCAGTGTCAATG
10 CCGGCGTTACAACACCCGTGTCTACCTACATGCTGACGAATTCTGAGCTTCTCTCTCTCATAAACG
ACATGCCCATTACGAATGACCAAAAAGAACTTATGTCCAACAACGTGCAGATTGTGCGACAGCAA
TCCTATAGCATTATGTGTATCATCAAGGAAGAGGTACTCGCTTATGTTGTGCAGCTACCACTCTAT
GGTGTGATTGACACCCCTGTTGGAAGCTGCATACCAGTCCACTCTGCACCACTAACACAAAGGAA
GGGAGCAATATTTGCCTCACTCGAACCGACAGGGGGTGGTATTGCGATAATGCGGGCTCCGTGTCC
15 TTCTTTCCACAGGCTGAAACTTGTAAGGTACAGTCAAACCGCGTGTCTGTGATACTATGAATTCTC
TGACTCTTCCCAGCGAGGTTAATCTCTGCAACGTGACATTTTCAATCCTAAATATGACTGCAAGA
TCATGACCAGCAAGACCGACGTCTCCAGCTCAGTAATCACTAGCCTAGGGGGCCATTGTAAGCTGCT
ATGGCAAGACCAAGTGTACTGCCTCTAATAAGAACAGAGGCATAATTAAGACCTTTTCAAATGGC
TGTGACTATGTGTGCAATAAGGGCGTCGACACGGTCTCAGTAGGGAATACCCTCTACTACGTTAAC
20 AAACAGGAAGGCAAATCCCTTTATGTAAAGGGCGAGCCATCATAAATTTCTACGACCCACTTGTG
TTCCCCAGTGATGAATTCGATGCATCAATCTCCAGGTGAACGAAAAGATCAATCAATCCCTTGCT
TTTATACGAAAGTCAGATGAACTCCTGCATAACGTGAATGCTGGGAAATCTACAACCAACATCATG
ATCACTACCATCATTATTGTGATTATCGTAATTCTGCTATCCTTGATTGCTGTGCGGGCTGCTTCTGT
ACTGTAAGGCCAGATCGACGCCTGTGACCCTTTCAAAGGACCAACTTAGCGGTATCAATAATATTG
25 CCTTTAGCAAT (SEQ ID NO: 257)

MRK_04_no4A**SQ-038058**

ATGGAAGTGCATTTTTGAAGGCAAACGCTATCACGACAATACTCACTGCAGTGACCTTCTGTTTT
30 GCCTCAGGCCAGAACATAACCGAGGAGTTTTATCAATCTACATGCAGCGCTGTATCTAAAGGCTAC
CTGAGTGCCTCCGCACAGGATGGTACACCTCCGTGATCACCATCGAGCTCAGCAATATTAAGA
GAACAAGTGCAATGGTACCGACGCTAAAGTCAAACCTTATCAAGCAGGAACCTCGACAAATATAAGA
ACGCTGTGACCGAGCTGCAGTTATTGATGCAGAGTACACCTGCCACCAATAACAGAGCTAGGAGG
GAGTTGCCTAGGTTTATGAACTACACTCTCAACAACGCGAAGAAGACCAATGTGACGCTATCCAA
35 GAAACGGAAGAGGAGGTTCCCTGGGGTTTCTTTTAGGGGTGGGCTCTGCCATTGCTTCCGGCGTGGC
TGTATGTAAAGTTCTCCACCTCGAGGGAGAGGTTAATAAGATTAAGTCGGCCCTGCTGAGTACTAA
CAAAGCAGTGGTGTGCTGAGTAACGGAGTAAGTGTGTTAACATTTAAGGTGCTGGACCTCAAGA
ATTATATTGACAAACAGTTGCTTCTATTCTAAACAAACAGAGCTGTTCAATAAGTAATATTGAAA
CTGTTATTGAGTTTCAGCAGAAGAACAACAGGCTTCTTGAGATTACACGCGAGTTCAGTGTCAATG
40 CCGGCGTTACAACACCCGTGTCTACCTACATGCTGACGAATTCTGAGCTTCTCTCTCATAAACG
ACATGCCCATTACGAATGACCAGAAGAACTTATGTCCAACAACGTGCAGATTGTGCGACAGCAA
TCCTATAGCATTATGTGTATCATCAAGGAAGAGGTACTCGCTTATGTTGTGCAGCTACCACTCTAT
GGTGTGATTGACACCCCTGTTGGAAGCTGCATACCAGTCCACTCTGCACCACTAACACAAAGGAA
GGGAGCAATATTTGCCTCACTCGAACCGACAGGGGGTGGTATTGCGATAATGCGGGCTCCGTGTCC
45 TTCTTTCCACAGGCTGAAACTTGTAAGGTACAGTCAAACCGCGTGTCTGTGATACTATGAATTCTC
TGACTCTTCCCAGCGAGGTTAATCTCTGCAACGTGACATTTTCAATCCTAAATATGACTGCAAGA
TCATGACCAGCAAGACCGACGTCTCCAGCTCAGTAATCACTAGCCTAGGGGGCCATTGTAAGCTGCT
ATGGCAAGACCAAGTGTACTGCCTCTAATAAGAACAGAGGCATAATTAAGACCTTTTCAAATGGC
TGTGACTATGTGTGCAATAAGGGCGTCGACACGGTCTCAGTAGGGAATACCCTCTACTACGTTAAC
50 AAACAGGAAGGCAAATCCCTTTATGTAAAGGGCGAGCCATCATAAATTTCTACGACCCACTTGTG
TTCCCCAGTGATGAATTCGATGCATCAATCTCCAGGTGAACGAGAAGATCAATCAATCCCTTGCT
TTTATACGAAAGTCAGATGAACTCCTGCATAACGTGAATGCTGGGAAATCTACAACCAACATCATG
ATCACTACCATCATTATTGTGATTATCGTAATTCTGCTATCCTTGATTGCTGTGCGGGCTGCTTCTGT
ACTGTAAGGCCAGATCGACGCCTGTGACCCTTTCAAAGGACCAACTTAGCGGTATCAATAATATTG
55 CCTTTAGCAAT (SEQ ID NO: 258)

MRK_04_nopolyA_3mut**SQ-038057**

ATGGAAGTGCATTTTTGAAGGCAAACGCTATCACGACAATACTCACTGCAGTGACCTTCTGTTTT
60 GCCTCAGGCCAGAACATAACCGAGGAGTTTTATCAATCTACATGCAGCGCTGTATCTAAAGGCTAC

CTGAGTGCCTCCGCACAGGATGGTACACCTCCGTGATCACCATCGAGCTCAGCAATATTAAAGA
 GAACAAGTGCAATGGTACCGACGCTAAAGTCAAACCTTATCAAGCAGGAACCTCGACAAATATAAGA
 ACGCTGTGACCGAGCTGCAGTTATTGATGCAGAGTACACCTGCCACCAATAACAGAGCTAGGAGG
 GAGTTGCCTAGGTTTATGAACTACACTCTCAACAACGCGAAGAAAACCAATGTGACGCTATCCAA
 5 GAAACGGAAGAGGAGGTTCCCTGGGGTTTCTTTTAGGGGTGGGCTCTGCCATTGCTTCCGGCGTGGC
 TGTATGTAAAGTTCTCCACCTCGAGGGAGAGGTTAATAAGATTAAGTCGGGCCCTGTGAGTACTAA
 CAAAGCAGTGGTGTGCTGAGTAACGGAGTAAGTGTGTTAACATTTAAGGTGCTGGACCTCAAGA
 ATTATATTGACAAACAGTTGCTTCTTATTCTAAACAAACAGAGCTGTTCAATAAGTAATATTGAAA
 10 CTGTTATTGAGTTTCAGCAGAAGAACAACAGGCTTCTTGAGATTACACGCGAGTTCAGTGTCAATG
 CCGGCGTTACAACACCCGTGTCTACCTACATGCTGACGAATTCTGAGCTTCTCTCTCATAAACG
 ACATGCCCATTACGAATGACCAAAAAGAACTTATGTCCAACAACGTGCAGATTGTGCGACAGCAA
 TCCTATAGCATTATGTGTATCATCAAGGAAGAGGTACTCGCTTATGTTGTGCAGCTACCACTCTAT
 GGTGTGATTGACACCCCTGTTGGAAGCTGCATACCAGTCCACTCTGCACCACTAACACAAAAGGAA
 15 GGGAGCAATATTTGCCTCACTCGAACCGACAGGGGGTGGTATTGCGATAATGCGGGCTCCGTGTCC
 TTCTTTCCACAGGCTGAAACTTGTAAGGTACAGTCAAACCGCGTGTCTGTGATACTATGAATTCTC
 TGACTCTTCCCAGCGAGGTTAATCTCTGCAACGTGACATTTTCAATCCTAAATATGACTGCAAGA
 TCATGACCAGCAAGACCGACGTCTCCAGCTCAGTAATCACTAGCCTAGGGGGCCATTGTAAGCTGCT
 ATGGCAAAACCAAGTGTACTGCCTCTAATAAGAACAGAGGCATAATTAAAACCTTTTCAATGGC
 20 TGTGACTATGTGTGCAATAAGGGCGTCGACACGGTCTCAGTAGGGAATACCCTCTACTACGTTAAC
 AAACAGGAAGGCAAATCCCTTTATGTAAAGGGCGAGCCATCATAAATTTCTACGACCCACTTGTG
 TTCCCAGTGATGAATTCGATGCATCAATCTCCAGGTGAACGAAAAGATCAATCAATCCCTTGCT
 TTTATACGAAAGTCAGATGAACTCTGCATAACGTGAATGCTGGGAAATCTACAACCAACATCATG
 ATCACTACCATCATTATTGTGATTATCGTAATTCTGCTATCCTTGATTGCTGTGCGGGCTGCTTCTGT
 25 ACTGTAAGGCCAGATCGACGCCTGTGACCCTTTCAAAAGACCAACTTAGCGGTATCAATAATATTG
 CCTTTAGCAAT (SEQ ID NO: 259)

Table 12. RSV mRNA Sequences

Name	mRNA Sequence	SEQ ID NO:
RSV #1	AUGGAGCUGCUCUAUCCUCAAGCAAAUGCCAUCACCACUAUCCU GACCGCCGUCACUUCUGCUUCGCCUCCGGCCAAAUAUACCGA AGAGUUCUAUCAGUCCACCUGCUCUGCCGUUUCUAAAGGUUACC UGUCAGCCCUUAGAACAGGGUGGUUAUACCUCUGUUAUUACCAU GAGUUGUCCAACAUAUAGAAGAACAAGUGCAAUGGCACAGACGC UAAGGUUAAGCUCUAUAGCAGGAGCUCGACAAAUAUAAAAAUG CCGUCACGGAGCUGCAGUUAUUGAUGCAGAGCACCCAGGCGACA AACAAACCGUGCACGACGCGAGCUACCCCGAUUCAUGAACUACAC CCUCAUAUAAUGCAAAGAAGACAAAUGUGACGCUCUCUAAGAAGC GCAAGCGUCGCUUUCUGGGCUUUCUUCUCGGGGUUGGGAGCGCG AUCGCAAGCGGCGUGGCUGUAUCAAAGUGCUUCAUCUUGAGGG AGAAGUGAAUAAAAUCAAAAGUGCUCUGCUAUCUACAAAAGAG CCGUUGUAUCACUGUCCAACGGAGUGUCCGUGCUCACGUCCAAA GUGCUAGAUUUGAAGAAUUAUCAUGAUAAAGCAGCUGCUCCCUAU UGUGAACAAACAUAUGUCCAUCAGUAACAUAUGAAACAGUCA UCGAGUUUCAACAGAAAAACAUAAGACUGCUGGAGAUUACCAGA GAAUUUUCGGUUAACGCCGCGUGACUACCCUGUAAGCACCUA CAUGUUGACAAACUCCGAACUUUUGUCACUGAUAAACGAUAUGC CUAUUACUAAUGAUCAGAAAAAAUUGAUGUCCAUAUAAUGUCCAA AUCGUCAGGCAACAGUCCUACAGUAUCAUGUCUAUUUAUUAAGGA GGAGGUCCUUGCAUACGUGGUGCAACUGCCAUUAUACGGAGUCA UUGAUACUCCUGUUGGAAACUCCAUAACAAGCCCCUGUGCACU ACUAAACACUAAAGAGGGAUCAAAUAUUUGUCUCACUCGGACAGA UAGAGGUUGGUACUGUGAUAAUGCUGGCUCAGUGCAUUCUUUC CACAGGCUGAAACCUGCAAGGUUCAGUCAACAGGGUGUUUUGC GAUACCAUGAAUUCUCUAACCCUCCCCAGUGAGGUGAACCUUGUG UAAUGUGGAUAUAUUAACCCCAAGUAUGAUUGUAAGAUAUGA CCUCCAAGACGGACGUGAGUAGCAGUGUUAUACCUCCUGGGG GCCAUUGUAUCCUGCUACGGAAAAACGAAAUUGUACUGCCUCGAA CAAAAUAGGGGAUAUCAAAACUUUUAUGUAAUGGAUGCGACU	260

Name	mRNA Sequence	SEQ ID NO:
	ACGUAUCUAAUAAAGGUGUUGACACAGUGUCAGUCGGCAACACA CUGUAUUACGUGAAUAAGCAAGAAGGGAAGUCGCUGUAUGUCA AGGGGAGCCUAUCAUUAUUUUUAUGACCCACUGGUUUUCCCCA GCGAUGAGUUCGACGCCAGCAUUAGUCAGGUUAAUGAGAAAAUC AACCAGUCCUUGGCAUUUAUUCGUAAGAGUGAUGAAUUGCUGCA UAAUGUGAACGCUGGUAAAUCCACUACCAACAUAUUGAUAACUA CCAUCAUCAUAGUAAUAAUAGUAAUUUUACUGUCUCUGAUCGCU GUGGGCCUGUACUGUAUUGCAAAGCCCGCAGUACUCCUGUCAC CUUAUCAAAAGGACCAGCUGUCUGGGAUAAACAACAUCGCGUUCU CCAAU	
RSV # 2	AUGGAACUGCUCAUUUUGAAGGCAAACGCUAUCACGACAAUACU CACUGCAGUGACCUUCUGUUUUGCCUCAGGCCAGAACAUAAACCG AGGAGUUUUAUCAAUCAUACAUGCAGCGCUGUAUCUAAAGGCUAC CUGAGUGCGCUCCGCACAGGAUGGUACACCUCCGUGAUCACCAU CGAGCUCAGCAAUAUUAAAGAGAACAAGUGCAAUGGUACCGACG CUAAAGUCAACUUAUCAAGCAGGAACUCGACAAUAUAAAAAC GCUGUGACCGAGCUGCAGUUAUUGAUGCAGAGUACACCUGCCAC CAAUAACAGAGCUAGGAGGGAGUUGCCUAGGUUUUAUGAACUACA CUCUCAACAACGCGAAAAAAACCAAUGUGACGCUAUCCAAGAAA CGGAAGAGGAGGUUCCUGGGGUUUUUUAGGGGUGGGCUCUGC CAUUGCUUCCGGCGUGGCUGUAUGUAAAGUUCUCCACCUCGAGG GAGAGGUUAAUAAGAUUAAGUCGGCCUGCUGAGUACUAAACAA GCAGUGGUGUCGUGAGUAACGGAGUAAGUGUGUUAACAUUUAA GGUGCUGGACCUCAGAAUUAUUAUUGACAAACAGUUGCUCUCCUA UUCUAAACAAACAGAGCUGUUAUUAAGUAAUUAUUGAAACUGUU AUUGAGUUUCAGCAGAAGAACAACAGGCUUCUUGAGAUUACACG CGAUUCAGUGUCAUUGCCGGCGUUAACAACACCCGUGUCUACCU ACAUGCUGACGAAUUCUGAGCUUCUCUCUCUCAUAAACGCAUG CCCAUUACGAAUGACCAAAAAAAACUUAUGUCCAACAACGUGCA GAUUGUGCGACAGCAAUCCUAUAGCAUUUUGUGUAUCAUCAAGG AAGAGGUACUCGCUUAUGUUGUGCAGCUACCACUCUAUGGUGUG AUUGACACCCCCUGUUGGAAGCUGCAUACCAGUCCACUCUGCAC CACUAACACAAAGGAAGGGAGCAAUAUUUGCCUCACUCGAACCG ACAGGGGGUGGUUAUUGCGAUAAUGCGGGCUCGUGUCCUUCUUU CCACAGGCUGAAACUUGUAAGGUACAGUCAAAACCGCGUGUUCUG UGAUACUAUGAAUUCUCUGACUCUCCCAGCGAGGUUAAUCUCU GCAACGUCGACAUUUCAAUCCUAAAUAUGACUGCAAGAUAUG ACCAGCAAGACCGACGUCUCCAGCUCAGUAAUCACUAGCCUAGG GGCCAUUGUAAGCUGCUAUGGCAAAACCAAGUGUACUGCCUCUA AUAAGAACAGAGGCAUAAUUAACCUUUUCAAUUGGCUGUGAC UAUGUGUCGAAUAAGGGCGUCGACACGGUCUCAGUAGGGAAUAC CCUCUACUACGUUAACAAACAGGAAGGCAAAUCCCUUUUAUGUAA AGGGCGAGCCCAUCAUAAAUUUCUACGACCCACUUGUGUUCCCC AGUGAUGAAUUCGAUGCAUCAAUCUCCCAGGUGAACGAAAAGAU CAAUCAAUCCCUUGCUUUUAUACGAAAGUCAGAUGAACUCCUGC AUAACGUGAAUGCUGGGAAAUCUACAACCAACAUAUGAUCACU ACCAUCAUUAUUGUGAUUAUCGUAAUUCUGCUAUCCUUGAUUGC UGUCGGGCUGCUUCUGUACUGUAAGGCCAGAUACGACCCUGUGA CCCUUCAAAGACCAACUUAAGCGGUAUCAUAAUUAUUGCCUUU AGCAAU	261
MRK-1 membrane-bound RSV F protein/MRK_01 _F (full length, Merck A2 strain)/SQ- 030268	AUGGAGCUGCUCAUCCUCAAAGCAAUUGCCAUCACCACUAUCCUG ACCGCCGUCACUUUCUGCUUCGCCUCCGGCCAAAAUAUACCCGAA GAGUUCUAUCAGUCCACCUGCUCUGCCGUUUCUAAAGGUUACCUG UCAGCCCUUAGAACAGGGUGGUUAUACCUCUGUUAUUAACAUUGAG UUGUCCAACAUUAAGAAGAACAAGUGCAAUGGCACAGACGCUAAG GUUAAGCUCAUCAAGCAGGAGCUCGACAAUAUAAAAAUGCCGUC ACGGAGCUGCAGUUAUUGAUGCAGAGCACCCAGGCGACAAACAAC CGUGCACGACGCGAGCUACCCCGAUUCAUGAACUACACCCUCAU AAUGCAAAGAAGACAAAUGUGACGCUCUCUAAGAAGCGCAAGCGU	262

Name	mRNA Sequence	SEQ ID NO:
	CGCUUUCUGGGCUUUCUUCUCGGGGUUGGGAGCGCGAUCGCAAGC GGCGUGGCUGUAUCAAAGUGCUUCAUCUUGAGGGAGAAGUGAAU AAAAUCAAAAGUGCUCUGCUAUCUACAAACAAAGCCGUUGUAUCA CUGUCCAACGGAGUGUCCGUGCUCACGUCCAAGUGCUAGAUUUG AAGAAUUACAUCGAUAAGCAGCUGCUCCCUAUUGUGAACAACAA UCAUGUCCAUCAGUAACAUAUGAAACAGUCAUCGAGUUUCAACAG AAAAACAUAAGACUGCUGGAGAUUACCAGAGAAUUUCGGUUAAC GCCGGCGUGACUACCCUGUAAGCACCACAUGUUGACAAACUCC GAACUUUUGUCACUGAUAAACGAUAUGCCUAUUACUAAUGAUCAG AAAAAAUUGAUGUCCAUAUUGUCCAAUUCGUCAGGCAACAGUCC UACAGUAUCAUGUCUAUUAAUUAAGGAGGAGGUCCUUGCAUACGUG GUGCAACUGCCAUAUACGGAGUCAUUGAUACUCCUGUUGGAAA CUCCAUAACAAGCCCCUGUGCACUACUAAACAUAAAGAGGGGAUCA AAUAUUUGUCUCACUCGGACAGAUAGAGGUUGGUACUGUGAUAAU GCUGGCUCAGUGUCAUUCUUCACAGGCUGAAACCUGCAAGGUU CAGUCAAAACAGGGUGUUUUGCGAUACCAUGAAUUCUCUAAACCCUC CCCAGUGAGGUGAACCUGUGUAAUGUGGAUAUAUUAACCCCAAG UAUGAUUGUAAGAUAUGACCUCCAAGACGGACGUGAGUAGCAGU GUUAUCACCUCUCCUGGGGGCCAUUGUAUCCUGCUACGGAAAAACG AAAUGUACUGCCUCGAACAAAAAUAGGGGAAUCAUAAAACUUUU AGUAAUGGAUGCGACUACGUAAUAAUAAAGGUGUUGACACAGUG UCAGUCGGCAACACACUGUAUACGUGAAUAAGCAAGAAGGGGAAG UCGCUGUAUGUCAAAAGGGGAGCCUAUCAUAAUUAUUUUAUGACCCA CUGGUUUUCCCCAGCGAUGAGUUCGACGCCAGCAUUAAGUCAGGUU AAUGAGAAAAUCAACCAGUCCUUGGCAUUAUUCGUAAGAGUGAU GAAUUGCUCCAUAUUGUGAACGCUGGUAUAAUCCACUACCAACAUA AUGAUAAUACCAUCAUAGUAUAAUAAUAGUAAUUAUACUGUCU CUGAUCGCGUGGGGCCUGUACUGUAUUGCAAAGCCCGCAGUACU CCUGUCACCUUAUCAAAAGGACCAGCUGUCUGGGAUAAACAACAUC GCGUUCUCCAUA	
MRK-4 membrane-bound DS-CAV1 (stabilized prefusion F protein)/MRK_0 4_Prefusion F/DS-CAV1 (Full length, S155C/S290C/S1 90F/V207L)/SQ- 030271	AUGGAACUGCUCAUUUUGAAGGCAAACGCUAUCACGACAAUACU CACUGCAGUGACCUUCUGUUUUGCCUCAGGCCAGAACAUAACCG AGGAGUUUUAUCAAUUCAUGCAGCGCUGUAUCUAAAGGCUAC CUGAGUGCGCUCCGCACAGGAUGGUACACCUCGGUGAUCACCAU CGAGCUCAGCAUAUUAAGAGAACAAGUGCAAUGGUACCGACG CUAAAGUCAAAACUUAUCAAGCAGGAACUCGACAAUAUAAAAAC GCUGUGACCGAGCUGCAGUUAUUGAUGCAGAGUACACCUGCCAC CAAUAACAGAGCUAGGAGGGAGUUGCCUAGGUUUAUGAACUACA CUCUCAACAACGCGAAAAAAACCAAUGUGACGCUAUCCAAGAAA CGGAAGAGGAGGUUCCUGGGGUUCUUUUAGGGGUGGGCUCUGC CAUUGCUUCCGGCGUGGCUGUAUGUAAAGUUCUCCACCUCGAGG GAGAGGUUAUAAGAUAUAGUCGGCCUUGCUGAGUACUAAACAA GCAGUGGUGUCGUGAGUAACGGAGUAAGUGUGUUAACAUAUUA GGUGCUGGACCUCAGAAUAUAUUGACAAACAGUUGCUUCCUA UUCUAAACAAACAGAGCUGUUAUAUAGUAAUUAUGAAACUGUU AUUGAGUUUCAGCAGAAGAACAACAGGCUUCUUGAGAUUACACG CGAGUUCAGUGUCAUUGCCGGCGUUAACAACCCCGUGUCUACCU ACAUGCUGACGAAUUCUGAGCUUCUCUCUCUCAUAAACGACAUG CCCAUUAACGAUAGACCAAAAAAACUUAUGUCCAACAACGUGCA GAUUGUGCGACAGCAAUCCUAUAGCAUUAUGUGUAUCAUAAGG AAGAGGUACUCGCUUAUGUUGUGCAGCUACCACUCUAUGGUGUG AUUGACACCCCGUGUUGGAAGCUGCAUACCAGUCCACUCUGCAC CACUAACACAAAGGAAGGGAGCAUAUUUGCCUCACUCGAACCG ACAGGGGGUGGUUAUUGCGAUAAUGCGGGCUCGUGUCCUUCUUU CCACAGGCUGAAACUUGUAAGGUACAGUCAAAACCGCGUGUUCUG UGAUACUAUGAAUUCUCUGACUCUCCCAGCGAGGUUAAUCUCU GCAACGUCGACAUUUUCAAUCCUAAUAUGACUGCAAGAUAUG ACCAGCAAGACCGACGUCUCCAGCUCAGUAAUCACUAGCCUAGG GGCAUUGUAAGCUGCUAUGGCAAAACCAAGUGUACUGCCUCUA	263

Name	mRNA Sequence	SEQ ID NO:
	AUAAGAACAGAGGCAUAAUUA AAAACCUUUUCAA AUGGCUGUGAC UAUGUGUCGAAUAAGGGCGUCGACACGGUCUCAGUAGGGAUAUAC CCUCUACUACGUUAACAAACAGGAAGGCAAUCCCUUUAUGUAA AGGGCGAGCCCAUCAUAAAUUUCUACGACCCACUUGUGUCCCC AGUGAUGAAUUCGAUGCAUCAAUCUCCCAGGUGAACGAAAAGAU CAAUCAAUCCCUUGCUUUUAUACGAAAGUCAGAUAACUCCUGC AUAACGUGAAUGCUGGGAAAUCUACAACCAACAUCAUGAUCACU ACCAUCAUUAUUGUGAUUAUCGUAAUUCUGCUAUCCUUGAUUGC UGUCGGGCUGCUUCUGUACUGUAAGGCCAGAU CGACGCCUGUGA CCCUUUCAAAAGACCAACUAGCGGUAUCAAUAAU AUUGCCUUU AGCAAU	
MRK-5 RSV F Construct	AUGGAACUGCUCAUCCUUAAGCCAACGCGAU AACGACCAUUCU GACCGCCGUGACCUUCUGCUUCGCCAGCGGCCAGAACAUUACCG AAGAGUUUUACCAGAGCACGUGCUCUGCCGUGAGCAAAGGUUAU CUGAGCGCUUUAAGAACUGGCUGGUACACCAGUGUUAUUAUUAU AGAGCUGUCAAAUAUUA AAAAGAAUAAAUGCAACGGGACCGAUG CCAAAGUAAAAUUAUUAAGCAGGAAUUGGACAAGUAUAAGAAU GCAGUGACAGAGUUGCAGCUCCUGAUGCAGAGCACACAAGCUAC AAACAAUCGCGCUCGCCAGCAGCAACAGCGGUUUUUAGGGUUC UGC UAGGGGUGGGGUCAGCCAUUGCCUCUGGAGUGGCAGUGUCC AAAGUGCUGCAUCUGGAAGGGGAAGUUAACAAGAUAAAAUCCGC ACUCCUCAGCACCAAUAAAGCCGUGGUCUCCUGUCCAAUGGAG UAUCAGUUUUGACAAGCAAGGUGCUGGACCUGAAGAAUUAUAUA GAUAAGCAGUUAUCUGCCAUAUGUGAAUAAACAGUCAUGCUGAAU UAGCAACAUGAGACAGUUAUCGAAUCCAGCAGAAAAAUAAUA GGCUUCUGGAAAUAACUCGCGAAUUCUCAGUAAAUGCCGGAGUG ACCAACCCGUAUCGACUUAUAUGCUUACAAACUCUGAAGCUU GUCCUUGAUUAACGAUAUGCCAUAACA AAUGACCAGAAGAGC UAAUGAGCAACAAUGUGCAGAUUGUAAGACAGCAGUCUUAUCUA AUAAUGUCUAUAAUAAAAGAGGAGGUGUUGGCAUAUGUGGUGC AACUGCCUCUCUAUGGCGUGAUCGAUACUCCUUGCUGGAAGUUA CAUACAUCUCCACUGUGUACAACUAUAUACUAAGGAGGGUAGCAA UAUUUGUCUGACACGCACAGAU CGGGGUUGGUUAUUGCGACAACG CGGGCAGUGUGAGCUUUUCCCU CAGGCCGAAACCUGUAAGGUU CAAUCUAAUCGGGU AUUUUGCGACACAAUGAACAGCCUGACCCU UCCGUCCGAAGUUA AUUUUGUGCAACGUCGACAUCUUAUCCUA AAUAUGACUGCAAAAUCAUGACUUCUAAAACCGACGUAUCCAGC UCAGUGAUACAAGCCUUGGGGCAAUUGUAAGCUGCUAUGGCAA GACGAAGUGCACCGCUAGUAACAAGAACCGGGGGAUUAUUAAGA CUUUUUCGAACGGAUGCGAUUACGUCUCCAACAAAGGCGUCGAU ACUGUGUCCGUGGGAAACACCCUCUACUAUGUGAACAAGCAGGA AGGCAAAAGCCUCUACGUCAAAAGGAGAGCCUAUCAUCAAUUUCU ACGACCCUCUAGUAU UCCCUUCAGACGAAUUGACGCAUCAAUU UCCAGGUGAACGAGAAAAUAAAUCAAGCUUAGCCUUUAUCCG CAAGAGUGAUGAGUUGCUUCACAACGUC AACGCCGGCAAAUCA CCACUAAU	264
MRK-6 RSV F Construct	AUGGAACUCUUGAUCCUGAAGGCUAAUGCAAUAACAACAAUUCU GACAGCAGUCACCUUUUGCUUCGCCAGCGGACAGAAUAUUAACGG AGGAGUUUUAUCAAUCUACCUGUAGUGCCGUGAGCAAAGGGGUAC CUGUCUGCCCUGAGGACGGGAUGGUACACAUCCGUGAUCACCAU CGAGUUGUCUAACAUAUAAAAGAACAAGUGCAACGGAACUGACG CCAAGGUGAAGCUCAUUAAGCAAGAGCUCGACAAUAUAAGAAU GCGGUUACAGAAACUACAGCUACUAAUGCAGUCCACACAGGCAAC CAAUAACCGAGCACGUCAGCAGCAGCAACGCUUCCUUGGCUUCC UGCUCGGGGUUGGCUCGGCAAUUGCAUCCGGAGUGGCUGUUUCC AAGGUUUUGCACCUUGAGGGAGAGGUCAUAUAAGAUCAAGAGCGC CCUCCUGUCAACUAUAAGGCCGUGGUCAGCCUUUCCAACGGUG UUUCUGUGUUAACCUCAAAAGUGCUCGACCUUAAAAACUAUAUC GAUAAGCAGCUGCUGCCCAUAGUGAACAACAGUCCUGUUCUAU	265

Name	mRNA Sequence	SEQ ID NO:
	CAGUAAUAUCGAGACAGUGAUCGAAUUCAGCAGAAGAACAUAUC GUCUGCUGGAAAUAACAAGGGAGUUCAGCGUAAACGCUGGAGUC ACAACCCCCGUGUCCACUUAACAUGCUGACCAAUUCCGAGCUGCU GAGUUUGAUUAAUGAUUAGCCCAUACGAACGAUCAGAAGAAAC UGAUGUCGAAUAAUGUUCAGAUUCGUUAGGCAGCAGUCUUAUAGC AUAUGAGUAUUAUCAAAGAGGAGGUCCUCGCCUAUGUGGUUCA GCUGCCUCUCUACGGCGUUAUAGACACCCCAUGCUGGAAGCUUC ACACCUCUCCUCUGUGUACGACCAAUACAAAGGAGGGCUCAAAC AUUUGCCUUAACCCGCACAGAUAGAGGAUGGUACUGCGAUAAUGC UGGCUCUGUGUCUUCUUCUCCUCAGGCCGAAACAUGUAAGGUAC AGUCCAAUAGGGUAUUUUGCGACACCAUGAACUCCCUAACCUUA CCAAGUGAAGUGAACCUCUGCAAUGUGGACAUCUUUAACCCGAA GUAUGACUGCAAAAUCAUGACUCCAAGACAGACGUGUCCAGUA GUGUGAUUACCUCACUGGGCGCAAUCGUUUCAGCUAUGGGAAG ACAAAGUGCACCGCAAGCAACAAGAAUCGGGGCAUCAUAAAAC CUUCAGUAACGGUUGUGACUAUGUUUCAACAAGGGAGUCGAUA CCGUGUCGGUGGGCAAUACUCUUUACUACGUGAAUAAAACAGGAG GGGAAAUCACUGUAUGUGAAAGGUGAGCCGAUCAUUAACUUUA CGACCCUCUCGUGUUUCCCUCCGAUGAGUUCGACGCAUCCAUA GUCAGGUCAAUGAGAAAAUCAACCAAUUCUCUGCCUUAUUAAGA AAAUCUGACGAAUACUGAGUGCCAUGGAGGAUAUAUUCGGAG <u>GGCUCCAGGGACGGGCAGGCUUACGUCCGAAAGGAUGGAGAAU</u> <u>GGGUCCUACUGAGCACAUUUCUA</u> (The underlined region represents a sequence coding for foldon. The underlined region can be substituted with alternative sequences which achieve a same or similar function.)	
MRK-7 RSV F Construct	AUGGAGCUCCUGAUCUUGAAGGCGAAUGCCAUUACCACCAUCCU CACCGCAGUAACUUCUGUUCGCAAGUGGCCAGAAUAUAACAG AAGAGUUCUAUCAGUCAACCUUGUAGCGCAGUCUCAAGGGGUUAU UUAUCAGCACUGAGAACCUGUUGGUUAUACCAGUGUUAUUAACA AGAGCUGAGUAACAUAAGGAGAAUAAUGGCAACGGCACUGACG CCAAGGUCAAGCUCAUCAAACAGGAACUCGAUAAAUAACAAGAAC GCUGUCACUGAACUGCAGCUGCUGAUGCAAAGCACCCCGCCACC AACAAUAGGGCCCGCAGAGAGCUUCCUAGAUUUUAUGAACUACAC UCUGAACAAACGCCAAAAAGACCAUGUAACACUGUCAAGAAAC AGAAACAGCAGGCUAUUGCAAGCGGUGUGGCUGUGUCUAAAGUG CUGCAUCUCGAGGGGGAGGUCAACAAGAUAUAAUCCGCAUUGCU CAGCACCAACAAGGCUGUGGUGAGCCUGUCCAUGGUGUCUCAG UGCUCACCAGCAAAGUGCUGGACCUGAAGAAUUAUUAUGAUAA CAGCUGCUACCCAUAUGUCAACAACAGUCAUGCUCCAUAUCUAA UAUUGAGACUGUCAUCGAGUCCAACAGAAGAACAUCGCCUGC UGGAGAUUACCAGGGAGUUCUCAGUCAUUGCCGGGGUCACGACA CCCGUUAGUACUUAUUAUGCUUACCAACUCCGAGCUUCUCUCUUU GAUCAUAGACAUGCCAAUUAUUAACGACCAGAAGAAGUUGAUGU CUAACAAUGUACAGAUUCGUUCGCCAGCAGUCCUAUUCCAUUAUG UCGAUUAUUAAGAGGAGGUUCUUGCAUACGUCGUGCAGUUGCC AUUAUUAUGGAGUCAUCGACACCCCUUGCUGGAAACUGCAUACGU CACCAUUAUGCACCACGAAUACAAAGGAGGGCAGUAAUUAUUGU CUUACACGGACUGAUCGAGGCUGGUUAUUGUGAUAAACGCAGGCUC GGUGUCAUUCUUCACAGGCUGAAACCUGUAAGGUGCAAUCUA AUAGGGUGUUUUGCGAUACCAUGAAUUCUCUGACUCUGCCAGU GAGGUCAAUUUGUGUAACGUGGACAUCUUAACCCAAAGUACGA CUGCAAGAUAUGACAUCUAAGACAGAUGUGUCAUCCAGCGUUA UCACGAGCCUCGGCGCUAUAGUCUCCUGUUAACGGCAAGACCAAG UGCACCGCUAGCAACAAGAAUCGGGGAAUCAUCAAACCUUUUC UAACGGUUGUGACUACGUGAGCAACAAGGGGGUGGAUACCGUCU CAGUCGGUAACACCCUGUACUACGUGAAUAAACAGGAGGGGAAG UCAUUGUACGUGAAGGGUGAACCUAUAUCAACUUUAUGACCC CCUCGUCUCCCAUCAGACGAGUUUGACGCGUCCAUCUCUCAGG UGAAUGAGAAGAUUAACCAGAGCCUGGCUUUUAUCCGCAAAUCA	266

Name	mRNA Sequence	SEQ ID NO:
	GACGAACUACUGCACA AUGUCAACGCUGGCAAGAGCACAACAAA UAUAAUGAUACAACCAUCAUCAUCGUCAUUAUUGUGAUCUUGU UAUCACUGAUCGCUGUGGGGCUCCUCCUUUAUUGCAAGGCUCGU AGCACCCCUGUCACCCUCAGUAAAGAUCAGCUGUCAGGGAUCAA UAAUAUCGCGUUUAGCAAC	
MRK8 RSV F Construct	AUGGAAUUAUUAUUUUGAAGACAAAUGCUAUAACCGCGAUACUA GCGGCUGUGACUCUUUGUUUCGCAUCAAGCCAGAAUUAUACAGAA GAAUUUAUCAAUCCACCUGCAGCGCUGUAUCGAAAGGUUACCUC AGCGCGCUUAGGACAGGAUGGUUAUACCUCGUAUACAGAUUGAA CUGAGUAAUAUCAAGGAAAACAAGUGUAACGGAACAGACGCCAAG GUCAAACUUUAUAAACAAGAACUGGACAAGUAUAAGUCUGCAGUG ACCGAAUUGCAGCUCCUGAUGCAGAGUACCCUGCAACUAACAAC AAGUUUUUGGGCUUUCUGCAAGGCGUGGGUAGCGCGAUCGCCUCC GGAAUCGCGGUCUCCAAAGUGUUGCACCUGGAGGGAGAAGUUAAAC AAGAUCAAAUCGGCUCUGUUGAGUACCAACAAGGCAGUGGUGUCA CUGAGCAACGGUGUAAGCGUGUUAACAAGCAAGGUAAUUGGACUUA AAGAACUAUAUUGACAAACAGCUGCUCCCCAUCGUGAACAAACAG AGCUGCUCAAUCUCCAAUAUAGAGACGGUGAUAGAGUUCCAGCAA AAAAUAAUUCGGCUCCUUGAGAUACCCGCGAAUUCUCAGUUAUU GCCGGCGUCACAACUCCGGUGUCUACAUACAUGCUGACCAACUCG GAGCUGUUAUCCUUAUAAUAAUGACAUGCCCAUCACCAAUGAUCAA AAAAACUGAUGUCAAAUAACGUCCAGAUAGUAAGACAGCAGAGC UACAGCAUCAUGUCGAUUAUCAAAAGAGGAGGUGCUGGCGUACGUG GUGCAGCUGCCCCUGUAUGGGGUGAUUGACACCCCUUGUUGGAAG CUGCACACCUCCCCACUAUGUACUACCAAUACCAAAGAAGGAUCC AACAUUCGCCUUAACCCGCACCGAUAGGGGAUGGUAAUUGCGACAAC GCCGGAUCCGUCAGCUUCUUUCCACUUGCCGAAACUUGCAAGGUU CAGUCAAAACCGGGUGUUCUGCGAUACA AUGAAUUCUUUACCUUG CCCAGCGAAGUUAAUCUCUGUAAUAUUGACAUCUUUAACCCCAA UACGAUUGCAAAAUUAUGACGUCAAAAACCGAUGUCAGUUAAGC GUUAUCACCAGCUUGGGUGCUAUCGUUUAUGCUAUGGCAAAACC AAGUGUACGGCUAGUAACAAAAACCGCGGAUAAUUAAGACAUUC AGCAAUGGUUGCGACUACGUACAUAUAAAGGGUGUCGACACCGUU UCCGUGGGCAAUACGCUGUACUAUGUUAUAAACAGGAAGGCAAG UCACUGUAUGUUAAGGUGAACCCAUCAUCAACUUCUACGACCCC CUGGUUUUCCCCUCCGACGAGUUUGAUGCCAGCAUAUCACAGGUU AAUGAAAAAAUAAACGGCACAUUGGCGUUUAUCAGAAAGUCUGAC GAGAAACUUCAUAACGUGGAAGACAAGAUAGAAGAGAUAAUUGAG <u>CAAAAUCUAUCAUAUUGAGAACGAGAUCGCCAGGAUCAAAGGCU</u> <u>UAUUGGGGAG</u> (The underlined region represents a region coding for GCN4. The underlined region can be substituted with alternative sequences which achieve a same or similar function.)	267
MRK9 membrane-bound RSV G protein	AUGUCUAAAAACAAGGACCAGCGCACUGCUAAGACGCUGGAACG CACAUGGGAUACCCUGAACCAUCUGUUAUUCAUUUCCAGCUGCC UCUACAAGCUAAACCUUAAAAGUGUUGCACAAAUCACACUCAGC <u>AUCCUGGCAAUGAUUAUUUCAACAUCCUGAUCAUAGCCGCAAU</u> <u>CAUAUUUAUCGCCUCAGCAAAUCACAAAGUUACCCGACCACAG</u> CCAUAUCCAGGACGCUACAUCCCAAUCAAACACACCACACCU ACAUAUCUCACUCAGAACCCGCAGCUGGGCAUUUCACCAUCCAA CCCUUCCGAGAUACCCUCUCAAUACACCACCAUUCUCGCCUCUACU ACCCCGGGAGUAAAGAGCACUCUUCAGAGCACAACCGUUAAAAC UAAAAAUACCACCACCACUCAGACUCAGCCUUCGAAACCAACGA CUAAACAGCGGCAAAAUAAAGCCUCCAUCCAAACCGAAUAACGAC UUUCAUUUCGAAGUCUUUAACUUUGUGCCAUGCAGUAUUUGCUC CAAUAAUCCUACUUGCUGGGCUAUCUGCAAGAGAAUCCCUAACA AGAAGCCUGGAAAGAAGACAACGACAAAGCCAACUAAGAAGCCG ACACUUAAGACUACCAAAAAAGACCCUAAGCCGCAGACUACCAA GAGCAAGGAGGUUCCCAACAACCAAGCCUACAGAGGAGCCGACUA UUAACACAACAAAGACCAACAUCAUACACCACCCUGCUUACUUCU	268

Name	mRNA Sequence	SEQ ID NO:
	AAUACUACCGGAAACCCAGAGCUGACGUCCCAGAUGGAGACGUU CCAUUCCACAUCUUCCGAAGGGAAUCCUAGUCCCAGCCAGGUGA GCACAACCUCAGAAUACCCGUCCCAGCCCUCAUCACCUCCUAAUA CCCCCGGCAG (The underlined region represents a region coding for Uransmembrane domain. The underlined region can be substituted with alternative sequences which achieve a same or similar function.)	
MRK11 truncated RSV F protein (ectodomain only); construct modified to include an Ig secretion peptide signal sequence	<u>AUGGAGACGCCUGCCCAGCUGCUGU</u> <u>UCCUGCUGUUGUUGUGGCU</u> <u>GCCAGAUACUACUGGGU</u> <u>UUGCAAGCGGACAAAACAUUACCGAAG</u> AGUUCUAUCAAUCCACAUGCUCUGCAGUGUCUAAGGGCUACCUU AGUGCAUUAACGAACCGGGUGGUUAACGAGUGUAAUACCAUUGA GCUGUCCAACAUCAAGAAGAACAAGUGCAAUGGGACUGAUGCCA AGGUGAAACUUAUCAAAACAAGAGCUCGACAAGUAUAAGAACGCC GUGACCGAACUACAACUCCUGAUGCAAUCGACUCAGGCUACUAA CAACAGAGCUCGGAGGGAGCUGCCCAGAUUCAUGAAUUAUACCU UAAACAACGCUAAAAAAACAAUUGUGACCCUGAGUAAGAAGCGG AAACGAAGGUUCCUGGGCUUCCUGCUCGGUGUGGGGUCUGCAAU AGCAAGCGGCGUCGUGUGUCAAGGUCCUUCACUUAAGAAGGUG AGGUCAAUAAGAUAAGUCCGCUUCCUCUCUACCAACAAGGCA GUGGUGAGCCUGUCUAACGGUGUGUCCGUGCUGACAUCGAAGGU ACUGGACCUGAAAAACUACAUCGACAAGCAGCUGCUGCCUUAUG UGAAUAAGCAAUCCUGCAGUAUCUCCAACAUUGAGACAGUGAUU GAAUUCAGCAAAAAGAACAAUCGUUUGUUGGAGAUAAACAAGAGA AUUCAGUGUUAUGCCGGCGUUAACACUCCCGUGUCGACAUACA UGCUAACAAAUAGCGAGCUGCUAUCUCUCAUUAUGAUUAGCCU AUCACCAAUGACCAGAAAAAACUUAUGUCCAAUAACGUGCAGAU AGUCAGGCAGCAGUCCUACAGCAUUAUGAGCAUAAUUAAGAGG AAGUGUUGGCUUACGUGUCCAGCUUCCACUGUAUGGCGUGAUC GAUACCCCUUGUUGGAAGCUGCAUACUUCUUUUUUGUACAAC UAAUACCAAAGAAGGGAGUAAUUAUUGCCUCACAAGGACUGACA GAGGCUGGUACUGCGACAACGCCGGGAGCGUCAGCUUUUUUCCCG CAGGCCGAGACAUGUAAGGUGCAGAGCAACCGUGUCUUUUUGCGA CACCAUGAAUAGCCUGACUUAUGCCAAGUGAGGUCAACCUUUGCA ACGUGGAUUAUUUUUAACCCUAAGUACGAUUGUAAGAUAAUGACA UCCAAAACCGAUGUUAAGUAGCUCGUGAUCACUUCGCUGGGUGC GAUAGUUAGCUGCUAUGGAAAGACAAAGUGUACCGCAAGUAACA AGAACCGCGGGAUUAUUAACAACAUUUAAGCAAUGGGUGCGACUAC GUAUCAAAACAAGGGGGUGGAUACAGUCAGCGUGGGAAACACACU UUACUACGUUAACAAGCAGGAAGGGAAAUCCCUUAUGUGAAGG GAGAACCAUUAUCAACUUAUUAUGAUCCCUUCGUGUUUCCAAGU GAUGAAUUCGACGCAAGCAUCUCGAGGUGAACGAGAAAAUCA UCAGAGUCUAGCUUUAUAAGGAAGUCUGAUGAACUGCUU <u>AGUG</u> <u>CCAUUGGCGGGUACAUAACCGGAAGCCCCACGCGACGGUCAGGCU</u> <u>UACGUGAGGAAGGACGGCGAGUGGGUUCUGCUGUCCACUUUCCU</u> <u>U</u> (The first underlined region represents region coding for human Igk signal peptide, second underlined region represents region coding for foldon. The underlined regions can be substituted with alternative sequences which achieves same or similar functions.)	269
MRK12 DS- CAV1 (non- membrane bound form); modified to include an Ig secretion peptide signal sequence	<u>AUGGAGACUCCCGCUCAGCUGCUGUUUUUGCUCCUCCUAUGGCUG</u> <u>CCGGAUACCACCGGCUUUGCCUCUGGACAGAACAUUACCGAGGAA</u> UUCUAUCAGUCGACUUGUCCCGCAGUCUCGAAGGGGUACCUAGU GCCCUGCGCACCGGGUGGUACACCAGUGUUAUCACUAUUGAGCUG UCCAACAUAAGAAGAAUAAUGUGAAUGGAACUGACGCGAAGGUG AAGUUGAUAAAACAGGAGCUGGAUAAUACAAGAAUGCAGUGACC GAACUGCAGCUCCUGAUGCAGUCCACUCCAGCAACAAUAAUCGC GCGAGACGCGAACUCCCCCGCUUAUGAACUACACUCUGAAUAAU GCGAAGAAAACGAAUGUGACACUAAGUAAGAAAAGAAAACGGCGA UUUCUUGGGUUCUGCUCGGGGUGGGAUCUGCCAUAAGCAAGCGGG GUGGCGGUAUGUAAAGUCCUUCACCUAGAAGGGGAGGUGAACAAA AUUAAGAGUGCCUGCUGAGCACCAACAAGGCUGUGGUUUCACUG	270

Name	mRNA Sequence	SEQ ID NO:
	UCAAACGGAGUAAGCGUGCUAACAUUUAAAGUCUUGGACCUGAAG AAUUAUAUUGACAAGCAGCUCCUGCCCAUUCUCAACAAACAGUCA UGUCCAUUAGCAACAUCGAAACAGUCAUUGAGUUUCAGCAAAAA AACAAACCGCCUCCUUGAGAUUACGCGUGAGUUUCCGUCAAUGCU GGAGUCACGACACCGGUGUCCACUUAACUGCUGACUAAACAGCGAA CUCCUGAGCCUAAUCAAUGACAUGCCCAUUAACUAAACGACCAGAAA AAAUUGAUGUCCAAUAAACGUGCAGAUAGUGCGCCAGCAAUCUUAAC UCCAUAUUGUGCAUUAUCAAGGAGGAAGUCCUGGCGUACGUUGUU CAGCUGCCCGCUGUAUGGUGUGAUAGAUACGCCAUGCUGGAAACUG CACACAUCCCCCUUUGCACAACGAAUACUAAAGAGGGAAGUAAC AUUUGCUUGACCAGAACAGAUCCGGGGCUGGUACUGCGACAACGCU GGUAGUGUGUCAUUUUUCCCCCAGGCAGAAACGUGUAAAGUCCAG AGCAAUCGCGUGUUCUGCGACACAAUGAACUCACUUAACUUUGCCC UCAGAGGUCAAUUUGUGUAAUGUGGAUAUCUUAACCCGAAAUAC GAUUGUAAGAUUAUGACGAGCAAAACAGACGUGUCUUAUCAGUG AUAACAAGUCUGGGCGCAAUAGUGUCAUGCUAUGGUAAGACUAAAG UGCACUGCCUCCAAUAAAAACCGCGGCAUCAUCAAGACAUUUUCA AAUGGAUGCGACUACGUGUCAAAACAAGGGCGUCGACACAGUAAGC GUUGGGAACACCCUUAUACUACGUCACAAAGCAGGAGGGGAAAAGC CUAUACGUGAAAGGCGAGCCAAUCAUCAAUUUCUACGAUCCACUG GUCUUUCCAAGUGACGAAUUGAUGCCAGCAUAUCGCAGGUGAAC GAGAAAAUAAUCAGUCACUCGCCUUAUCAGGAAGUCAGAUGAG CUGCUGUCCGCCAUCGGAGGAUACA<u>UCCAGAAGCCCCACGCGAC</u> <u>GGCCAGGCAUACGUGCGGAAGGACGGCGAAUGGGUCCUUUUGAGC</u> <u>ACUUUUCUA</u> (The first underlined region represents a region coding for human Igκ signal peptide, The second underlined region represents a region coding for a foldon. The underlined regions can be substituted with alternative sequences which achieves same or similar functions.)	
MRK13 MRK-5 construct modified to include an Ig secretion peptide signal sequence	<u>AUGGAGACUCCAGCCCAAUACUGUUCUGCUACUCCUUUGGCU</u> <u>GCCCGAUACUACUGGAUUCGCUUCGGGUCAGAAUUAUACAGAGG</u> AGUUCUACCAAAGUACUUGCUCUGCAGUCUCCAAGGGAUACCUG UCCGCUCUGCGGACGGGAUGGUUAUACCAGUGUUUAUACGAUCGA GUUGAGCAACAUAAGAAGAACAUAUGUAAUGGAACAGAUGCCA AGGUGAAACUGAUCAAACAGGAGUUGGAUAAAUUAAGAAUGCU GUCACCGAACUGCAGCUAUUGAUGCAGUCCACCCAGGCUACCAA CAACCGGGCCAGGCAGCAACAACAGAGAUUUUUGGGUUUCUUGC UGGGCGUGGGGUCUGCCAUCGCUUCAGGGGUGGCGGUGAGUAAA GUCCUGCACCUGGAAGGCGAAGUCAACAAGAUCAAGUCUGCAUU ACUAAGUACCAAUAAGGCUGUAGUUAGCCUGUCCAAUGGCGUGA GUGUGCUUACUUCUAAGGUACUGGACCUGAAGAACUACAUCGAC AAGCAACUACUACCCAUUGUAAAUAAGCAGUCAUGUAGCAUAUC AAACAUCGAGACAGUGAUUGCAAUUUCAACAGAAGAAUAACCGGC UGUUGGAGAUAAACACGGGAGUUCUCUGUAAAUGCCGGCGUGACG ACCCUGUCAGCACCUAACAUGCUCACGAAUAGCGAGUUGCUUUC CCUGAUUAAUGAUUAGCCGAUUACAAUAGACCAGAAGAAGCUGA UGAGUAAUAAUGUCCAAAUUGUCCGUCAGCAGAGCUAUUCGAUU AUGUCCAUCAUAAAGGAGGAAGUCUUAGCCUUAUGUGGUGCAGCU CCCCCUACGAGAGUGAUUGACACACCGUGCUGGAAGCUGCACA CCUCCCCUUGUGUACAACCAAUACCAAGGAGGGCUCCAACAUC UGCCUUACUAGGACCGACAGGGGAUGGUAAUUGCGACAACGCCGG GUCCGUCUAUUUUUCCUCAGGCGGAAACCUGUAAGGUACAGU CGAAUCGAGUGUUUUGUGACACUAUGAACAGCCUGACCUGCCU AGCGAGGUGAAUCUGUGUAACGUUGAUUUCUUAACCCUAAGUA UGACUGUAAGAUAUGACUUAACAAACUGAUGUCUCCUCAAGCG UGAUCACCUCUUUGGGCGCCAUCGUGUCAUGCUACGGAAAGACG AAGUGCACCGCCUCUAACAAGAACCGAGGGAUCAUCAAACAUAU CUCCA AUGGUGUGAUUACGUCAGUAACAAGGUGUGGACACAG UCUCCGUGGGCAAUACGUUAUAUUAUGUGAAUAAGCAGGAGGGA AAAAGUCUCUAUGUGAAGGGUGAACC GAUAAUCAAUUUCUACGA	271

Name	mRNA Sequence	SEQ ID NO:
	UCCCUUGGUGUUUCCAAGCGACGAGUUCGACGCCUCGAUCAGCC AGGUGAACGAGAAAAUCAACCAGUCUUUGGCAUUCAUCCGCAAG AGCGACGAGCUACUGCAUAACGUGAACGCAGGCAAGAGUACUAC CAAU (The underlined region represents a region coding for human Igk signal peptide. The underlined region can be substituted with alternative sequences which achieve a same or similar function)	
MRK14 MRK-6 construct modified to include an Ig secretion peptide signal sequence:	<u>AUGGAGACUCCCGCUCAGUUGUUGUUCUGCUACUGCUGUGGCUG</u> <u>CCUGAUACAACCGGAUUUGCUAGUGGGCAGAAUAUCACCGAAGAA</u> UUCUAUCAGAGCACUUGCAGUGCAGUGUCCAAAGGAUAUUUGAGC GCCCUGCGCACUGGGUGGUACACAAGUGUCAUCACAAUCGAGCUA AGUAACAUAUAAAAAAAAACAAUGCAACGGGACUGACGCAAAGGUC AAACUCAUUAAGCAAGAACUUGACAAAUAUAAGAACGCUGUUAACA GAGUUGCAGCUGCUAAUGCAAAGCACUCAGGCUACCAUAUACCGA GCGAGACAGCAGCAGCAACGUUUCUGGGUUUCCUGUUAGGUGUG GGUAGCGCAAUUGCCAGUGGUGUAGCCGUGUCCAAGGUGCUGCAC CUGGAAGGGGAAGUGAAUAAGAUAAGUCUGCACUGCUGUCCACC AAUAAGGCGGUCGUUUCGCUGUCUAACGGCGUCUCGGUCCUAACA AGUAAAGUUCUGGAUUUAAAGAACUAUAUUGAUAAAGCAAUUGCU GCCUAUCGUAAAUAAGCAGAGUUGCAGCAUUAAGCAAUAUCGAGAC AGUGAUAGAAUUUCAGCAAAAGAACAAUCGAUUAUCUGAAAUCAC ACGCGAAUUCAGUGUCAUUGCCGGGGUUACAACCCUGUGUCGAC CUACAUGC UUACCAAUUCCGAGCUUCUGUCUCUUAUUAACGAUUA GCCCCAUCACGAACGAUCAGAAGAAACUGAUGUCAAAUAACGUCCA AAUUGUGCGGCAGCAAAGCUACAGUAUCAUGAGCAUCAUCAAGA GGAGGUGCUCGCCUAUGUGGUCCA AUUGCCGCUAUACGGGGUCAU UGAUACACCCUGUUGGAAGCUCCAUAUACUCCCAUUGUACAAC GAAUACCAAGGAGGGGUCUAACA AUUUGUCUGACCCGGACCGACAG AGGUGGU AUUUGCGAUAAUGCUGGAAGCGUUAAGUUUCUUCUCA GGCAGAAACAUGCAAGGUGCAGUCAACAGAGUUUUCUGUGACAC CAUGAAUUCUUGACGCUGCCUUCAGAAGUGAAUCUGUGUAACGU GGAUAUUCUUUAAUCCGAAGUACGAUUGUAAAAUUAUGACUAGCAA GACAGAUGUCUCGUCCUCUGUGAUCACUAGCCUGGGAGCGAUUGU GAGCUGUUAUGGUAAAACAAAGUGUACUGCUAGCAAUAAGAACAG GGGGAUUAUCAAAACGUUCAGUAACGGCUGUGAUUACGUAUCCAA CAAGGGGGUGGACACCGUGUCAGUCGGGAACACGCUCUACUACGU GAACAAGCAGGAAGGUAAGUCGCUAUACGUGAAGGGGGAAACCAU AAUCAAUUUCUACGAUCCGCUUGUGUUUCCUAGCGACGAAUUCGA CGAUCUAUCAGCCAGGUGAACGAGAAGAUCAAUCAGAGUCUGGC CUUCAUCCGCAAGUCCGACGAGCUGCUU <u>AGUGCUAUCGGAGGUUA</u> <u>UAUCCUGAGGCCCGAGGGACGGCCAAGCGUAUGUGAGAAAGGA</u> <u>CGGGGAUUGGGUACUGUUGUCAACUUUCCUA</u> (The first underlined region represents a region coding for human Igk signal peptide, The second underlined region represents a region coding for a foldon. The underlined regions can be substituted with alternative sequences which achieves same or similar functions.)	272
MRK16 MRK-8 construct modified to include an Ig secretion peptide signal sequence:	<u>AUGGAGACACCUGCCCAACUUCUGUUCUUCUUUUGCUCUGGCU</u> <u>GCCUGACACAACCGGCUUCGCAUCUUCACAAAACAUCACGGAAG</u> AGUUUUACCAGAGCACAUUGCUCGCGGUCUCUAAAGGCUAUCUU UCUGCCCUGCGGACUGGCUUGUAUACCAGCGUCAUCACCAUAGA GCUGUCAAAACAUAAGGAGAACAAGUGUAACGGCACUGACGCCA AGGUCAAGCUUAUAAAGCAGGAACUGGACAAGUAUAAGAGUGCU GUUACCGAGCUCCAGUUGCUUAUGCAGUCCACCCCGCAACAAA CAAUAAA AUUCUGGGCUUUCUACAGGGGCGUCGGAAGCGCCAUCG CAAGCGGCAUCGCUGUGAGCAAGGUGUUGCAUCUGGAGGGAGAG GUGAAUAAGAUAAAGAGUGCUCUGCUUUCACUAACAAAGCCGU GGUGAGCCUGAGCAAUGGCGUAUCUGUUCUGACUUCUAAAAGUCC UGGAUCUCAAGAACUAUAUCGACAAGCAGCUCUUGCCCAUUGUC AACAAACAGUCCUGCUCCA AUUCCAUAUUGAGACCGUCAUUGA GUCCAACAGAAGAAUAACCGUUUGCUGGAAAUACAAGGGAAU	273

Name	mRNA Sequence	SEQ ID NO:
	UCAGUGUUA AUGCCGGUGUA ACCACCCCUGUGAGCACCUAUAUG CUCACCAACUCUGAACUGCUGAGUCUGAUUAACGAUAUGCCCAU UACUAAUGAUCAGAAAGAAACUAAUGAGUAACAAUGUCCAGAUAG UUCGGCAGCAGUCAUAUCCAUUAUGAGUAUAAUCAAGGAGGAA GUGCUAGCCUACGUAGUUCAGCUCUCCCCUCUACGGCGUUAUAGAC ACGCCAUGUUGGAAGCUGCAUACGAGUCCUCUGUGCACUACAAA UACCAAGGAGGGCAGUAACAUAUGCUUGACUAGAACUGAUAGAG GCUGGUACUGCGACAAUGCAGGCUCCGUGUCAUUCUUUCCUCUC GCCGAGACGUGUAAAGUGCAGAGUAACAGAGUGUUUUGUGACAC AAUGAACUCAUUGACCCUGCCUAGCGAAGUGAACUUAUGCAACA UCGACAUUUUUAACCCAAAAUACGAUUGCAAGAUUAUGACCUCU AAGACUGACGUAUCUUCAUCCGUCUAACUUCUCUAGGAGCGAU CGUGAGCUGCUACGGUAAGACUAAAUGCACGGCUAGUAAUAAAA AUAGAGGUAUCAUUAAGACUUAUAGUAACGGUUGCGAUUAUGUG UCAACAAGGGAGUCGACACUGUUUCAGUGGGCAAUACUCUCUA CUACGUUAACAAACAGGAGGGUAAAUCCCUUAUGUGAAAGGGG AACCCAUCAUUAUUUUUAUGACCCACUUGUGUUCCUAGUGAC GAGUUUGACGCUUCAUCAGUCAAGUGAACGAAAAAAUUAUUGG CACGCUCGCGUUUAUCAGGAAAAGCGACGAGAAGCUGCAUAACG <u>UGGAAGAUAGAUCGAGGAGAUUCUCUCGAAAAUUUAUCAUAUA</u> <u>GAGAAUGAAAUCGCAAGAAUCAAAGGCUUAUUGGGGAG</u> (The first underlined region represents a region coding for human Igk signal peptide, The second underlined region represents a region coding for GCN4. The underlined regions can be substituted with alternative sequences which achieves same or similar functions.)	
MRK-2 non-membrane bound form RSV F protein/MRK_02_F (soluble, Merck A2 strain)/	AUGGAGCUGUUGAUCCUUAAGGCCAACGCCAUCACUACUUAUCU CACCGCGGUAACAUCUCUGCUUCGCCUCCGGGCAGAACAUACCG AGGAGUUCUACAGUCUACGUGCUCCGCCGUCUCCAAAGGUUAC CUGUCCGCAUUAAGGACGGGGUGGUACACUUCCGUCAUAACUUAU UGAACUGAGUAACAUA AAAAAGAACAAGUGUA AUGGGACGGAUG CCAAGGUGAAGCUCAUCAAGCAAGAGCUUGACAAAUAACAAGAAU GCAGUGACAGAGCUCCAACUUCUCAUGCAGUCUACACAGGCCAC GAAUAACCGUGCCCGAAGAGAACUGCCUAGAUUUUAUGAAUUAACA CUUUGAACAACGCCAAAAAGACCAACGUGACUCUAAGCAAAAAA AGGAAACGGCGUUUUCUGGGCUUUCUGCUGGGGGUUGGUAGCGC CAUCGCAUCUGGCGUGGCAGUCAGUAAAGUUUUGCACCUUGAGG GGGAGGUCAACAAAAUCAAGAGCGCGCUGUUAUCAACAAACAAG GCAGUCGUGUCCCUCCAAUGGCGUGUCUGUCCUGACCUCUAA AGUACUGGAUCUCAAGAACUAUAUCGACAAACAACUGCUACCAA UCGUCAUAAGCAGAGUUGCUCUAUUUCCAAUAUUGAGACCGUG AUCGAGUUUCAACAGAAGAAUAACAGAUUGUUGGAGAUACCCAG GGAUUUCAGCGUCA AUGCAGGGGUGACCACACCCGUAUCUACCU ACAUGCUGACCAACUCGGAACUCCUCUCCUUAUAUAAACGACAUG CCUAUUACUAACGACCAAAAAAAGUUGAUGUCCAACAAUGUCCA GAUCGUGCGACAGCAAUCUUAUUCAAUUAUGUCCAUAUAAAAG AGGAGGUGCUGGCGUACGUAGUGCAGCUGCCCCUUUACGGAGUG AUCGACACCCCAUGCUGGAAGCUCCACACCUCUCCCCCUGUGCACC ACUAAUACCAAAGAAGGCAGCAACAUCUGUCUGACCCGUACCGA CCGCGGAUGGUACUGCGAUAAUGCAGGUAGCGUCUCUUUUUUUC CCCAGGCUGAAACUUGCAAGGUUCAGUCCAACCGGGUAUUCUGU GACACGAUGAACAGUCUCACCCUACCAUCAGAGGGUGAACCCUGU CAAUGUGGACAUUUUAACCCUAAAUAUGACUGUAAGAUAUGA CCUCCAAAACUGACGUUUCAGCAGUGUCAUAACCUCACUGGGC GCAUAAGUUUCAUGCUAUGGAAAAGACUAAGUGCACUGCCUCUAA CAAAAAUCGAGGUUAUUAUUAAGACCUUUAAGCAAUGGCUGCGAUU AUGUCAGUAACAAAGGUGUUGAUACAGUGAGUGUGGGCAACACA UUUAUCUAUGUUAACAAGCAAGAAGGCAAGAGCCUCUAUGUGAA GGGAGAACCAAUCAUUAUUUUUACGAUCCGCGUGGUCUUUCCCA GCGAUGAGUUCGAUGCAUCCAUCUCUCAGGUGAAUGAAAAAAU	274

Name	mRNA Sequence	SEQ ID NO:
	AACCAAUCACUGGCUUUAUACGGAAGAGCGAUGAACUCGUGAG <u>CGCCAUCCGGGGGAUACAUCCUGAAGCUCCGAGGGACGGCCAAG</u> <u>CUUAUGUCCGCAAAGACGGAGAGUGGGUGUUGCUCAGUACCUUC</u> <u>CUC</u> (The underlined region represents a region coding for a foldon. The underlined region can be substituted with alternative sequences which achieve a same or similar function.)	
MRK-3 non-membrane bound form DS-CAV1 (stabilized prefusion F protein)//MRK_03_DS-CAV1 (soluble, S155C/S290C/S190F/V207L)/SQ-030271	AUGGAACUCGUGAUUCUUAAGGCGAAUGCCAUAAACCACUAUCUU GACCGCAGUUACUUUUUGCUUCGCCUCUGGGCAGAAUAAUUAACCG AAGAGUUCUACCAGUCCACGUGCAGUGCCGUGUCUAAGGGCUAC CUUUCGCGCUUCGCACUGGCUGGUACACGUCAGUCAUAACGAU CGAACUCUCUAAUUAUAAAGGAAAAUAAAGUGUAACGGAACAGACG CUAAGGUCAAGUUAUCAAGCAGGAGCUGGACAAAUAUAAGAAU GCCGUAACGGAGCUCCAGCUGCUCAUGCAGAGCACGCCAGCUAC AAACAACAGGGCACGCCGUGAGCUCUCCCCGAUUUAUGAACUACA CAUUGAACAAACGCCAAGAAAACUAACGUGACUUUGUCCAAGAAG AGGAAGCGGCGAUUCUUAGGGUCCUUUUGGGGGUAGGCUCGGC GAUUGCCAGUGGGGUUGCCGU AUGCAAGGUGCUCCACCUGGAAG GGGAGGUGAACAAGAUUAAGUCGGCUCUGCUCAGUACAAACAAA GCUGUCGUCUUAUUGUCAAAACGGAGUCAGUGUAUUGACAUUUAA AGUCCUCGACCUGAAGAACUAUAUAGAUAAACAGUUACUCCCAA UCUUGAAUAAGCAGUCCUGUAGCAUCAGCAACAUUGAGACAGUG AUCGAGUUCAGCAGAAGAAUAAUCGCCUACUCGAGAUCACCGAG AGAAUUCUCAGUCA AUGCCGGAGUAACCACUCCUGUCAGCACAU ACAUGCUCACAAACUCUGAACUCCUAAGCCUGAUUAAUGAU AUG CCUAUCACAAAUGAUCAGAAAGAAACUCAUGAGCAAUA AUGUGCA GAUUGUAAGACAGCAGAGUUUAUUCUAUAAUGUGUAUUAUUAAG GAGGAGGUACUGGCCUAUGUGGUUCAACUCCUCUGUAUGGGGU GUAAGAUACACCAUGCUGGAAGCUGCACACCAGCCACUGUGUA CGACCAAUACAAAGGAGGGCUCCAUAUUGCUUAACACGGACU GACCGGGGGUGGUUAUUGCGACAAUGCCGGAUCAGUCUCCUUCUU CCCCAAGCAGAGACCUGCAAGGUGCAGUCCAUAUAGAGUUUUCU GCGACACAAUGAACUCGCUGACCCUACCUAGCGAAGUUAACUUA UGCAACGUGGAUAUUUUUAUCCGAAGUAUGAUUGUAAAAUCAU GACUAGCAAAACGGAUGUUAAGCUCCAGCGUAAUACCUCCCUAG GCGCUAUCGUGAGCUGUUAUGGCAAGACGAAGUGCACUGCAUCU AAUAAAAAUAGGGGUUAUUAUUAUAAACCUUCAGCAAUGGCUGCGA CUAUGUGAGCAAUAAGGGCGUGGACACCGUGUCAGUGGGAAACA CCCUCUAUUAUGUGAACAAGCAGGAGGGAAAAUCCCUUUAUGUA AAGGGCGAACCCAUAUCAAUUUCUAUGACCCCCUGGUUUUCCC AAGCGACGAGUUCGACGCAUCUAUCUCUCAAGUGAACGAGAAAA UCAUUCAGAGUCUUGCCUUUAUCAGAAAAUCCGAUGAGCUGCUU <u>UCCGCCAUCGGUGGCUAUUCCCAAGAGCCCAAGAGACGGACA</u> <u>AGCGUACGUCCGGAAAGAUGGUGAGUGGGUCCUCCUCUCUACCU</u> <u>UUCUU</u> (The underlined region represents a region coding for a foldon. The underlined region can be substituted with alternative sequences which achieve a same or similar function)	275
Influenza M-1 (A/California/04/2009(H1N1), ACP44152)+hIgκ	AUGGAGACUCCUGCACAGCUGCUGUUUCUGCUAUUGUUGUGGCUU <u>CCGGACACUACUGGGUCCCUCCUACCGAGGUGGAAACAUACGUG</u> <u>CUGUCCAUCAUACCAUCCGGGCCCUUGAAAGCCGAGAU CGCCAG</u> AGACUCGAAUCUGUAUUCGCAGGAAAGAACACGGAUUUGGAGGCA CUAAUGGAAUGGCUGAAGACCCGUCCGAUCCUGUCUCCUCACACA AAGGGGAUUCUUGGAUUUGCUUUACCCUCACCGUCCGAGCGAG CGCGGUCUCCAGCGCAGAGCUUUUGUACAGAAUGCACUGAUGGC AACGGCGAUCCCAAUAACAUGGAUCGUGCGGUAAGGCUUUAUAAA AAGCUGAAGAGAGAAAUCACUUUCCAUGGGGCUAAAGAGGUGAGU CUCUCCUAUUAACCGGGGCAUUGGCCUCUUGCAUGGGUCUUAUA UACAAUCGAAUGGGCACCGUUAACACCGAGGCCGCAUUGGUCUG GUUUGUGCUACGUGCGAGCAAUUCGCAGAUAGCCAGCAUCGGUCC CAUCGGCAGAUGGCCACCACUACGAACCCUCUAAUUCGACAUGAA	276

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Name	mRNA Sequence	SEQ ID NO:
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EQUIVALENTS

Those skilled in the art will recognize, or be able to 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.

- 5 All references, including patent documents, disclosed herein are incorporated by reference in their entirety.

CLAIMS

1. A respiratory syncytial virus (RSV) vaccine, comprising:
at least one messenger ribonucleic acid (mRNA) polynucleotide having an open reading frame encoding at least one RSV antigenic polypeptide, wherein the at least one RSV antigenic polypeptide is glycoprotein F or an immunogenic fragment thereof or glycoprotein G or an immunogenic fragment thereof, and
a lipid nanoparticle.
2. The RSV vaccine of claim 1, wherein the amino acid sequence of the RSV antigenic polypeptide has at least 85% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.
3. The RSV vaccine of claim 1 or 2, wherein the amino acid sequence of the RSV antigenic polypeptide has at least 90% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.
4. The RSV vaccine of any one of claims 1-3, wherein the amino acid sequence of the RSV antigenic polypeptide has at least 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.
5. The RSV vaccine of any one of claims 1-4, wherein
 - (a) the open reading frame is codon-optimized; and/or
 - (b) the vaccine is multivalent; and/or
 - (c) the at least one mRNA polynucleotide encodes at least 2 antigenic polypeptides;
and/or
 - (d) the at least one mRNA polynucleotide encodes at least 10 antigenic polypeptides;
and/or
 - (e) the at least one mRNA polynucleotide encodes at least 100 antigenic polypeptides
and/or
 - (f) the at least one mRNA polynucleotide encodes 2-100 antigenic polypeptides.
6. The RSV vaccine of any one of claims 1-4, wherein the at least one mRNA polynucleotide comprises at least one chemical modification, optionally wherein the at least one

chemical modification is selected from the group consisting of pseudouridine, N1-methylpseudouridine, N1-ethylpseudouridine, 2-thiouridine, 4'-thiouridine, 5-methylcytosine, 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-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.

7. The RSV vaccine of any one of claims 1-5, wherein the lipid nanoparticle comprises a cationic lipid, a polyethylene glycol (PEG)-modified lipid, a sterol and a non-cationic lipid.

8. The RSV vaccine of claim 6, wherein the cationic lipid is an ionizable cationic lipid, the non-cationic lipid is a neutral lipid, and the sterol is a cholesterol.

9. The RSV vaccine of claim 8, wherein the lipid nanoparticle comprises 40-60% ionizable cationic lipid, 5-15% neutral lipid, 1-2% PEG-modified lipid, and 30-50% cholesterol.

10. A method of inducing an antigen specific immune response in a subject, comprising administering to the subject the RSV vaccine of any one of claims 1-9 in an amount effective to produce an antigen specific immune response.

11. The method of claim 10, wherein:

(a) the method of inducing an antigen specific immune response involves a single administration of the RSV vaccine and/or a booster dose of the vaccine; and/or

(b) the vaccine is administered to the subject by intradermal or intramuscular injection.

12. The RSV vaccine of any one of claims 1-9, wherein the glycoprotein F or immunogenic fragment thereof is in a prefusion conformation.

13. The method of claim 10 or 11, wherein the effective amount is a total dose of 25-100 μg .

14. The method of any one of claims 10, 11, or 13, wherein:

(a) the subject is about 5 years old or younger, wherein the subject is between the ages of about 1 year and about 5 years, wherein the subject is between the ages of about 6 months and

about 1 year, wherein the subject is about 6 months or younger, or wherein the subject is about 12 months or younger; or

(b) the subject is about 60 years old, about 70 years old, or older; or

(c) the subject is pregnant.

15. The method of any one of claims 10, 11, 13, or 14, wherein the subject has a chronic pulmonary disease (*e.g.*, chronic obstructive pulmonary disease (COPD) or asthma) and/or wherein the subject is immunocompromised.

16. The RSV vaccine of any one of claims 1-9 or 12, wherein the open reading frame further encodes a signal peptide linked to the RSV antigenic peptide.

17. The RSV vaccine of any one of claims 1-9, 12, or 16, wherein the RSV vaccine further comprises at least one mRNA having an open reading frame encoding a nucleoprotein (N) or an immunogenic fragment thereof, a phosphoprotein (P) or an immunogenic fragment thereof, a large polymerase protein (L) or an immunogenic fragment thereof, a matrix protein (M) or an immunogenic fragment thereof, a small hydrophobic protein (SH) or an immunogenic fragment thereof, a nonstructural protein1 (NS1) or an immunogenic fragment thereof, and/or a nonstructural protein 2 (NS2) or an immunogenic fragment thereof.

18. The RSV vaccine of claim 16, wherein the signal peptide is an IgE signal peptide or an IgGκ signal peptide, optionally wherein the IgE signal peptide is an IgE HC (Ig heavy chain epsilon-1) signal peptide, further optionally wherein the IgE HC signal peptide has the sequence MDWTWILFLVAAATRVHS (SEQ ID NO: 281).

19. The RSV vaccine of claim 18, wherein the IgGκ signal peptide has the sequence METPAQLLFLLLLWLPDTTG (SEQ ID NO: 282), or wherein the signal peptide is selected from: a Japanese encephalitis PRM signal sequence (MLGSNSGQRVVFTILLLLVAPAYS; SEQ ID NO: 283), VSVg protein signal sequence (MKCLLYLAFLFIGVNCA; SEQ ID NO: 284) and Japanese encephalitis JEV signal sequence (MWLVSLAIVTACAGA; SEQ ID NO: 285).

20. A respiratory syncytial virus (RSV) vaccine, comprising:

at least one messenger ribonucleic acid (mRNA) polynucleotide having an open reading frame encoding membrane-bound RSV glycoprotein F, membrane-bound DS-Cav1 (stabilized prefusion of RSV glycoprotein F), or a combination of membrane-bound RSV glycoprotein F and RSV membrane-bound DS-Cav1, and
a lipid nanoparticle.

Fig. 1

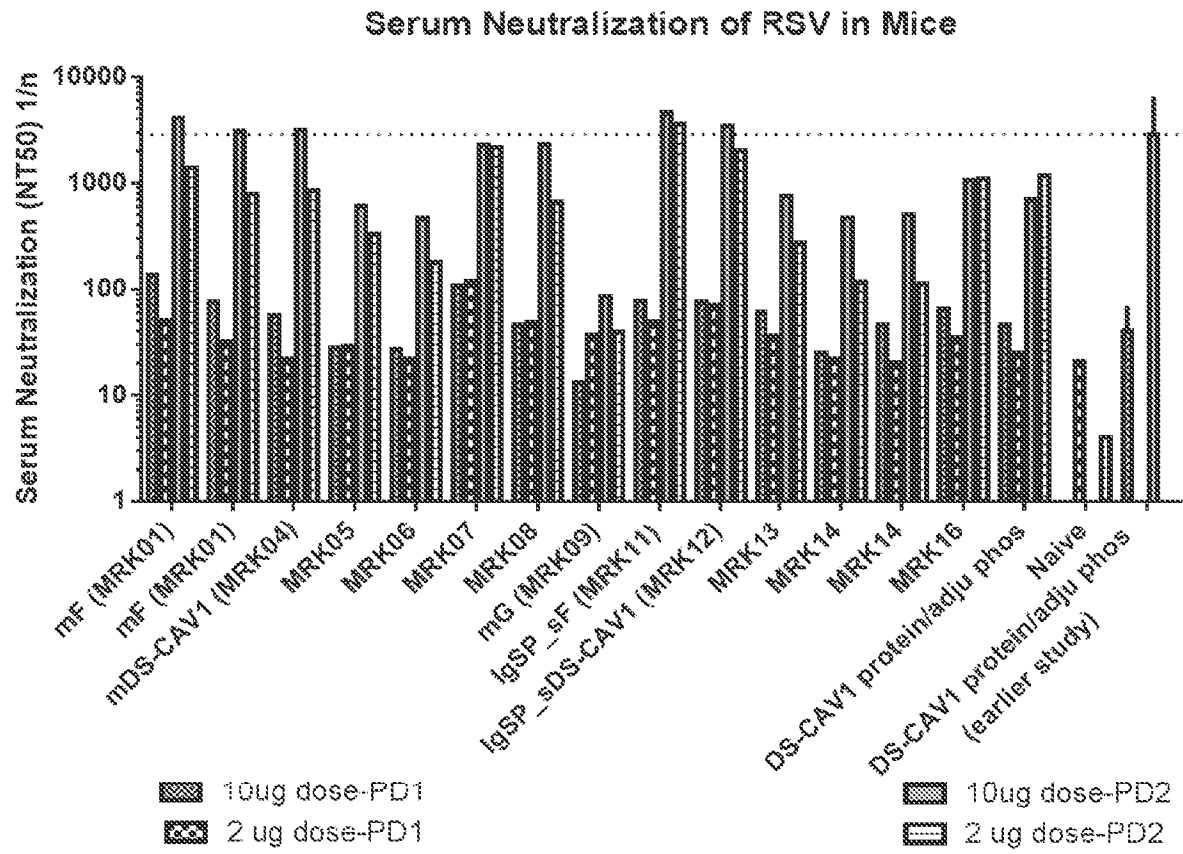


Fig. 2

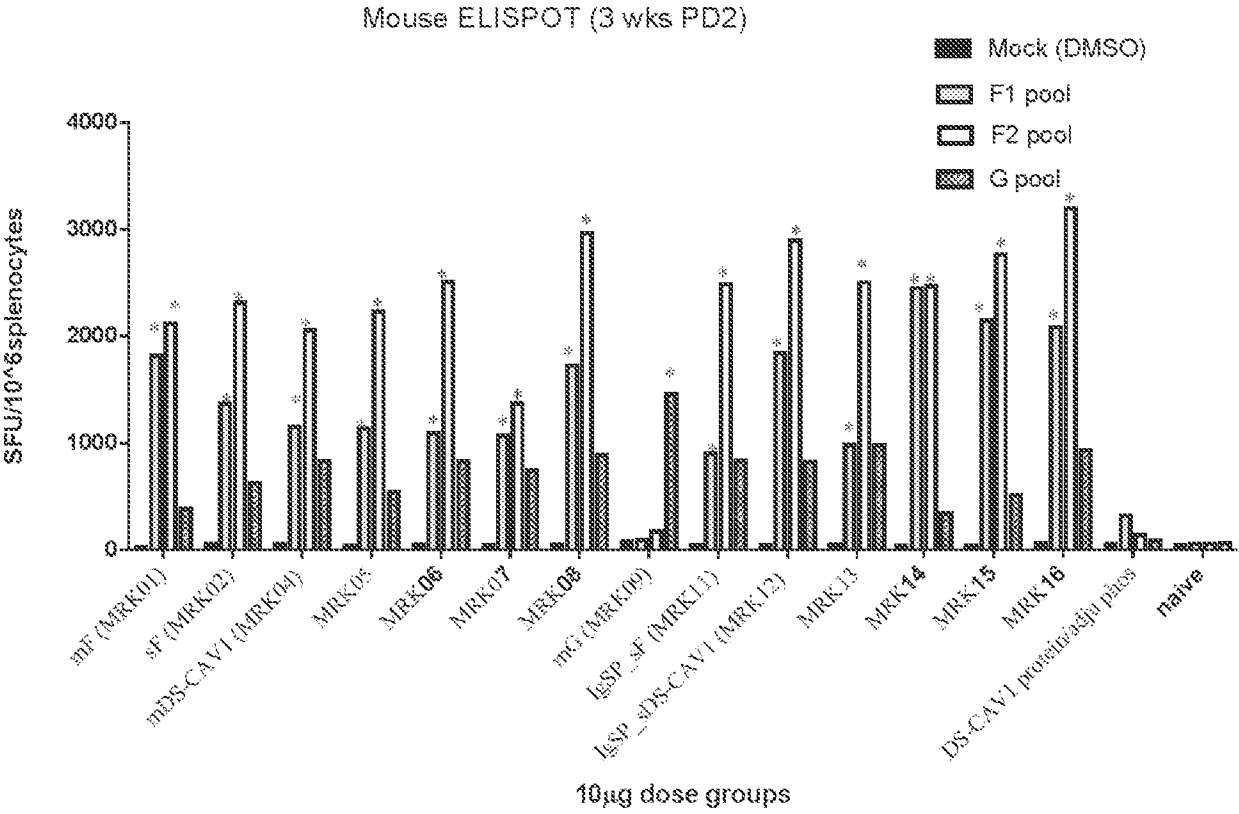


Fig. 3A

Fig. 3B

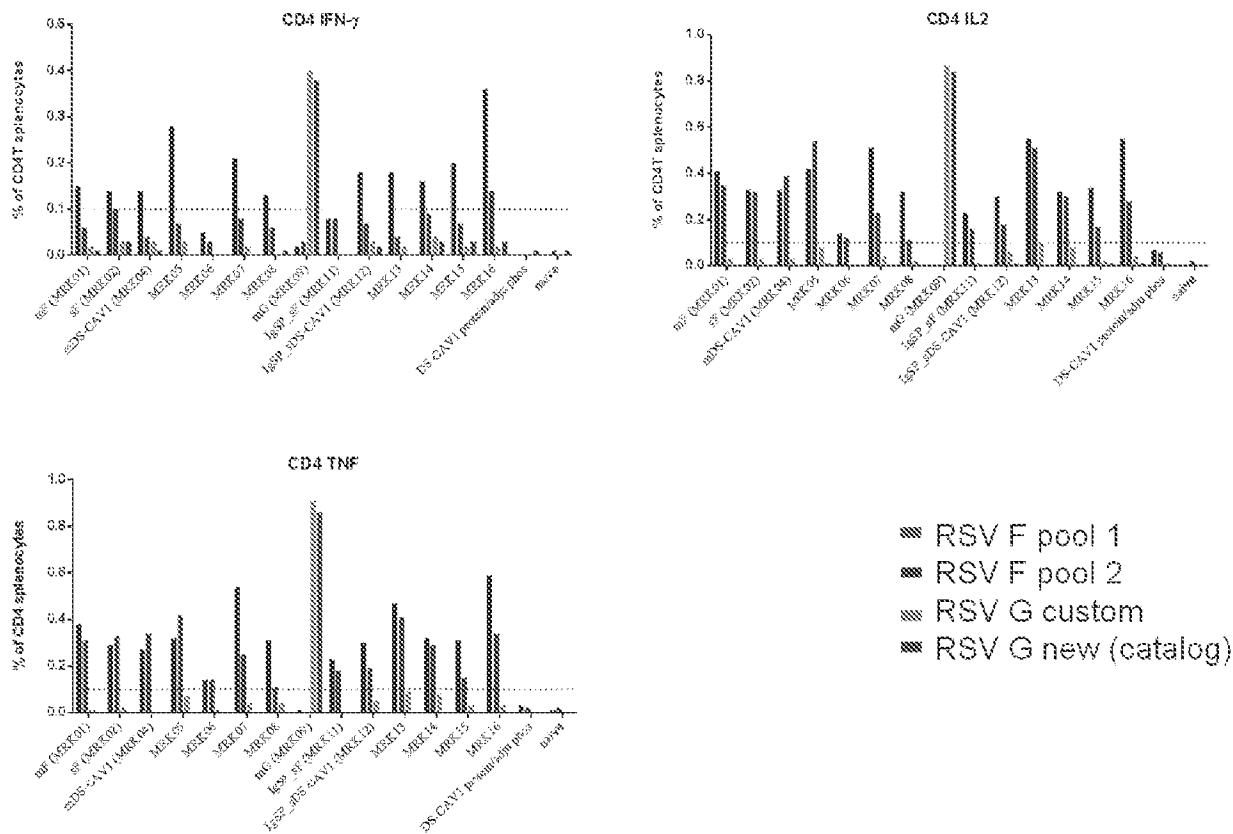


Fig. 3C

Fig. 4A

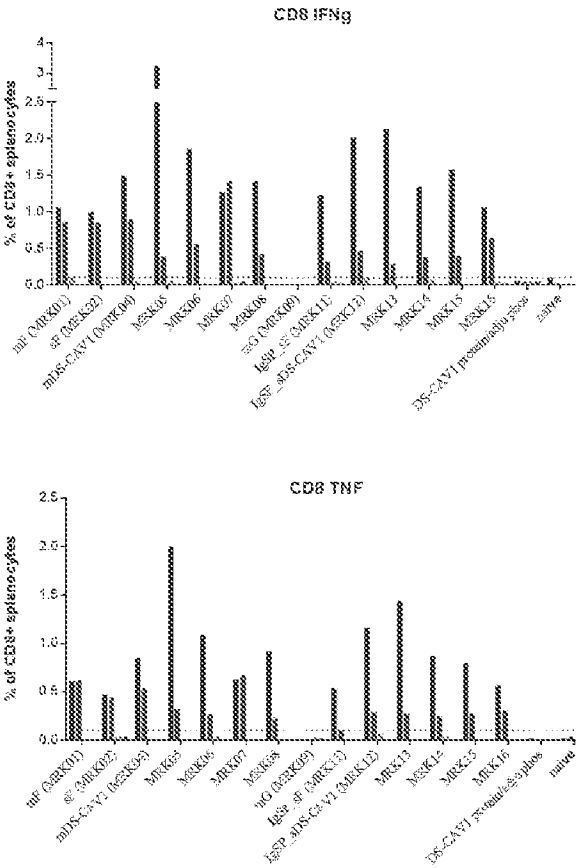


Fig. 4B

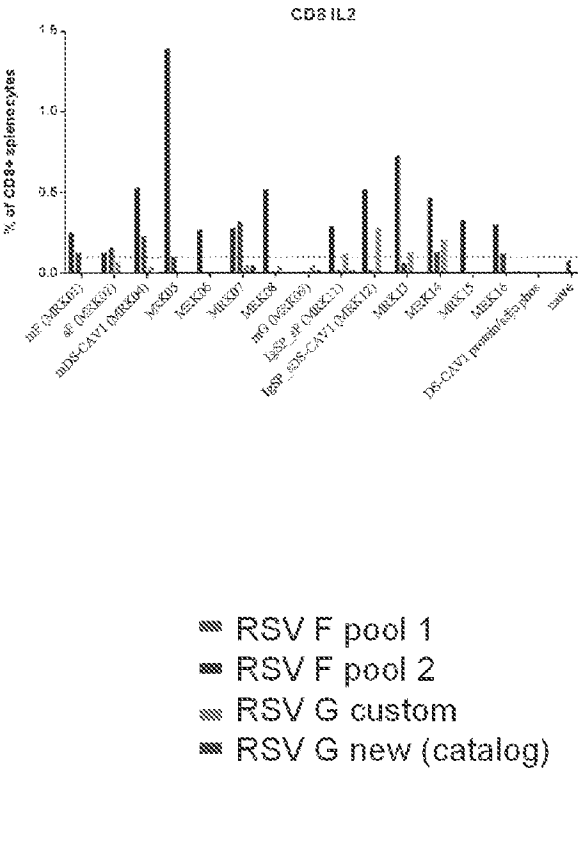
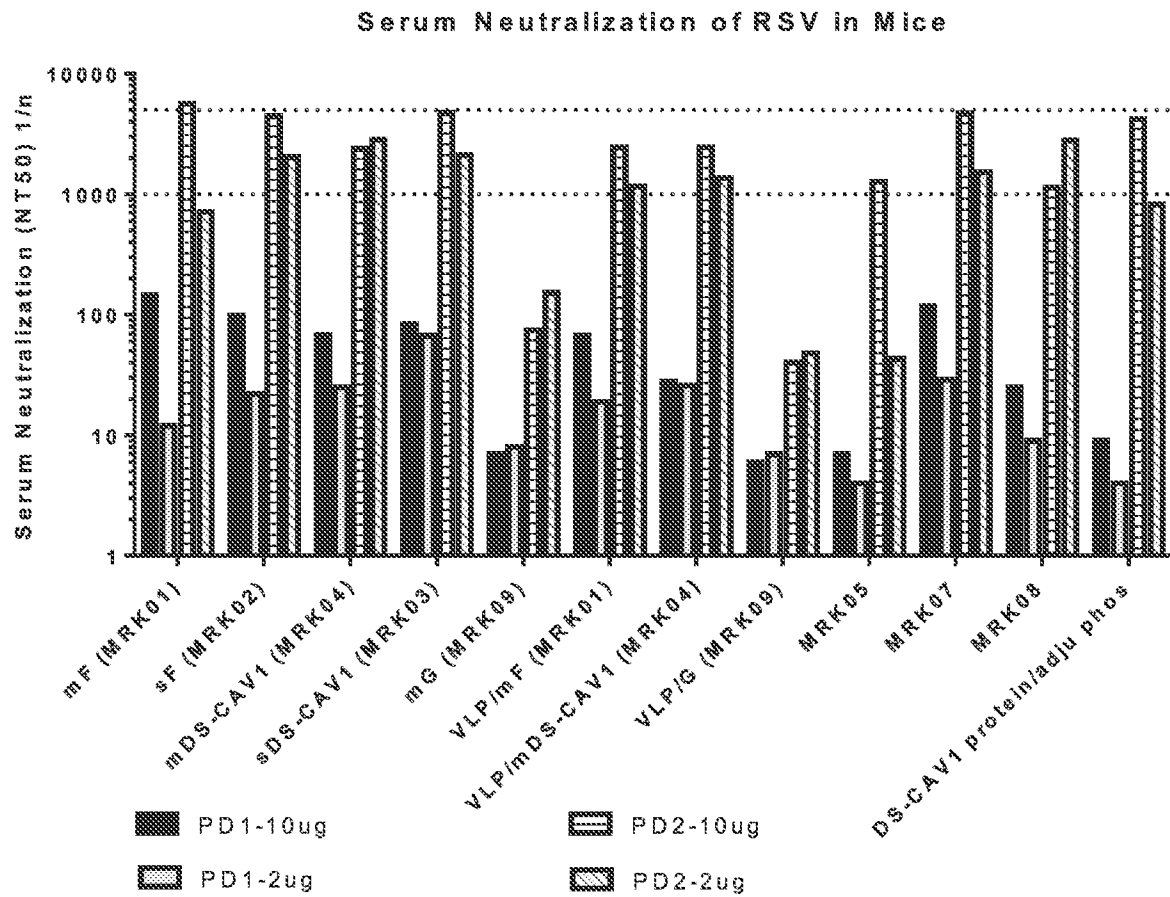


Fig. 4C

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Fig. 5



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Fig. 6A

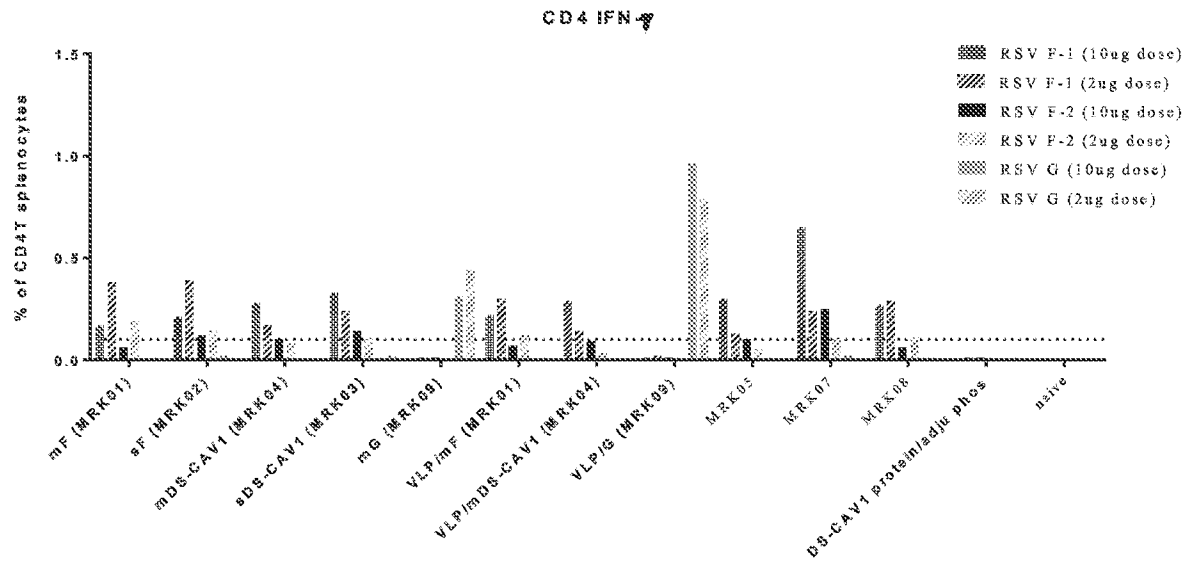


Fig. 6B

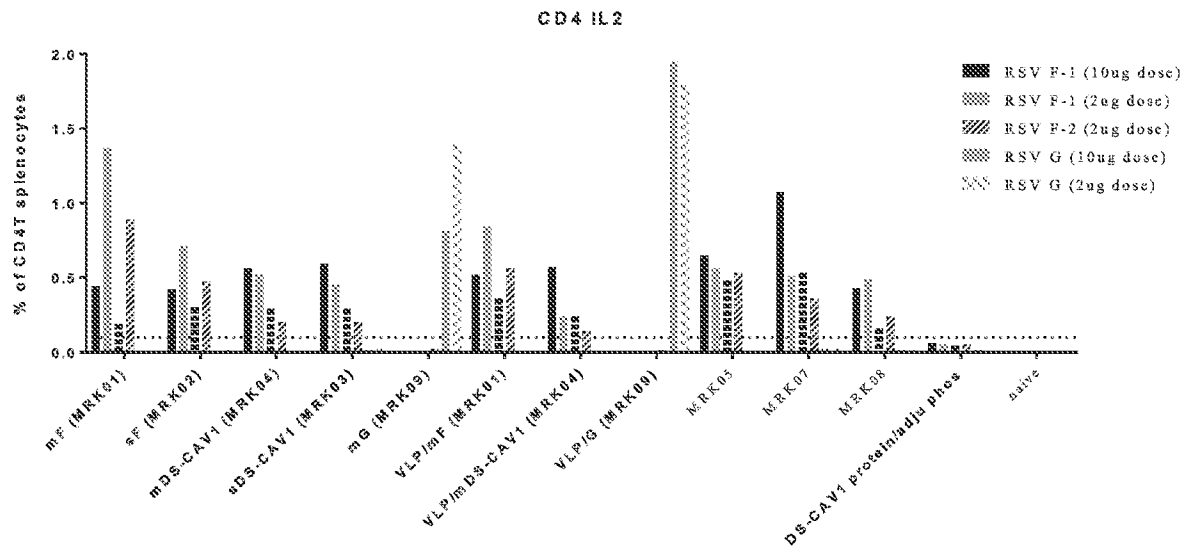
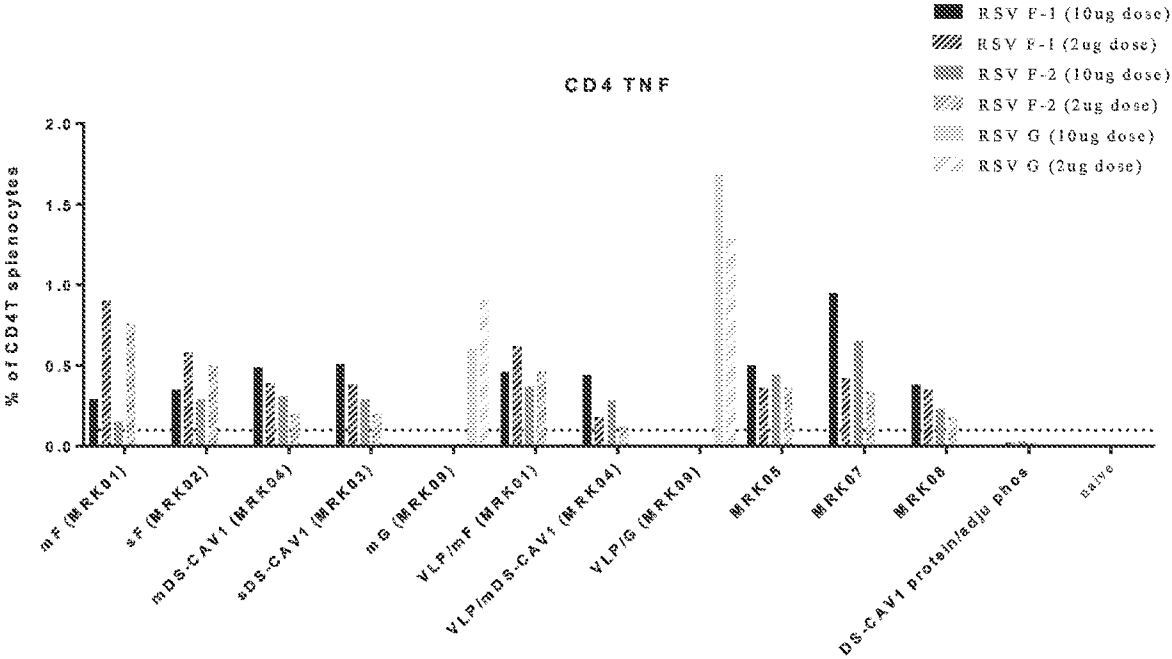


Fig. 6C



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Fig. 7A

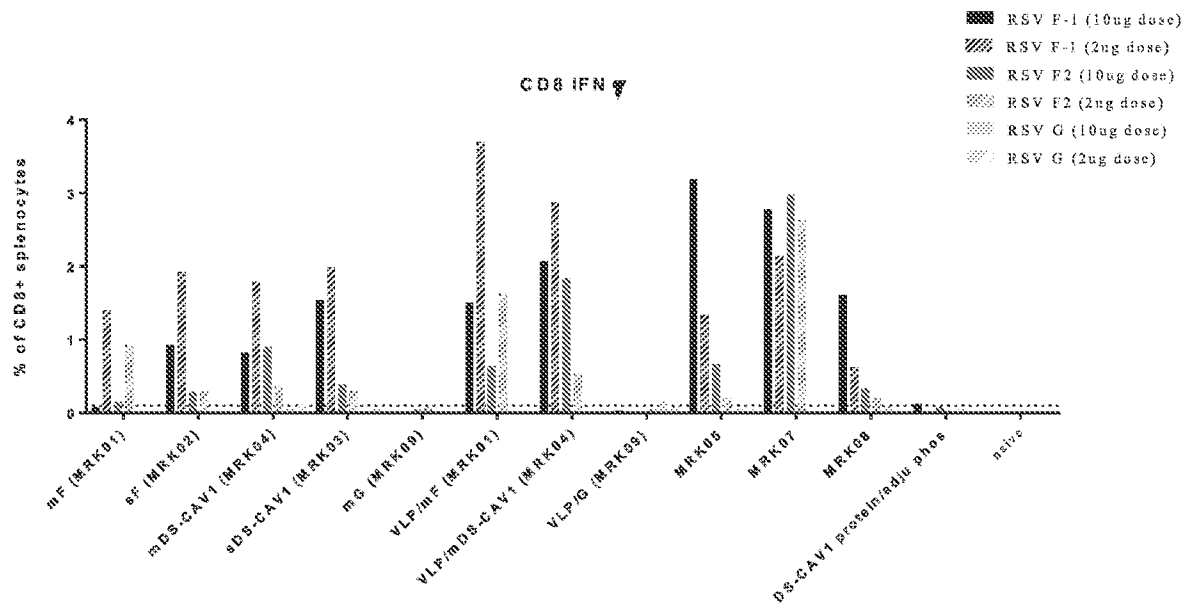


Fig. 7B

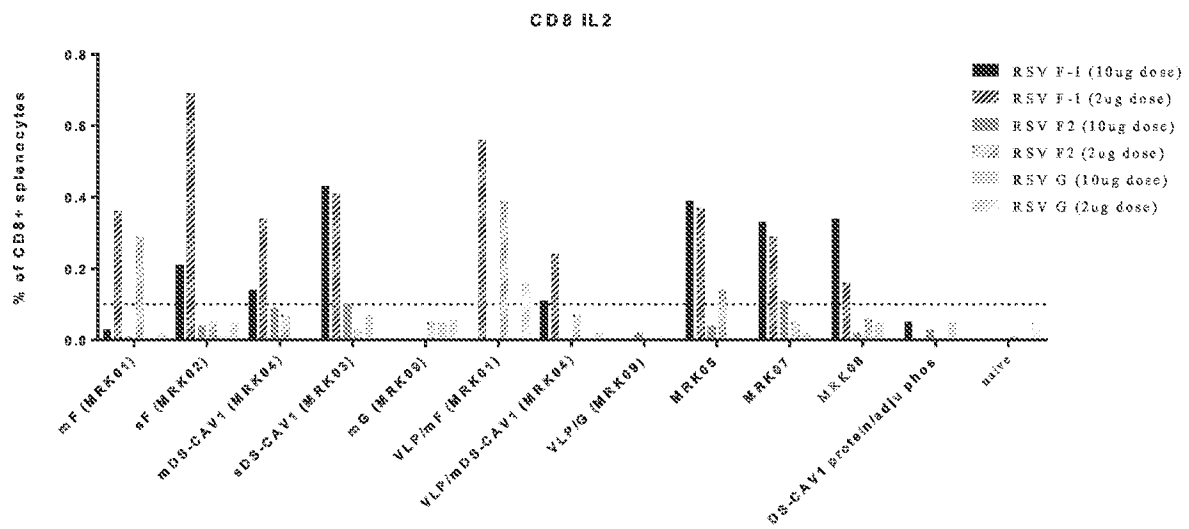
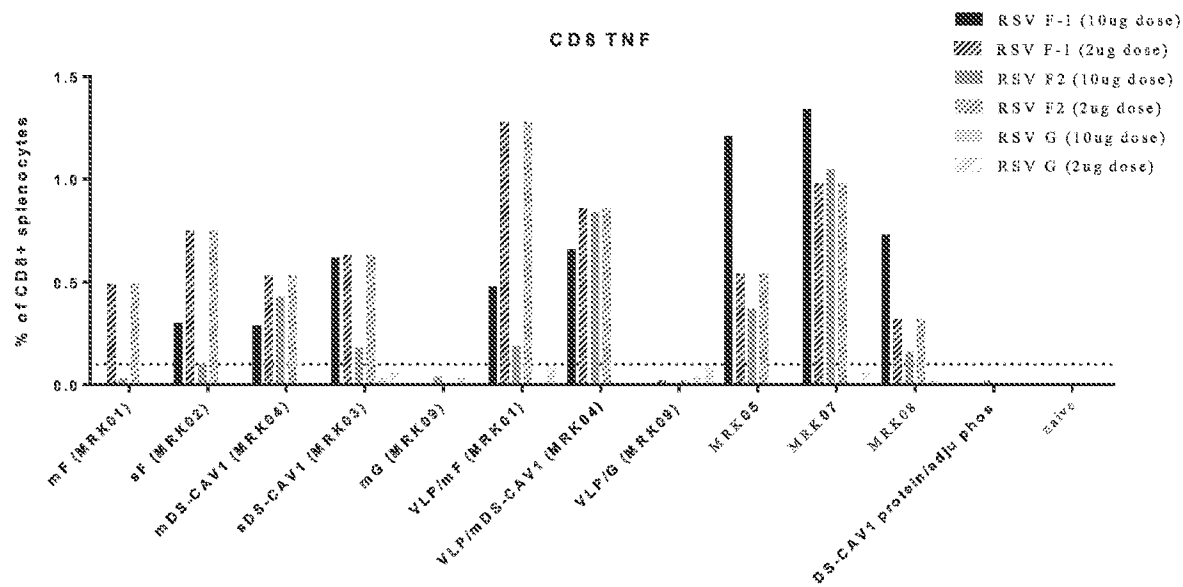
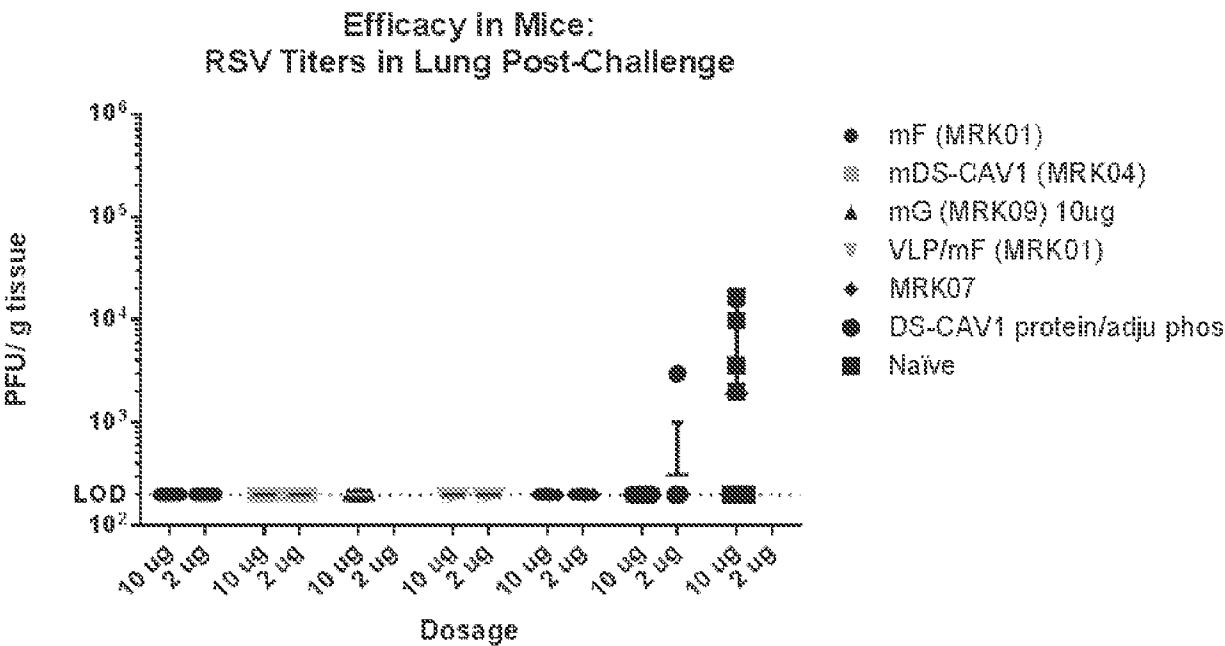


Fig. 7C



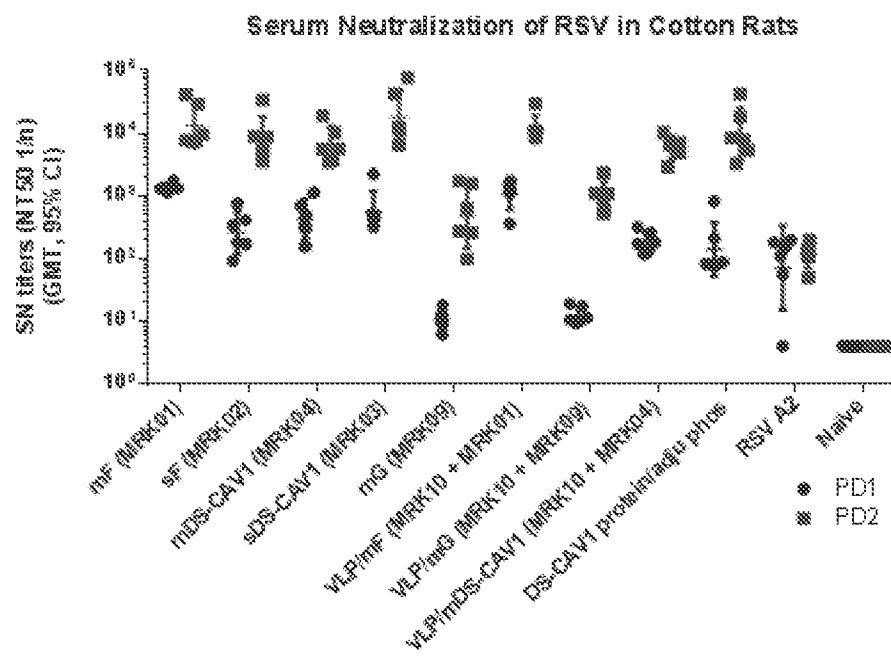
10/20

Fig. 8



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Fig. 9



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Fig 10. Competition ELISA from Cotton Rat Immunogenicity Study

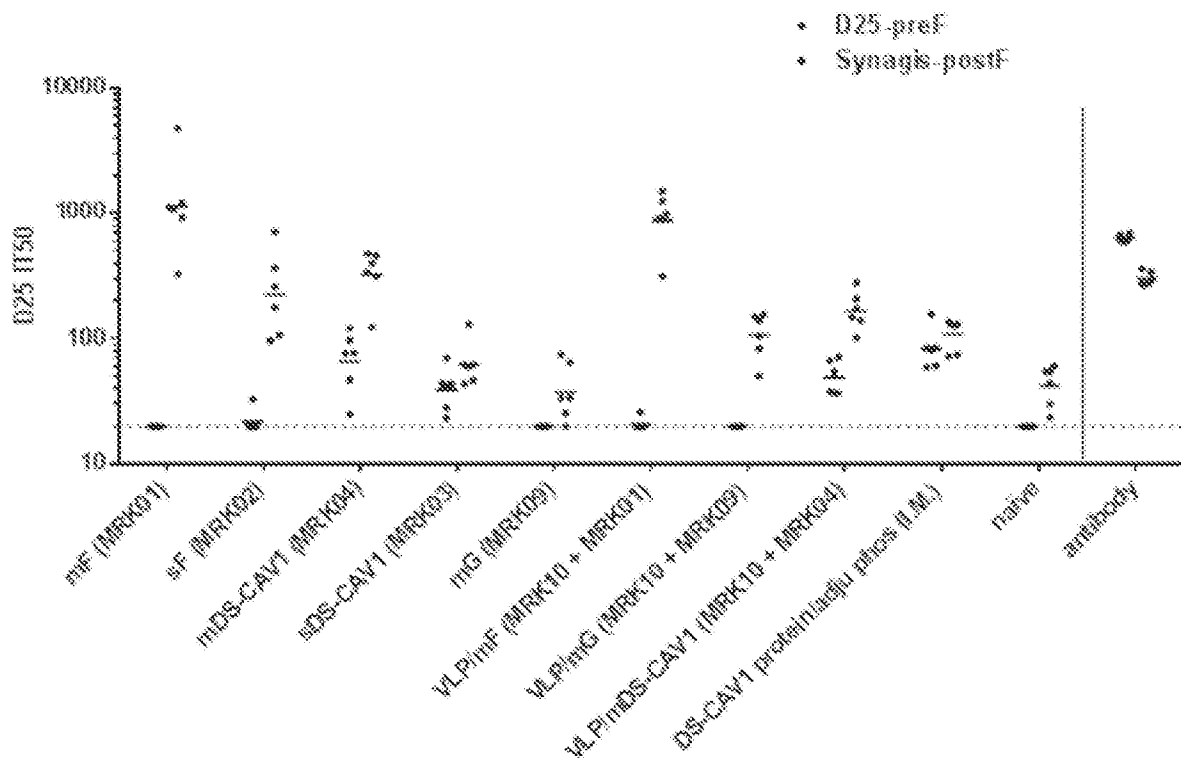
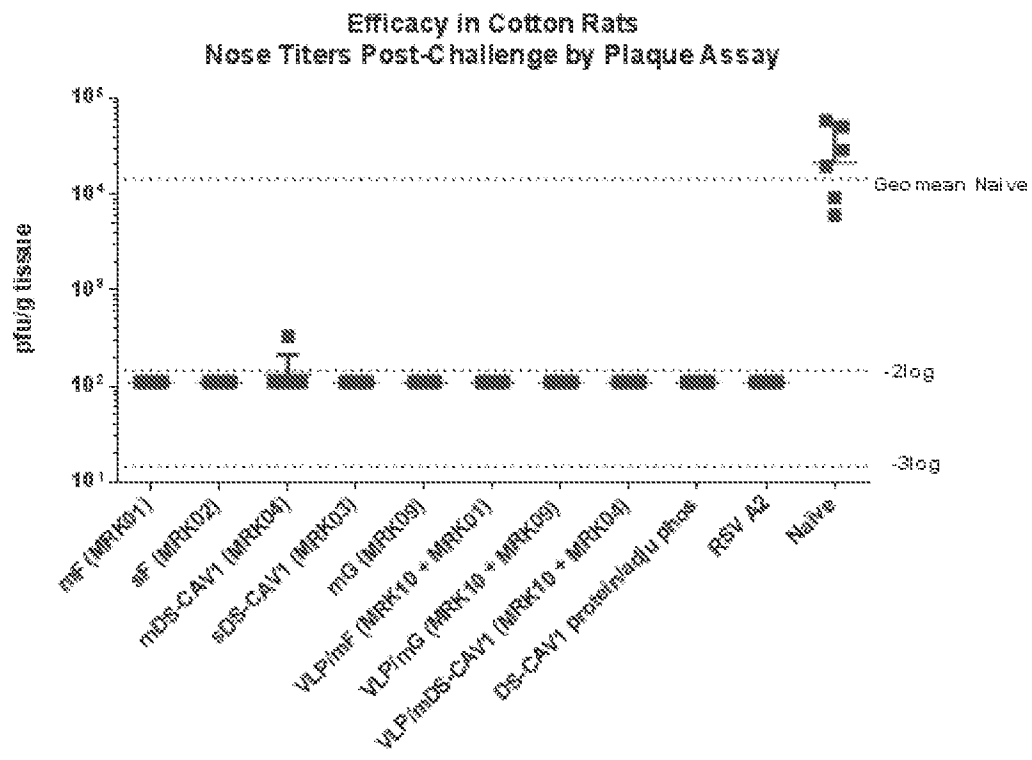
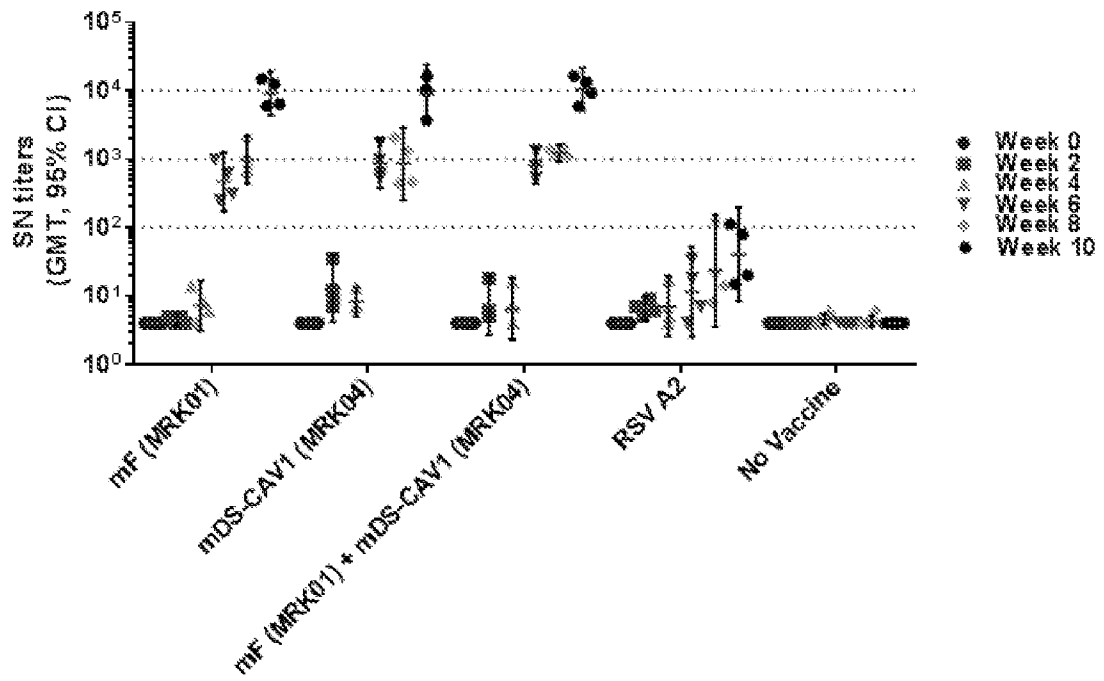


Fig. 11



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Fig. 12



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Fig. 13A

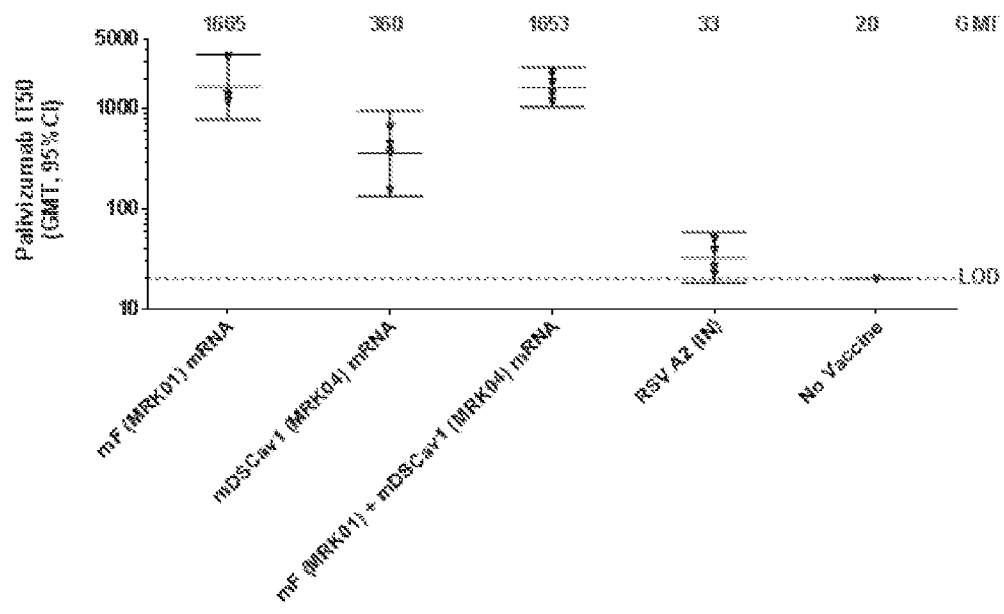
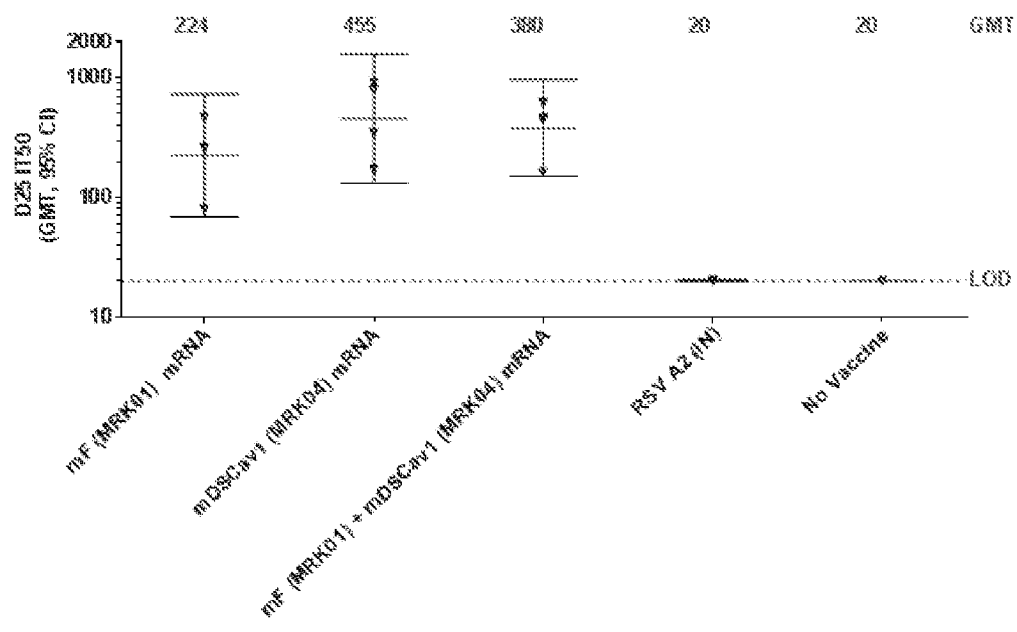


Fig. 13B



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Fig. 14A

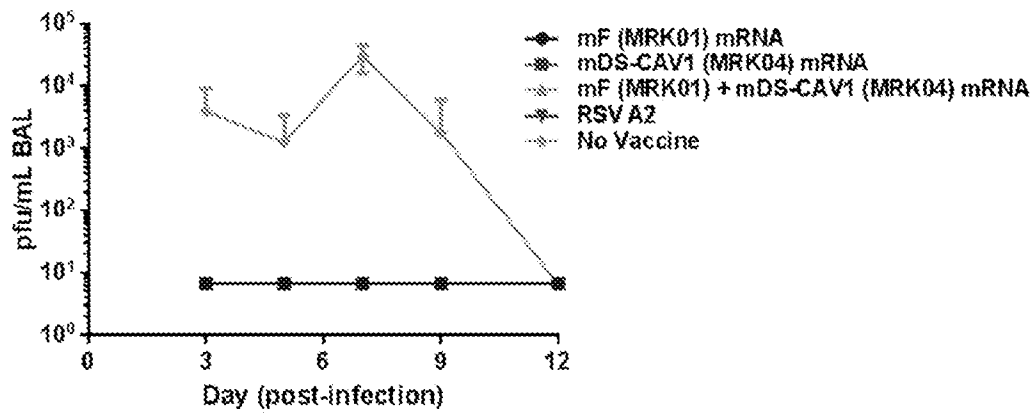
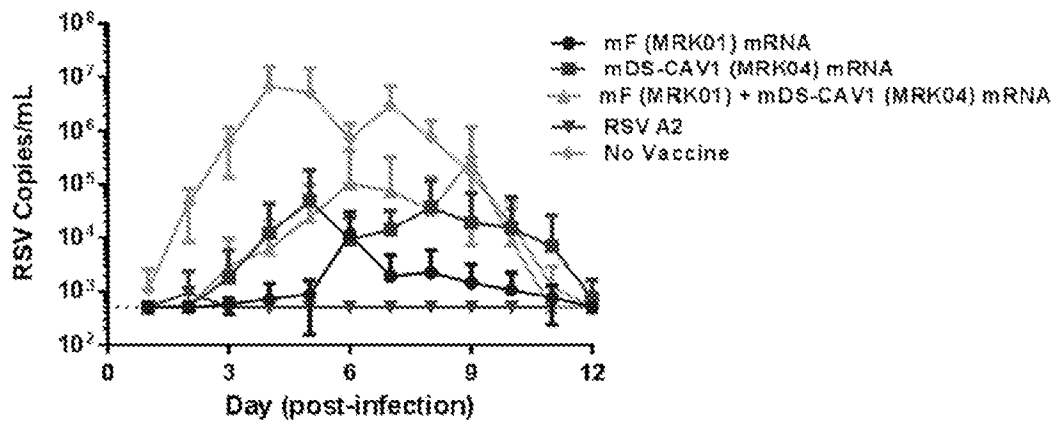


Fig. 14B



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Fig. 15

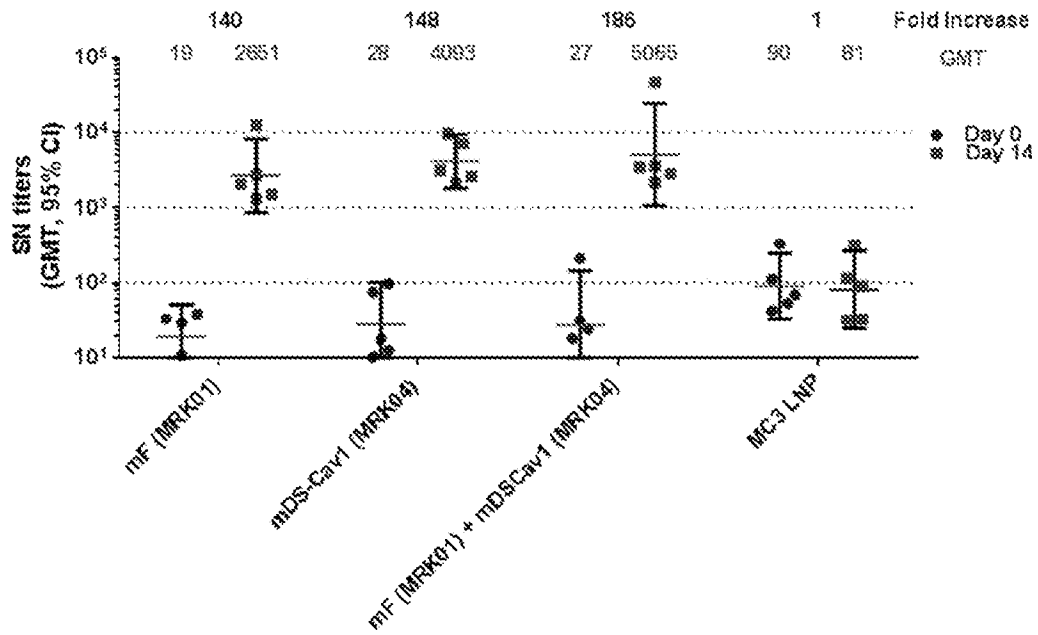
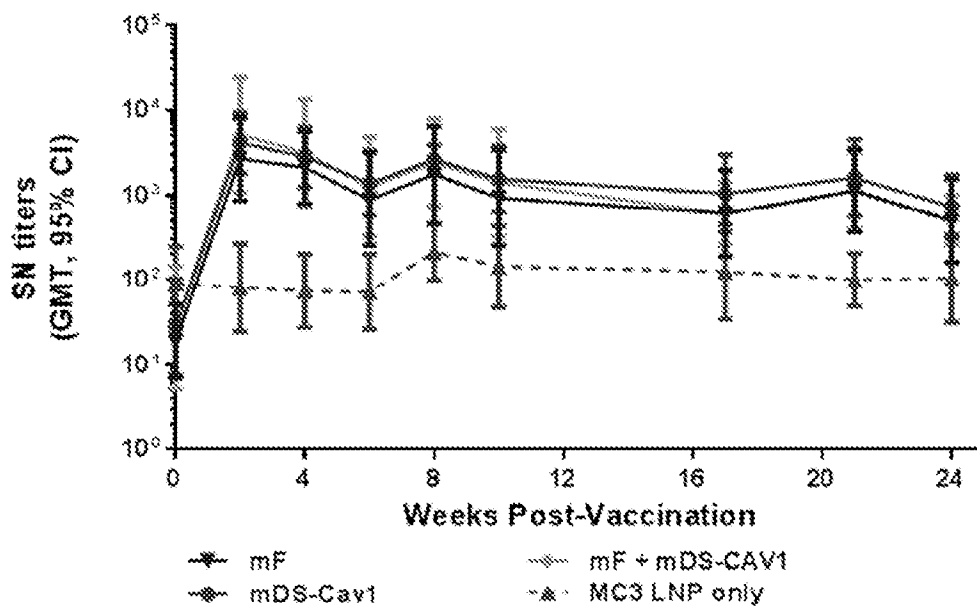


Fig. 16



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Fig. 17A

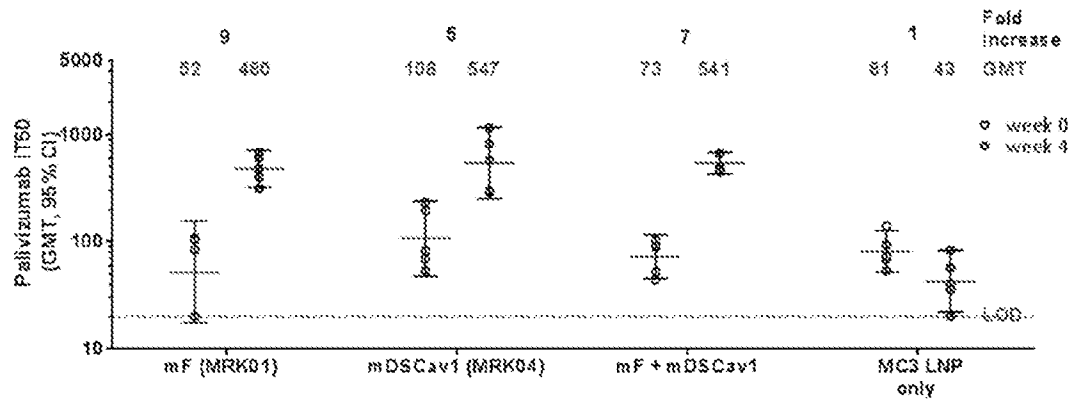
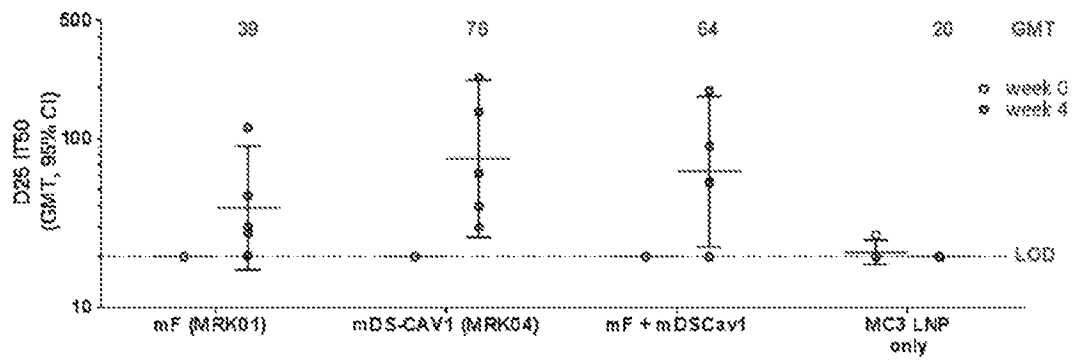


Fig. 17B



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Fig. 18A

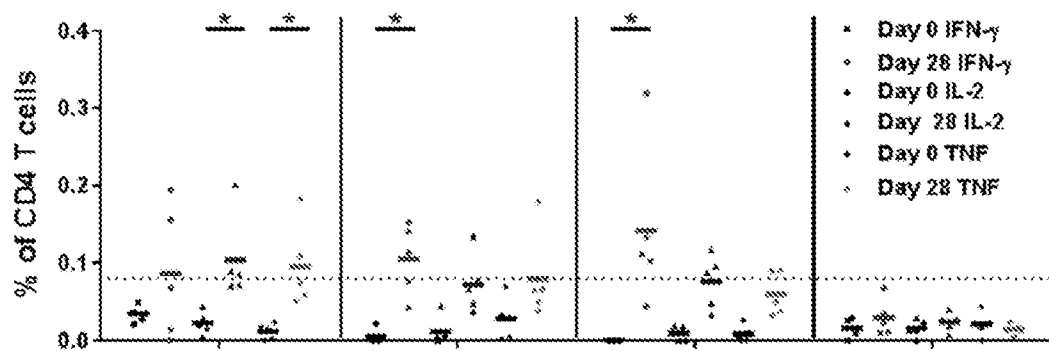


Fig. 18B

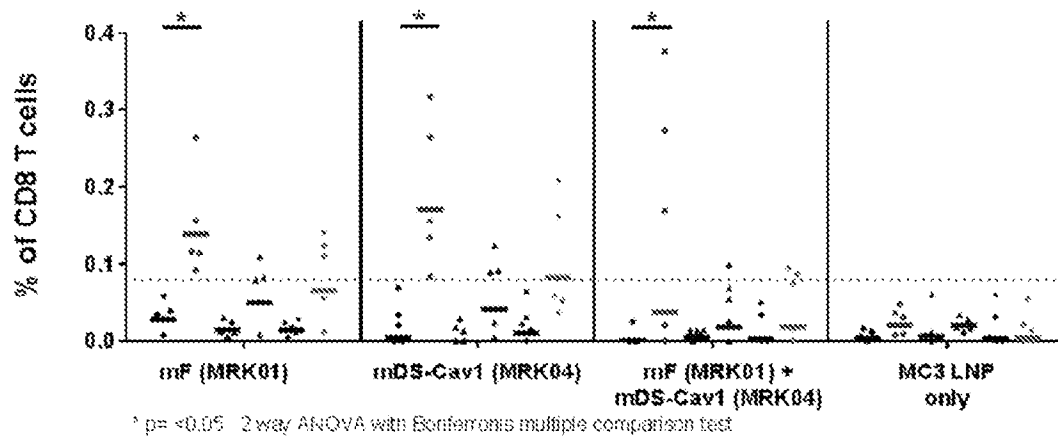


Fig. 19

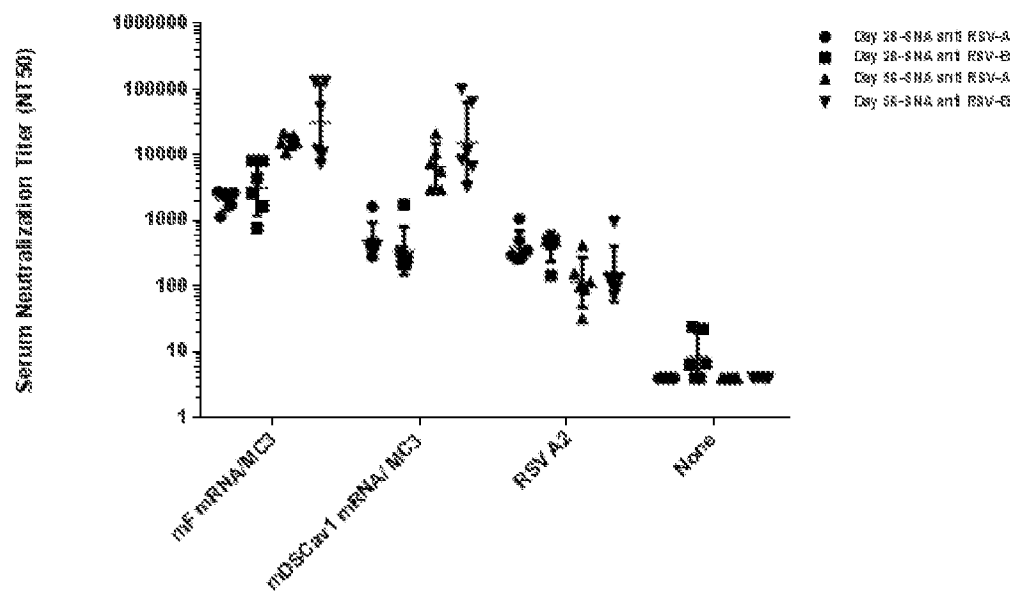
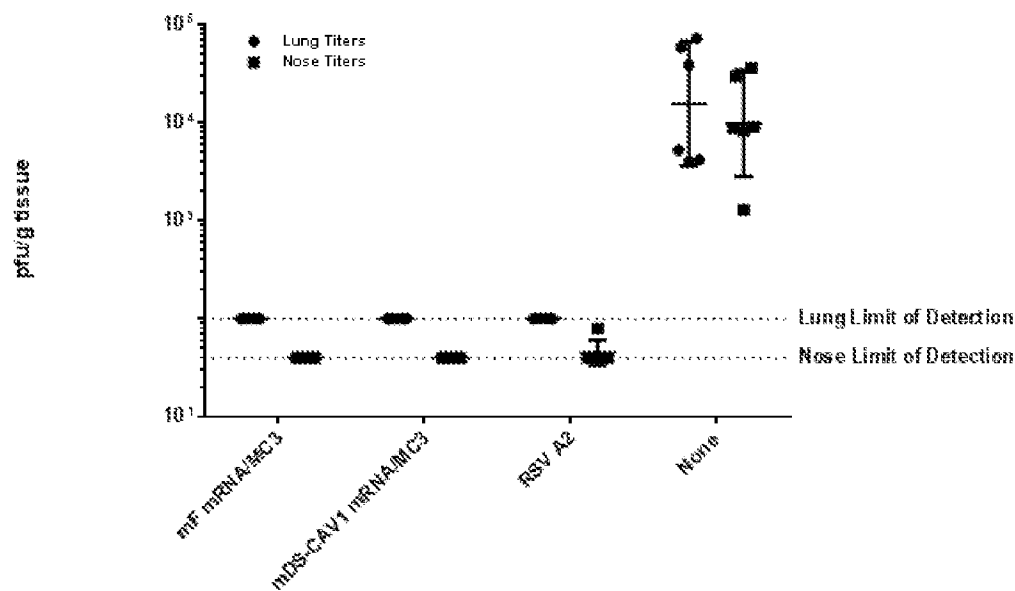


Fig. 20



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 Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
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 Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
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 Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
 180 185 190
 Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
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 Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
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 Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
 225 230 235 240
 Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
 245 250 255
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 260 265 270
 Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
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 Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
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Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
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 325 330 335
 Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
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 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 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
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 Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
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 Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
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 Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
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 485 490 495
 Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
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 Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
 515 520 525
 Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
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 Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
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Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
 50 55 60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
 65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
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Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
 115 120 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
 130 135 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Cys Lys Val Leu His Leu
 145 150 155 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
 165 170 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Phe Lys Val
 180 185 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Leu Asn
 195 200 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
 210 215 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
 Page 12

225 230 235 240

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu

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505

510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
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Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
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Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
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65					70					75				80	

Gln	Glu	Leu	Asp	Lys	Tyr	Lys	Asn	Ala	Val	Thr	Glu	Leu	Gln	Leu	Leu
				85					90					95	

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			100					105					110		

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180

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Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp
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Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln
 245 250 255

Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu
 260 265 270

Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr
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Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys
 290 295 300

Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys
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Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys
 325 330 335

Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu
 340 345 350

Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr
 355 360 365

Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile
 370 375 380

Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr
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Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys
 405 410 415

Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr
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Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly
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460

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Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
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Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
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Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
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Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
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Met Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Gln Gln Gln Gln
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Arg Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly
115 120 125

Val Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile
130 135 140

Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn
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Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile
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Asp Lys Gln Leu Leu Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser
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 Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln
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 Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu
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 Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr
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 Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys
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 Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys
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 325 330 335
 Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu
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 Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr
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 Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr
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 Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys
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 Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr
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Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu Ser Ala Ile Gly Gly Tyr
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 35 40 45

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 50 55 60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
 65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
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 100 105 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
 115 120 125

Leu Ser Lys Lys Gln Lys Gln Gln Ala Ile Ala Ser Gly Val Ala Val
 130 135 140

Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala
 145 150 155 160

Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser

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165

170

175

Val Leu Thr Ser₁₈₀ Lys Val Leu Asp Leu₁₈₅ Lys Asn Tyr Ile Asp₁₉₀ Lys Gln

Leu Leu Pro₁₉₅ Ile Val Asn Lys Gln₂₀₀ Ser Cys Ser Ile Ser₂₀₅ Asn Ile Glu

Thr Val₂₁₀ Ile Glu Phe Gln Gln₂₁₅ Lys Asn Asn Arg Leu₂₂₀ Leu Glu Ile Thr

Arg Glu Phe Ser Val Asn₂₃₀ Ala Gly Val Thr Thr₂₃₅ Pro Val Ser Thr Tyr₂₄₀

Met Leu Thr Asn Ser₂₄₅ Glu Leu Leu Ser Leu₂₅₀ Ile Asn Asp Met Pro₂₅₅ Ile

Thr Asn Asp Gln₂₆₀ Lys Lys Leu Met Ser₂₆₅ Asn Asn Val Gln Ile₂₇₀ Val Arg

Gln Gln Ser₂₇₅ Tyr Ser Ile Met Ser₂₈₀ Ile Ile Lys Glu Glu₂₈₅ Val Leu Ala

Tyr Val₂₉₀ Val Gln Leu Pro Leu₂₉₅ Tyr Gly Val Ile Asp₃₀₀ Thr Pro Cys Trp

Lys Leu His Thr Ser Pro₃₁₀ Leu Cys Thr Thr Asn₃₁₅ Thr Lys Glu Gly Ser₃₂₀

Asn Ile Cys Leu Thr₃₂₅ Arg Thr Asp Arg Gly₃₃₀ Trp Tyr Cys Asp Asn₃₃₅ Ala

Gly Ser Val Ser₃₄₀ Phe Phe Pro Gln Ala₃₄₅ Glu Thr Cys Lys Val₃₅₀ Gln Ser

Asn Arg Val₃₅₅ Phe Cys Asp Thr Met₃₆₀ Asn Ser Leu Thr Leu₃₆₅ Pro Ser Glu

Val Asn₃₇₀ Leu Cys Asn Val Asp₃₇₅ Ile Phe Asn Pro Lys₃₈₀ Tyr Asp Cys Lys

Ile Met Thr Ser Lys Thr₃₉₀ Asp Val Ser Ser Ser₃₉₅ Val Ile Thr Ser Leu₄₀₀

Gly Ala Ile Val Ser₄₀₅ Cys Tyr Gly Lys Thr₄₁₀ Lys Cys Thr Ala Ser₄₁₅ Asn

Lys Asn Arg Gly₄₂₀ Ile Ile Lys Thr Phe₄₂₅ Ser Asn Gly Cys Asp₄₃₀ Tyr Val

Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr

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435

440

445

Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile
450 455 460

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

Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile
485 490 495

Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly Lys Ser Thr
500 505 510

Thr Asn Ile Met Ile Thr Thr Ile Ile Ile Val Ile Ile Val Ile Leu
515 520 525

Leu Ser Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser
530 535 540

Thr Pro Val Thr Leu Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile
545 550 555 560

Ala Phe Ser Asn

<210> 15
<211> 1539
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 15
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tgtttcgcat caagccagaa tattacagaa gaattttatc aatccacctg cagcgctgta 120
tcgaaagggt acctcagcgc gcttaggaca ggatgggtata cctccgttat cagcattgaa 180
ctgagtaata tcaaggaaaa caagtgtaac ggaacagacg ccaagggtcaa acttattaaa 240
caagaactgg acaagtataa gtctgcagtg accgaattgc agctcctgat gcagagtacc 300
cctgcaacta acaacaagtt tttgggcttt ctgcaaggcg tgggtagcgc gatcgctcc 360
ggaatcgcg tctccaaagt gttgcacctg gagggagaag ttaacaagat caaatcggct 420
ctgttgagta ccaacaaggc agtggtgtca ctgagcaacg gtgtaagcgt gttacaagc 480
aaggatttgg acttaaagaa ctatattgac aaacagctgc tccccatcgt gaacaaacag 540
agctgctcaa tctccaatat agagacggtg atagagttcc agcaaaaaaa taatcggctc 600
cttgagatca cccgcgaatt ctcatgtaat gccggcgctca caactccggt gtctacatac 660
atgctgacca actcggagct gttatcctta ataaatgaca tgcccatcac caatgatcaa 720

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accccttggt ggaagctgca cacctcccca ctatgtacta ccaataccaa agaaggatcc      900
aacatctgcc ttacccgcac cgatagggga tggatttgcg acaacgccgg atccgtcagc      960
ttctttccac ttgccgaaac ttgcaagggt cagtcaaacc ggggtgttctg cgatacaatg     1020
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ataattaaga cattcagcaa tggttgcgac tacgtatcaa ataagggtgt cgacaccggt     1260
tccgtgggca atacgtgta ctatgttaat aaacaggaag gcaagtcact gtatgttaaa     1320
ggtgaacca tcatcaactt ctacgacccc ctggttttcc cctccgacga gtttgatgcc     1380
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<210> 16
 <211> 513
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 16

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Ala Val Thr Leu Cys Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe
 20 25 30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
 35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
 50 55 60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
 65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Ser Ala Val Thr Glu Leu Gln Leu Leu
 85 90 95

Met Gln Ser Thr Pro Ala Thr Asn Asn Lys Phe Leu Gly Phe Leu Gln
 100 105 110

Gly Val Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu

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115

120

125

His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr
 130 135 140

Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser
 145 150 155 160

Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile
 165 170 175

Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu
 180 185 190

Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser
 195 200 205

Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn
 210 215 220

Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln
 225 230 235 240

Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr
 245 250 255

Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln
 260 265 270

Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr
 275 280 285

Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu
 290 295 300

Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser
 305 310 315 320

Phe Phe Pro Leu Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe
 325 330 335

Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys
 340 345 350

Asn Ile Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser
 355 360 365

Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val
 370 375 380

Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly

385 390 395 400

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 cagatggaga cgttcattc cacatcttcc gaaggggaatc ctagtcccag ccaggtgagc 840
 acaacctcag aatacccgtc ccagccctca tcacctccta ataccccccg gcag 894

<210> 18
 <211> 298
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 18

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

Trp Asp Thr Leu Asn His Leu Leu Phe Ile Ser Ser Cys Leu Tyr Lys
20 25 30

Leu Asn Leu Lys Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met
35 40 45

Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser
50 55 60

Ala Asn His Lys Val Thr Pro Thr Thr Ala Ile Ile Gln Asp Ala Thr
65 70 75 80

Ser Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Asn Pro Gln
85 90 95

Leu Gly Ile Ser Pro Ser Asn Pro Ser Glu Ile Thr Ser Gln Ile Thr
100 105 110

Thr Ile Leu Ala Ser Thr Thr Pro Gly Val Lys Ser Thr Leu Gln Ser
115 120 125

Thr Thr Val Lys Thr Lys Asn Thr Thr Thr Thr Gln Thr Gln Pro Ser
130 135 140

Lys Pro Thr Thr Lys Gln Arg Gln Asn Lys Pro Pro Ser Lys Pro Asn
145 150 155 160

Asn Asp Phe His Phe Glu Val Phe Asn Phe Val Pro Cys Ser Ile Cys
165 170 175

Ser Asn Asn Pro Thr Cys Trp Ala Ile Cys Lys Arg Ile Pro Asn Lys
180 185 190

Lys Pro Gly Lys Lys Thr Thr Thr Lys Pro Thr Lys Lys Pro Thr Leu
195 200 205

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Lys Thr Thr Lys Lys Asp Pro Lys Pro Gln Thr Thr Lys Ser Lys Glu
 210 215 220

Val Pro Thr Thr Lys Pro Thr Glu Glu Pro Thr Ile Asn Thr Thr Lys
 225 230 235 240

Thr Asn Ile Ile Thr Thr Leu Leu Thr Ser Asn Thr Thr Gly Asn Pro
 245 250 255

Glu Leu Thr Ser Gln Met Glu Thr Phe His Ser Thr Ser Ser Glu Gly
 260 265 270

Asn Pro Ser Pro Ser Gln Val Ser Thr Thr Ser Glu Tyr Pro Ser Gln
 275 280 285

Pro Ser Ser Pro Pro Asn Thr Pro Arg Gln
 290 295

<210> 19
 <211> 1629
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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 aagggctacc ttagtgcatt acgaaccggg tggatatacga gtgtaatcac cattgagctg 180
 tccaacatca agaagaacaa gtgcaatggg actgatgcca aggtgaaact tatcaaacaa 240
 gagctcgaca agtataagaa cgccgtgacc gaactacaac tcctgatgca atcgactcag 300
 gctactaaca acagagctcg gagggagctg cccagattca tgaattatac cttaaacaac 360
 gctaaaaaaaa caaatgtgac cctgagtaag aagcggaaac gaagggttcct gggcttcctg 420
 ctcggtgtgg ggtctgcaat agcaagcggc gtcgctgtgt ccaaggctcct tcacttagaa 480
 ggtgaggtca ataagatcaa gtccgctctc ctctctacca acaaggcagt ggtgagcctg 540
 tctaacggtg tgtccgtgct gacatcgaag gtactggacc tgaaaaacta catcgacaag 600
 cagctgctgc ctattgtgaa taagcaatcc tgcagtatct ccaacattga gacagtgatt 660
 gaatttcagc aaaagaacaa tcgtttgttg gagataacaa gagaattcag tgtaaatgcc 720
 ggcgttacca ctcccgtgtc gacatacatg ctaacaaata gcgagctgct atctctcatt 780
 aatgatatgc ctatcaccaa tgaccagaaa aaacttatgt ccaataacgt gcagatagtc 840
 aggagcagc cctacagcat tatgagcata attaaagagg aagtgttggc ttacgtcgtc 900
 cagcttccac tgtatggcgt gatcgatacc cttgttgga agctgcatac ttccccctt 960
 tgtacaacta ataccaaaga agggagtaat atatgcctca caaggactga cagaggctgg 1020

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tgcaacgtgg atatttttaa ccctaagtac gattgtaaga taatgacatc caaaaccgat 1200
gtagtagct ccgtgatcac ttcgctgggt gcgatagtta gctgctatgg aaagacaaag 1260
tgtaccgcaa gtaacaagaa ccgcgggatt attaaaacat ttagcaatgg gtgcgactac 1320
gtatcaaaca aggggggtgga tacagtcagc gtgggaaaca cactttacta cgttaacaag 1380
caggaaggga aatcccttta tgtgaaggga gaaccaatta tcaactttta tgatcccctc 1440
gtgtttccaa gtgatgaatt cgacgcaagc atctcgcagg tgaacgagaa aatcaatcag 1500
agtctagctt tcataaggaa gtctgatgaa ctgcttagtg ccattggcgg gtacataccg 1560
gaagccccac gcgacggtca ggcttacgtg aggaaggacg gcgagtgggt tctgctgtcc 1620
actttcctt 1629

<210> 20
<211> 543
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 20

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr
20 25 30

Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg
35 40 45

Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys
50 55 60

Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys Gln
65 70 75 80

Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met
85 90 95

Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg
100 105 110

Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu
115 120 125

Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val Gly
130 135 140

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Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu Glu
 145 150 155 160
 Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala
 165 170 175
 Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu
 180 185 190
 Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn Lys
 195 200 205
 Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln
 210 215 220
 Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala
 225 230 235 240
 Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu
 245 250 255
 Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu
 260 265 270
 Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met
 275 280 285
 Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu
 290 295 300
 Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu
 305 310 315 320
 Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr
 325 330 335
 Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro
 340 345 350
 Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr
 355 360 365
 Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp
 370 375 380
 Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp
 385 390 395 400
 Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr
 405 410 415

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Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys
420 425 430

Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr
435 440 445

Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys
450 455 460

Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu
465 470 475 480

Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu
485 490 495

Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu
500 505 510

Ser Ala Ile Gly Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala
515 520 525

Tyr Val Arg Lys Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu
530 535 540

<210> 21
<211> 1629
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

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aaggggtacc tgagtgcctt gcgaccggg tggtacacca gtgttatcac tattgagctg 180
tccaacatta aagaaaataa gtgtaatgga actgacgcga aggtgaagtt gataaaacag 240
gagctggata aatacaagaa tgcagtgacc gaactgcagc tcctgatgca gtccactcca 300
gcaacaaata atcgcgcgag acgcgaactc ccccgcttta tgaactacac tctgaataat 360
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cagctcctgc ccattctcaa caaacagtca tgttccatta gcaacatcga aacagtcatt 660
gagtttcagc aaaaaaacia cgcctcctt gagattacgc gtgagttttc cgtcaatgct 720
ggagtcacga caccggtgtc cacttacatg ctgactaaca gcgaactcct gaggcctaac 780

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cagctgccgc tgtatggtgt gatagatacg ccatgctgga aactgcacac atccccctt 960
tgcacaacga atactaaaga gggaagtaac atttgcttga ccagaacaga tcggggctgg 1020
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gtgtcttcat cagtataac aagtctgggc gcaatagtgt catgctatgg taagactaag 1260
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gtgtcaaaca agggcgtcga cacagtaagc gttgggaaca ccctatacta cgtcaacaag 1380
caggagggga aaagcctata cgtgaaaggc gagccaatca tcaatttcta cgatccactg 1440
gtctttccaa gtgacgaatt tgatgccagc atatcgagg tgaacgagaa aataaatcag 1500
tcactcgct tcacagga gtcagatgag ctgctgtccg ccatcggagg atacattcca 1560
gaagccccac gcgacggcca ggcatacgtg cggaaggacg gcgaatgggt ccttttgagc 1620
acttttcta 1629

<210> 22
<211> 543
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 22

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Asp Thr Thr Gly Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr
20 25 30

Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg
35 40 45

Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys
50 55 60

Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys Gln
65 70 75 80

Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met
85 90 95

Gln Ser Thr Pro Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg
100 105 110

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Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu
 115 120 125
 Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val Gly
 130 135 140
 Ser Ala Ile Ala Ser Gly Val Ala Val Cys Lys Val Leu His Leu Glu
 145 150 155 160
 Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala
 165 170 175
 Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Phe Lys Val Leu
 180 185 190
 Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Leu Asn Lys
 195 200 205
 Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln
 210 215 220
 Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala
 225 230 235 240
 Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu
 245 250 255
 Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu
 260 265 270
 Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met
 275 280 285
 Cys Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu
 290 295 300
 Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu
 305 310 315 320
 Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr
 325 330 335
 Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro
 340 345 350
 Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr
 355 360 365
 Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp
 370 375 380

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Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp
385 390 395 400

Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr
405 410 415

Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys
420 425 430

Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr
435 440 445

Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys
450 455 460

Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu
465 470 475 480

Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu
485 490 495

Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu
500 505 510

Ser Ala Ile Gly Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala
515 520 525

Tyr Val Arg Lys Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu
530 535 540

<210> 23
<211> 1500
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

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aagggatacc tgtccgctct gcggacggga tggatataca gtgttataac gatcgagttg 180
agcaacatca agaagaacaa atgtaatgga acagatgcc aagtgaaact gatcaaacag 240
gagttggata aatataagaa tgctgtcacc gaactgcagc tattgatgca gtccaccag 300
gctaccaaca accgggccag gcagcaacaa cagagatttt tgggtttctt gctgggcgtg 360
gggtctgcc tgccttcagg ggtggccgtg agtaaagtc tgcacctgga aggcgaagtc 420
aacaagatca agtctgcatt actaagtacc aataaggctg tagttagcct gtccaatggc 480
gtgagtgtgc ttacttctaa ggtactggac ctgaagaact acatcgacaa gcaactacta 540

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agcgacgagt tcgacgcctc gatcagccag gtgaacgaga aaatcaacca gtctttggca     1440
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Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg
 35 40 45

Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys
 50 55 60

Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys Gln
 65 70 75 80

Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met
 85 90 95

Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Gln Gln Gln Gln Arg

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100

105

110

Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val
 115 120 125

Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys
 130 135 140

Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly
 145 150 155 160

Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp
 165 170 175

Lys Gln Leu Leu Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn
 180 185 190

Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu
 195 200 205

Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser
 210 215 220

Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met
 225 230 235 240

Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile
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Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val
 260 265 270

Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro
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Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu
 290 295 300

Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp
 305 310 315 320

Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val
 325 330 335

Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro
 340 345 350

Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp
 355 360 365

Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr
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370

375

380

Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala
 385 390 395 400

Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp
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Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu
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Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe
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Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala
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Ser Thr Thr Asn
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Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg
 35 40 45

Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys
 50 55 60

Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys Gln
 65 70 75 80

Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met
 85 90 95

Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Gln Gln Gln Gln Arg
 100 105 110

Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val

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115

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125

Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys
 130 135 140

Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly
 145 150 155 160

Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp
 165 170 175

Lys Gln Leu Leu Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn
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Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu
 195 200 205

Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser
 210 215 220

Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met
 225 230 235 240

Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile
 245 250 255

Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val
 260 265 270

Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro
 275 280 285

Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu
 290 295 300

Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp
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Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val
 325 330 335

Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro
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Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp
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Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala
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385 390 395 400

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Gln	Ser	Thr	Cys	Ser	Ala	Val	Ser	Lys	Gly	Tyr	Leu	Ser	Ala	Leu	Arg
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Thr	Gly	Trp	Tyr	Thr	Ser	Val	Ile	Thr	Ile	Glu	Leu	Ser	Asn	Ile	Lys
	50					55					60				

Glu	Asn	Lys	Cys	Asn	Gly	Thr	Asp	Ala	Lys	Val	Lys	Leu	Ile	Lys	Gln
65					70					75					80

Glu	Leu	Asp	Lys	Tyr	Lys	Ser	Ala	Val	Thr	Glu	Leu	Gln	Leu	Leu	Met
			85						90					95	

Gln	Ser	Thr	Pro	Ala	Thr	Asn	Asn	Lys	Phe	Leu	Gly	Phe	Leu	Gln	Gly
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Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys
 145 150 155 160

Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val
 165 170 175

Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe
 180 185 190

Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val
 195 200 205

Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser
 210 215 220

Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys
 225 230 235 240

Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser
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Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu
 260 265 270

Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser
 275 280 285

Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr
 290 295 300

Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe
 305 310 315 320

Phe Pro Leu Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys
 325 330 335

Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn
 340 345 350

Ile Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys
 355 360 365

Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser
 370 375 380

Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile

385 390 395 400

Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val
405 410 415

Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu
420 425 430

Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp
435 440 445

Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val
450 455 460

Asn Glu Lys Ile Asn Gly Thr Leu Ala Phe Ile Arg Lys Ser Asp Glu
465 470 475 480

Lys Leu His Asn Val Glu Asp Lys Ile Glu Glu Ile Leu Ser Lys Ile
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Tyr His Ile Glu Asn Glu Ile Ala Arg Ile Lys Lys Leu Ile Gly Glu
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Asn Ala Ile Thr Thr Ile Leu Thr Ala Val Thr Phe Cys Phe Ala
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Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly
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Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser
 1 5 10 15

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<400> 65

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Gly	Ser	Ala	Ile	Ala	Ser	Gly	Ile	Ala	Val	Ser	Lys	Val	Leu	His
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<400> 66

Ala	Ser	Gly	Ile	Ala	Val	Ser	Lys	Val	Leu	His	Leu	Glu	Gly	Glu
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<400> 67

Ala	Val	Ser	Lys	Val	Leu	His	Leu	Glu	Gly	Glu	Val	Asn	Lys	Ile
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<400> 68

Val	Leu	His	Leu	Glu	Gly	Glu	Val	Asn	Lys	Ile	Lys	Ser	Ala	Leu
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<400> 69

Glu	Gly	Glu	Val	Asn	Lys	Ile	Lys	Ser	Ala	Leu	Leu	Ser	Thr	Asn
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<400> 70

Asn	Lys	Ile	Lys	Ser	Ala	Leu	Leu	Ser	Thr	Asn	Lys	Ala	Val	Val
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Ser	Ala	Leu	Leu	Ser	Thr	Asn	Lys	Ala	Val	Val	Ser	Leu	Ser	Asn
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<400> 72

Ser	Thr	Asn	Lys	Ala	Val	Val	Ser	Leu	Ser	Asn	Gly	Val	Ser	Val
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Ala	Val	Val	Ser	Leu	Ser	Asn	Gly	Val	Ser	Val	Leu	Thr	Ser	Lys
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<400> 74

Leu	Ser	Asn	Gly	Val	Ser	Val	Leu	Thr	Ser	Lys	Val	Leu	Asp	Leu
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<400> 75

Val	Ser	Val	Leu	Thr	Ser	Lys	Val	Leu	Asp	Leu	Lys	Asn	Tyr	Ile
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<400> 76

Thr	Ser	Lys	Val	Leu	Asp	Leu	Lys	Asn	Tyr	Ile	Asp	Lys	Gln	Leu
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<400> 77

Leu	Asp	Leu	Lys	Asn	Tyr	Ile	Asp	Lys	Gln	Leu	Leu	Pro	Ile	Val
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<400> 78

Asn	Tyr	Ile	Asp	Lys	Gln	Leu	Leu	Pro	Ile	Val	Asn	Lys	Gln	Ser
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<400> 79

Lys	Gln	Leu	Leu	Pro	Ile	Val	Asn	Lys	Gln	Ser	Cys	Ser	Ile	Ser
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<400> 80

Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr
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Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe
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Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn
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<400> 83

Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu
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<400> 84

Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg
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<210> 85

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<400> 85

Gln	Lys	Asn	Asn	Arg	Leu	Leu	Glu	Ile	Thr	Arg	Glu	Phe	Ser	Val
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<400> 86

Arg	Leu	Leu	Glu	Ile	Thr	Arg	Glu	Phe	Ser	Val	Asn	Ala	Gly	Val
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<400> 87

Ile	Thr	Arg	Glu	Phe	Ser	Val	Asn	Ala	Gly	Val	Thr	Thr	Pro	Val
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<210> 88
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<400> 88

Phe	Ser	Val	Asn	Ala	Gly	Val	Thr	Thr	Pro	Val	Ser	Thr	Tyr	Met
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<400> 89

Ala	Gly	Val	Thr	Thr	Pro	Val	Ser	Thr	Tyr	Met	Leu	Thr	Asn	Ser
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Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser
 1 5 10 15

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<400> 91

Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp
 1 5 10 15

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<400> 92

Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr
 1 5 10 15

<210> 93
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<400> 93

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys
 1 5 10 15

<210> 94
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<400> 94

Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser
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1 5 10 15

<210> 95
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<400> 95

Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln
 1 5 10 15

<210> 96
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<400> 96

Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln
 1 5 10 15

<210> 97
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<400> 97

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser
 1 5 10 15

<210> 98
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<400> 98

Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile
 1 5 10 15

<210> 99
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<400> 99

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Val	Arg	Gln	Gln	Ser	Tyr	Ser	Ile	Met	Ser	Ile	Ile	Lys	Lys	Glu
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Ser	Tyr	Ser	Ile	Met	Ser	Ile	Ile	Lys	Lys	Glu	Val	Leu	Ala	Tyr
1				5					10					15

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<400> 101

Met	Ser	Ile	Ile	Lys	Lys	Glu	Val	Leu	Ala	Tyr	Val	Val	Gln	Leu
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<400> 102

Lys	Lys	Glu	Val	Leu	Ala	Tyr	Val	Val	Gln	Leu	Pro	Leu	Tyr	Gly
1				5					10					15

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<400> 103

Leu	Ala	Tyr	Val	Val	Gln	Leu	Pro	Leu	Tyr	Gly	Val	Ile	Asp	Thr
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<400> 104

Val	Gln	Leu	Pro	Leu	Tyr	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Lys
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<211> 15

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<220>

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<400> 105

Leu	Tyr	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Lys	Leu	His	Thr	Ser
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<210> 106

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<220>

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<400> 106

Ile	Asp	Thr	Pro	Cys	Trp	Lys	Leu	His	Thr	Ser	Pro	Leu	Cys	Thr
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<400> 107

Cys	Trp	Lys	Leu	His	Thr	Ser	Pro	Leu	Cys	Thr	Thr	Asn	Thr	Lys
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His	Thr	Ser	Pro	Leu	Cys	Thr	Thr	Asn	Thr	Lys	Glu	Gly	Ser	Asn
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<212> PRT

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<220>

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<400> 109

Leu	Cys	Thr	Thr	Asn	Thr	Lys	Glu	Gly	Ser	Asn	Ile	Cys	Leu	Thr
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<211> 15

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<220>

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<400> 110

Asn	Thr	Lys	Glu	Gly	Ser	Asn	Ile	Cys	Leu	Thr	Arg	Thr	Asp	Arg
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<400> 111

Gly	Ser	Asn	Ile	Cys	Leu	Thr	Arg	Thr	Asp	Arg	Gly	Trp	Tyr	Cys
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Cys	Leu	Thr	Arg	Thr	Asp	Arg	Gly	Trp	Tyr	Cys	Asp	Asn	Ala	Gly
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<400> 113

Thr	Asp	Arg	Gly	Trp	Tyr	Cys	Asp	Asn	Ala	Gly	Ser	Val	Ser	Phe
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<400> 114

Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala
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<210> 115

<211> 15

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<400> 115

Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys
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<210> 116

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<400> 116

Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn
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<210> 117

<211> 15

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<220>

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<400> 117

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys
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<210> 118

<211> 15

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<213> Artificial Sequence

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<400> 118

Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn
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<210> 119

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<400> 119

Gln	Ser	Asn	Arg	Val	Phe	Cys	Asp	Thr	Met	Asn	Ser	Leu	Thr	Leu
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<400> 120

Val	Phe	Cys	Asp	Thr	Met	Asn	Ser	Leu	Thr	Leu	Pro	Ser	Glu	Val
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<400> 121

Thr	Met	Asn	Ser	Leu	Thr	Leu	Pro	Ser	Glu	Val	Asn	Leu	Cys	Asn
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<400> 122

Leu	Thr	Leu	Pro	Ser	Glu	Val	Asn	Leu	Cys	Asn	Val	Asp	Ile	Phe
1				5					10					15

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<400> 123

Ser	Glu	Val	Asn	Leu	Cys	Asn	Val	Asp	Ile	Phe	Asn	Pro	Lys	Tyr
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M137870026W000-SEQLIST-HJD

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Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile
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<210> 125
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 <212> PRT
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<400> 125

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys
 1 5 10 15

<210> 126
 <211> 15
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<400> 126

Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser
 1 5 10 15

<210> 127
 <211> 15
 <212> PRT
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<400> 127

Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile
 1 5 10 15

<210> 128
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 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 128

Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly

<400> 129

$\langle 400 \rangle$ 130

<400> 131

<400> 132

<400> 133

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Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile
1 5 10 15

<210> 134
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<212> PRT
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<400> 134

Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe
1 5 10 15

<210> 135
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<400> 135

Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys
1 5 10 15

<210> 136
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<400> 136

Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser
1 5 10 15

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<400> 137

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val
1 5 10 15

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M137870026W000-SEQLIST-HJD

<400> 138

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<210> 139

<211> 15

<212> PRT

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<400> 139

Tyr	Val	Ser	Asn	Lys	Gly	Val	Asp	Thr	Val	Ser	Val	Gly	Asn	Thr
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<210> 140

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<400> 140

Lys	Gly	Val	Asp	Thr	Val	Ser	Val	Gly	Asn	Thr	Leu	Tyr	Tyr	Val
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<210> 141

<211> 15

<212> PRT

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<400> 141

Thr	Val	Ser	Val	Gly	Asn	Thr	Leu	Tyr	Tyr	Val	Asn	Lys	Gln	Glu
1				5					10					15

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<220>

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<400> 142

Gly	Asn	Thr	Leu	Tyr	Tyr	Val	Asn	Lys	Gln	Glu	Gly	Lys	Ser	Leu
1				5					10					15

<210> 143

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<212> PRT

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M137870026W000-SEQLIST-HJD

<220>

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<400> 143

Tyr	Tyr	Val	Asn	Lys	Gln	Glu	Gly	Lys	Ser	Leu	Tyr	Val	Lys	Gly
1				5					10					15

<210> 144

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

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<400> 144

Lys	Gln	Glu	Gly	Lys	Ser	Leu	Tyr	Val	Lys	Gly	Glu	Pro	Ile	Ile
1				5					10					15

<210> 145

<211> 15

<212> PRT

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<400> 145

Lys	Ser	Leu	Tyr	Val	Lys	Gly	Glu	Pro	Ile	Ile	Asn	Phe	Tyr	Asp
1				5					10					15

<210> 146

<211> 15

<212> PRT

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<220>

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<400> 146

Val	Lys	Gly	Glu	Pro	Ile	Ile	Asn	Phe	Tyr	Asp	Pro	Leu	Val	Phe
1				5					10					15

<210> 147

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 147

Pro	Ile	Ile	Asn	Phe	Tyr	Asp	Pro	Leu	Val	Phe	Pro	Ser	Gly	Glu
1				5					10					15

<210> 148

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

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<400> 148

Phe Tyr Asp Pro Leu Val Phe Pro Ser Gly Glu Phe Asp Ala Ser
1 5 10 15

<210> 149

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 149

Leu Val Phe Pro Ser Gly Glu Phe Asp Ala Ser Ile Ser Gln Val
1 5 10 15

<210> 150

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 150

Ser Gly Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile
1 5 10 15

<210> 151

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

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<400> 151

Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu
1 5 10 15

<210> 152

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 152

Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg
1 5 10 15

<210> 153

M137870026W000-SEQLIST-HJD

<211> 15
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<220>
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<400> 153

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu
 1 5 10 15

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<400> 154

Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu His Asn
 1 5 10 15

<210> 155
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<400> 155

Phe Ile Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly
 1 5 10 15

<210> 156
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<400> 156

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Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile
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<400> 158

Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr Ala Ile Ile
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 1 5 10 15

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Val Ile Val Val Ile Leu Leu Ser Leu Ile Ala Val Gly Leu Leu

1 5 10 15

<210> 163
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 <212> PRT
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Ile Leu Leu Ser Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys
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Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr
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<220>
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Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu
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Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser Lys Asp Gln
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Val Thr Leu Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala
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<400> 170

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<400> 171

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Trp	Asp	Thr	Leu	Asn	His	Leu	Leu	Phe	Ile	Ser	Ser	Cys	Leu	Tyr
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<211> 15

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<400> 175

Asn	His	Leu	Leu	Phe	Ile	Ser	Ser	Cys	Leu	Tyr	Lys	Leu	Asn	Leu
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<400> 176

Phe	Ile	Ser	Ser	Cys	Leu	Tyr	Lys	Leu	Asn	Leu	Lys	Ser	Val	Ala
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<220>

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<400> 178

Leu Asn Leu Lys Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala
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Ser Val Ala Gln Ile Thr Leu Ser Ile Leu Ala Met Ile Ile Ser
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<400> 181

Ile Leu Ala Met Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile
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Ile Ile Ser Thr Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala
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Ser Leu Ile Ile Ala Ala Ile Ile Phe Ile Ala Ser Ala Asn His
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<400> 187

Val Thr Ser Thr Thr Thr Ile Ile Gln Asp Ala Thr Ser Gln Ile
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Thr Thr Ile Ile Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr Thr
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<400> 189

Gln Asp Ala Thr Ser Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu
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<400> 190

Ser Gln Ile Lys Asn Thr Thr Pro Thr Tyr Leu Thr Gln Ser Pro
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<400> 191

Asn Thr Thr Pro Thr Tyr Leu Thr Gln Ser Pro Gln Leu Gly Ile
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<400> 192

Thr Tyr Leu Thr Gln Ser Pro Gln Leu Gly Ile Ser Pro Ser Asn
 1 5 10 15

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<400> 193

Gln Ser Pro Gln Leu Gly Ile Ser Pro Ser Asn Pro Ser Glu Ile
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<400> 194

Leu Gly Ile Ser Pro Ser Asn Pro Ser Glu Ile Thr Ser Gln Ile
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Pro Ser Asn Pro Ser Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu
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<400> 196

Ser Glu Ile Thr Ser Gln Ile Thr Thr Ile Leu Ala Ser Thr Thr

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1 5 10 15

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Thr Ile Leu Ala Ser Thr Thr Pro Gly Val Lys Ser Thr Leu Gln
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<400> 199

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<400> 203

Thr Lys Asn Thr Thr Thr Thr Gln Ala Gln Pro Ser Lys Pro Thr
1 5 10 15

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Thr Thr Thr Gln Ala Gln Pro Ser Lys Pro Thr Thr Lys Gln Arg
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<400> 206

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<400> 207

Lys	Gln	Arg	Gln	Asn	Lys	Pro	Pro	Ser	Lys	Pro	Asn	Asn	Asp	Phe
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<400> 208

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<220>

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<400> 209

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<400> 210

Asn	Asp	Phe	His	Phe	Glu	Val	Phe	Asn	Phe	Val	Pro	Cys	Ser	Ile
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<210> 211

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<400> 211

Phe	Glu	Val	Phe	Asn	Phe	Val	Pro	Cys	Ser	Ile	Cys	Ser	Asn	Asn
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Asn	Phe	Val	Pro	Cys	Ser	Ile	Cys	Ser	Asn	Asn	Pro	Thr	Cys	Trp
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<400> 214

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<400> 218

Lys Pro Gly Lys Lys Thr Thr Thr Lys Pro Thr Glu Glu Pro Thr
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<400> 221

Glu Pro Thr Phe Lys Thr Ala Lys Glu Asp Pro Lys Pro Gln Thr
 1 5 10 15

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Lys Thr Ala Lys Glu Asp Pro Lys Pro Gln Thr Thr Gly Ser Gly
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Glu Asp Pro Lys Pro Gln Thr Thr Gly Ser Gly Glu Val Pro Thr
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Gly Ser Gly Glu Val Pro Thr Thr Lys Pro Thr Gly Glu Pro Thr
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Val Pro Thr Thr Lys Pro Thr Gly Glu Pro Thr Ile Asn Thr Thr
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 1 5 10 15

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1 5 10 15

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1 5 10 15

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Ser Ser Glu Gly Asn Pro Ser Pro Ser Gln Val Ser Ile Thr Ser
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Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95

Met Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
100 105 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
115 120 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
130 135 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
145 150 155 160

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Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
 165 170 175
 Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
 180 185 190
 Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
 195 200 205
 Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
 210 215 220
 Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
 225 230 235 240
 Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
 245 250 255
 Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
 260 265 270
 Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
 275 280 285
 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 Val
 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 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

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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 Ser Ala Ile Gly Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln
515 520 525

Ala Tyr Val Arg Lys Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu
530 535 540

<210> 244
<211> 1632
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

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tctaagggtc acctttccgc gcttcgcact ggctggtaca cgtcagtcac aacgatcgaa 180
ctctctaata taaaggaaaa taagtgtaac ggaacagacg ctaagggtcaa gttaatacaag 240
caggagctgg acaaatataa gaatgccgta acggagctcc agctgctcat gcagagcacg 300
ccagctacaa acaacagggc acgccgtgag ctccccgat ttatgaacta cacattgaac 360
aacgccaaga aaactaacgt gactttgtcc aagaagagga agcggcgatt cttaggggtc 420
cttttggggg taggctcggc gattgccagt ggggttgccg tatgcaaggt gctccacctg 480
gaaggggagg tgaacaagat taagtcggct ctgctcagta caaacaagc tgcgtctca 540
ttgtcaaacg gagtcagtgt attgacattt aaagtcctcg acctgaagaa ctatatagat 600
aaacagttac tccaatctt gaataagcag tcctgtagca tcagcaacat tgagacagtg 660
atcgagttcc agcagaagaa taatcgcta ctcgagatca ccagagaatt ctgagtcatt 720
gccggagtaa cactcctgt cagcacatac atgctcaca actctgaact cctaagcctg 780
attaatgata tgcctatcac aatgatcag aagaaactca tgagcaataa tgtgcagatt 840
gtaagacagc agagttattc tataatgtgt attattaagg aggaggtact ggcctatgtg 900

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gttcaacttc ctctgtatgg ggtgatagat acaccatgct ggaagctgca caccagccca      960
ctgtgtacga ccaatacaaa ggagggctcc aatatttgct taacacggac tgaccggggg      1020
tggtattgcg acaatgccgg atcagtctcc ttcttccccc aagcagagac ctgcaagggtg      1080
cagtccaata gagttttctg cgacacaatg aactcgctga ccctacctag cgaagttaac      1140
ttatgcaacg tggatatttt taatccgaag tatgattgta aaatcatgac tagcaaaacg      1200
gatgttagct ccagcgtaat cacctcccta ggcgctatcg tgagctgtta tggcaagacg      1260
aagtgcactg catctaataa aaataggggt attattaaaa ccttcagcaa tggctgcgac      1320
tatgtgagca ataagggcgt ggacaccgtg tcagtgggaa acaccctcta ttatgtgaac      1380
aagcaggagg gaaaatccct ttatgtaaag ggcgaaccca ttatcaattt ctatgacccc      1440
ctggttttcc caagcgacga gttcgacgca tctatctctc aagtgaacga gaaaatcaat      1500
cagagtcttg cttttatcag aaaatccgat gagctgcttt cgcctatcgg tggctatatc      1560
ccagaagccc caagagacgg acaagcgtag gtccggaaag atggtgagtg ggtcctcctc      1620
tctacctttc tt                                                                1632

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<210> 245
<211> 544
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 245

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1           5           10           15

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Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
           20           25           30

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Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
           35           40           45

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```

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
           50           55           60

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Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65           70           75           80

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```

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
           85           90           95

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Met Gln Ser Thr Pro Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
           100          105          110

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Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
           115          120          125

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Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
 130 135 140
 Gly Ser Ala Ile Ala Ser Gly Val Ala Val Cys Lys Val Leu His Leu
 145 150 155 160
 Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
 165 170 175
 Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Phe Lys Val
 180 185 190
 Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Leu Asn
 195 200 205
 Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
 210 215 220
 Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
 225 230 235 240
 Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
 245 250 255
 Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
 260 265 270
 Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
 275 280 285
 Met Cys 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 Val
 370 375 380
 Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
 385 390 395 400

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Asp Val Ser 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 Ser Ala Ile Gly Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln
515 520 525

Ala Tyr Val Arg Lys Asp Gly Glu Trp Val Leu Leu Ser Thr Phe Leu
530 535 540

<210> 246
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 246
atggagactc ctgcacagct gctgtttctg ctattgttgt ggcttccgga cactactggg 60
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gccgagatcg cccagagact cgaatctgta ttcgcaggaa agaacacgga tttggaggca 180
ctaattggaat ggctgaagac ccgtccgata ctgtctcctc tcacaaaggg gattcttgga 240
tttgtcttta ccctaccgt cccgagcgag cgcggtctcc agcgagacg tttgtacag 300
aatgcactga atggcaacgg cgatcccaat aacatggatc gtgcggtaaa gctttataaa 360
aagctgaaga gagaaatcac tttccatggg gctaaagagg tgagtctctc ctattcaacc 420
ggggcattgg cctcttgcat gggctttata tacaatcgaa tgggcaccgt taccaccgag 480
gccgcatttg gtctggtttg tgctacgtgc gagcaaatcg cagatagcca gcatcggtcc 540
catcggcaga tggccaccac tacgaaccct ctaattcgac atgaaaatcg catggtcctg 600
gctagcacca ccgcaaaggc aatggagcag atggcgggct ctagtgaaca ggcagccgag 660

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gcaatggaag tggccaatca gaccaggcag atgggtccatg ctatgcggac tatttggtacc 720
 caccctgtcca gcagtgtctgg actgaaggat gacctccttg agaacctgca ggcataaccag 780
 aaacgaatgg ggggtgcaaata gcagagattc aag 813

<210> 247
 <211> 271
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 247

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

Asp Thr Thr Gly Ser Leu Leu Thr Glu Val Glu Thr Tyr Val Leu Ser
 20 25 30

Ile Ile Pro Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu
 35 40 45

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

Leu Lys Thr Arg Pro Ile Leu Ser Pro Leu Thr Lys Gly Ile Leu Gly
 65 70 75 80

Phe Val Phe Thr Leu Thr Val Pro Ser Glu Arg Gly Leu Gln Arg Arg
 85 90 95

Arg Phe Val Gln Asn Ala Leu Asn Gly Asn Gly Asp Pro Asn Asn Met
 100 105 110

Asp Arg Ala Val Lys Leu Tyr Lys Lys Leu Lys Arg Glu Ile Thr Phe
 115 120 125

His Gly Ala Lys Glu Val Ser Leu Ser Tyr Ser Thr Gly Ala Leu Ala
 130 135 140

Ser Cys Met Gly Leu Ile Tyr Asn Arg Met Gly Thr Val Thr Thr Glu
 145 150 155 160

Ala Ala Phe Gly Leu Val Cys Ala Thr Cys Glu Gln Ile Ala Asp Ser
 165 170 175

Gln His Arg Ser His Arg Gln Met Ala Thr Thr Thr Asn Pro Leu Ile
 180 185 190

Arg His Glu Asn Arg Met Val Leu Ala Ser Thr Thr Ala Lys Ala Met
 195 200 205

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Glu Gln Met Ala Gly Ser Ser Glu Gln Ala Ala Glu Ala Met Glu Val
210 215 220

Ala Asn Gln Thr Arg Gln Met Val His Ala Met Arg Thr Ile Gly Thr
225 230 235 240

His Pro Ser Ser Ser Ala Gly Leu Lys Asp Asp Leu Leu Glu Asn Leu
245 250 255

Gln Ala Tyr Gln Lys Arg Met Gly Val Gln Met Gln Arg Phe Lys
260 265 270

<210> 248
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 248
ctcaatttcc tcacttctcc agtgt 25

<210> 249
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 249
cttgattcct cgggtgtacct ctgt 24

<210> 250
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 250
tcccattatg cctaggccag cagca 25

<210> 251
<211> 1729
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 251
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aaagaagagt aagaagaaat ataagagcca ccatggcaca agtcattaat acaaacagcc 120
tgtcgctgtt gaccagaat aacctgaaca aatcccagtc cgcactgggc actgctatcg 180

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agcgtttgtc	ttccgggtctg	cgtatcaaca	gcgcgaaaga	cgatgcggca	ggacaggcga	240
ttgctaaccg	ttttaccgcg	aacatcaaag	gtctgactca	ggcttcccgt	aacgctaacg	300
acggtatctc	cattgcgcag	accactgaag	gcgcgctgaa	cgaaatcaac	aacaacctgc	360
agcgtgtgcg	tgaactggcg	gttcagtctg	cgaatggtac	taactcccag	tctgacctcg	420
actccatcca	ggctgaaatc	accagcgcc	tgaacgaaat	cgaccgtgta	tccggccaga	480
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ccaacgacgg	tgaaactatc	gatattgatt	taaaagaaat	cagctctaaa	acactgggac	600
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aaactaccta	taaaaatggt	acagatccta	ttacagccca	gagcaatact	gatatccaaa	720
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caggtgcaat	tactgctaaa	accactactt	atacagatgg	tactggcggt	gctcaaactg	1200
gagctgtgaa	atttggtggc	gcaaattgta	aatctgaagt	tgttactgct	accgatggta	1260
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ttgatacact	tcgttctgac	ctgggtgctg	ttcagaaccg	tttcaactcc	gctatcacca	1440
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tcctgcaccc	gtacccccgt	ggtctttgaa	taaagtctga	gtgggcggc		1729

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<211> 1518

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Polynucleotide

<400> 252

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gcgaaagacg	atgcggcagg	acaggcgatt	gctaaccggt	ttaccgcgaa	catcaaaggt	180

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ctgactcagg	cttccccgtaa	cgctaacgac	ggtatctcca	ttgcgagac	cactgaaggg	240
gcgctgaacg	aaatcaacaa	caacctgcag	cgtgtgcgtg	aactggcgg	tcagtctgcg	300
aatgggtacta	actcccagtc	tgacctcgac	tccatccagg	ctgaaatcac	ccagcgcctg	360
aacgaaatcg	accgtgtatc	cggccagact	cagttcaacg	gcgtgaaagt	cctggcgcag	420
gacaacaccc	tgaccatcca	ggttggtgcc	aacgacgggtg	aaactatcga	tattgattta	480
aaagaaatca	gctctaaaac	actgggactt	gataagctta	atgtccaaga	tgcctacacc	540
ccgaaagaaa	ctgctgtaac	cgttgataaa	actacctata	aaaatgggtac	agatcctatt	600
acagcccaga	gcaataactga	tatccaaact	gcaattggcg	gtgggtgcaac	gggggttact	660
ggggctgata	tcaaatttaa	agatgggtcaa	tactattttag	atgttaaagg	cggtgcttct	720
gctggtgttt	ataaagccac	ttatgatgaa	actacaaaga	aagttaatat	tgatacgact	780
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cacaacaaa	ttgctgaagt	aacaaaagag	ggtgttgata	cgaccacagt	tgcggctcaa	900
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gcccgtagcc	gtatcgaaga	ttccgactac	gcaaccgaag	tctccaacat	gtctcgcgcg	1440
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<210> 253
 <211> 1790
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 253	
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auuaauacaa	acagccuguc gcuguugacc cagaauaacc ugaacaaauc ccaguccgca 120
cugggcacug	cuaucgagcg uuugucuucc ggucugcgua ucaacagcgc gaaagacgau 180
gcggcaggac	aggcgauugc uaaccguuuu accgcgaaca ucaaaggucu gacucaggcu 240
ucccguaacg	cuaacgacgg uaucuccauu gcgcagacca cugaaggcgc gcugaacgaa 300
aucaacaaca	accugcagcg ugugcgugaa cuggcgguuu agucugcgaa ugguacuaac 360

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ucccagucug	accucgacuc	cauccaggcu	gaaaucaccc	agcgccugaa	cgaaaucgac	420
cguguauccg	gccagacuca	guucaacggc	gugaaagucc	uggcgagga	caacaccug	480
accauccagg	uuggugccaa	cgacggugaa	acuaucgaua	uugauuuaaa	agaaaucagc	540
ucuaaaacac	ugggacuuga	uaagcuuaau	guccaagaug	ccuacacccc	gaaagaaacu	600
gcuguaaccg	uugauaaaa	uaccuauaaa	aaugguacag	auccuauuac	agcccagagc	660
aauacugaua	uccaaacugc	aaauggcggu	ggugcaacgg	ggguuacugg	ggcugauauc	720
aaaauuuuag	auggucaaua	cuauuuagau	guuaaaggcg	gugcuucugc	ugguguuuau	780
aaagccacuu	augaugaaac	uacaaagaaa	guuaauauug	auacgacuga	uaaaacuccg	840
uuggcaacug	cggaagcuac	agcuauucgg	ggaacggcca	cuauaaccca	caaccaaauu	900
gcugaaguaa	caaaagaggg	uguugauacg	accacaguug	cggcucaacu	ugcugcagca	960
gggguuacug	gcgccgauaa	ggacaauacu	agccuuguaa	aacuaucguu	ugaggauaaa	1020
aacgguaagg	uuauugaugg	uggcuauuca	gugaaaaugg	gcgacgauuu	cuaugccgcu	1080
acauaugaug	agaaaacagg	ugcaauuacu	gcuaaaacca	cuacuauuac	agaugguacu	1140
ggcguugcuc	aaacuggagc	ugugaaauuu	gguggcgcaa	augguaaauc	ugaaguuguu	1200
acugcuaccg	augguaagac	uuacuuaagc	agcgaccuug	acaaacauaa	cuucagaaca	1260
ggcggugagc	uuaaagaggu	uaauacagau	aagacugaaa	accacugca	gaaaauugau	1320
gcugccuugg	cacagguuga	uacacuucgu	ucugaccugg	gugcgguuca	gaaccguuuc	1380
aacuccgcua	ucaccaaccu	gggcaauacc	guaaaauaacc	ugucuucugc	ccguagccgu	1440
aucgaagauu	ccgacuacgc	aaccgaaguc	uccaacaugu	cucgcgcgca	gauucugcag	1500
caggccggua	ccuccguucu	ggcgcaggcg	aaccagguuc	cgcaaaacgu	ccucucuuaa	1560
cugcguugau	aaauaggcugg	agccucggug	gccaugcuuc	uugcccuug	ggccuccccc	1620
cagccccucc	uccccuuccu	gcacccguac	ccccgugguc	uuugaauaaa	gucugagugg	1680
gcggcaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1740
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaucuag		1790

<210> 254
 <211> 506
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 254

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Asn	Leu	Asn	Lys	Ser	Gln	Ser	Ala	Leu	Gly	Thr	Ala	Ile	Glu	Arg	Leu
			20					25					30		

Ser	Ser	Gly	Leu	Arg	Ile	Asn	Ser	Ala	Lys	Asp	Asp	Ala	Ala	Gly	Gln

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35

40

45

Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys Gly Leu Thr Gln Ala
 50 55 60

Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala Gln Thr Thr Glu Gly
 65 70 75 80

Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg Val Arg Glu Leu Ala
 85 90 95

Val Gln Ser Ala Asn Gly Thr Asn Ser Gln Ser Asp Leu Asp Ser Ile
 100 105 110

Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile Asp Arg Val Ser Gly
 115 120 125

Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala Gln Asp Asn Thr Leu
 130 135 140

Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr Ile Asp Ile Asp Leu
 145 150 155 160

Lys Glu Ile Ser Ser Lys Thr Leu Gly Leu Asp Lys Leu Asn Val Gln
 165 170 175

Asp Ala Tyr Thr Pro Lys Glu Thr Ala Val Thr Val Asp Lys Thr Thr
 180 185 190

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 Ala
 260 265 270

Ile Arg Gly Thr Ala Thr Ile Thr His Asn Gln Ile Ala Glu Val Thr
 275 280 285

Lys Glu Gly Val Asp Thr Thr Thr Val Ala Ala Gln Leu Ala Ala Ala
 290 295 300

Gly Val Thr Gly Ala Asp Lys Asp Asn Thr Ser Leu Val Lys Leu Ser
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305 310 315 320
 Phe Glu Asp Lys Asn Gly Lys Val Ile Asp Gly Gly Tyr Ala Val Lys
 325 330 335
 Met Gly Asp Asp Phe Tyr Ala Ala Thr Tyr Asp Glu Lys Thr Gly Ala
 340 345 350
 Ile Thr Ala Lys Thr Thr Thr Tyr Thr Asp Gly Thr Gly Val Ala Gln
 355 360 365
 Thr Gly Ala Val Lys Phe Gly Gly Ala Asn Gly Lys Ser Glu Val Val
 370 375 380
 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
 405 410 415
 Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu Ala Gln Val Asp Thr
 420 425 430
 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
 450 455 460
 Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser Asn Met Ser Arg Ala
 465 470 475 480
 Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu Ala Gln Ala Asn Gln
 485 490 495
 Val Pro Gln Asn Val Leu Ser Leu Leu Arg
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<210> 255
 <211> 698
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 255

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

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Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn Asn Gly Lys Thr Ile
 305 310 315 320
 Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp Tyr Tyr Ser Ala Thr
 325 330 335
 Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr Thr Lys Tyr Thr Ala
 340 345 350
 Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys Leu Gly Gly Ala Asp
 355 360 365
 Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys Thr 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
 Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys Ile Asp Ala Ala Leu
 405 410 415
 Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly Ala Val Gln Asn Arg
 420 425 430
 Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr Val Asn Asn Leu Thr
 435 440 445
 Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr Ala Thr Glu Val Ser
 450 455 460
 Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala Gly Thr Ser Val Leu
 465 470 475 480
 Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu Ser Leu Leu Arg Gly
 485 490 495
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Met Ala Pro Asp Pro Asn
 500 505 510
 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
 515 520 525
 Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn
 530 535 540
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 545 550 555 560
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Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Lys Asn Asn Gln
580 585 590

Gly Asn Gly Gln Gly His Asn Met Pro Asn Asp Pro Asn Arg Asn Val
595 600 605

Asp Glu Asn Ala Asn Ala Asn Asn Ala Val Lys Asn Asn Asn Asn Glu
610 615 620

Glu Pro Ser Asp Lys His Ile Glu Gln Tyr Leu Lys Lys Ile Lys Asn
625 630 635 640

Ser Ile Ser Thr Glu Trp Ser Pro Cys Ser Val Thr Cys Gly Asn Gly
645 650 655

Ile Gln Val Arg Ile Lys Pro Gly Ser Ala Asn Lys Pro Lys Asp Glu
660 665 670

Leu Asp Tyr Glu Asn Asp Ile Glu Lys Lys Ile Cys Lys Met Glu Lys
675 680 685

Cys Ser Ser Val Phe Asn Val Val Asn Ser
690 695

<210> 256
<211> 692
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 256

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20 25 30

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
35 40 45

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
50 55 60

Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala Asn Pro Asn Ala
65 70 75 80

Asn Pro Asn Lys Asn Asn Gln Gly Asn Gly Gln Gly His Asn Met Pro
85 90 95

Asn Asp Pro Asn Arg Asn Val Asp Glu Asn Ala Asn Ala Asn Asn Ala
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100

105

110

Val Lys Asn Asn Asn Asn Glu Glu Pro Ser Asp Lys His Ile Glu Gln
 115 120 125

Tyr Leu Lys Lys Ile Lys Asn Ser Ile Ser Thr Glu Trp Ser Pro Cys
 130 135 140

Ser Val Thr Cys Gly Asn Gly Ile Gln Val Arg Ile Lys Pro Gly Ser
 145 150 155 160

Ala Asn Lys Pro Lys Asp Glu Leu Asp Tyr Glu Asn Asp Ile Glu Lys
 165 170 175

Lys Ile Cys Lys Met Glu Lys Cys Ser Ser Val Phe Asn Val Val Asn
 180 185 190

Ser Arg Pro Val Thr Met Ala Gln Val Ile Asn Thr Asn Ser Leu Ser
 195 200 205

Leu Leu Thr Gln Asn Asn Leu Asn Lys Ser Gln Ser Ala Leu Gly Thr
 210 215 220

Ala Ile Glu Arg Leu Ser Ser Gly Leu Arg Ile Asn Ser Ala Lys Asp
 225 230 235 240

Asp Ala Ala Gly Gln Ala Ile Ala Asn Arg Phe Thr Ala Asn Ile Lys
 245 250 255

Gly Leu Thr Gln Ala Ser Arg Asn Ala Asn Asp Gly Ile Ser Ile Ala
 260 265 270

Gln Thr Thr Glu Gly Ala Leu Asn Glu Ile Asn Asn Asn Leu Gln Arg
 275 280 285

Val Arg Glu Leu Ala Val Gln Ser Ala Asn Ser Thr Asn Ser Gln Ser
 290 295 300

Asp Leu Asp Ser Ile Gln Ala Glu Ile Thr Gln Arg Leu Asn Glu Ile
 305 310 315 320

Asp Arg Val Ser Gly Gln Thr Gln Phe Asn Gly Val Lys Val Leu Ala
 325 330 335

Gln Asp Asn Thr Leu Thr Ile Gln Val Gly Ala Asn Asp Gly Glu Thr
 340 345 350

Ile Asp Ile Asp Leu Lys Gln Ile Asn Ser Gln Thr Leu Gly Leu Asp
 355 360 365

Thr Leu Asn Val Gln Gln Lys Tyr Lys Val Ser Asp Thr Ala Ala Thr
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370

375

380

Val Thr Gly Tyr Ala Asp Thr Thr Ile Ala Leu Asp Asn Ser Thr Phe
 385 390 395 400

Lys Ala Ser Ala Thr Gly Leu Gly Gly Thr Asp Gln Lys Ile Asp Gly
 405 410 415

Asp Leu Lys Phe Asp Asp Thr Thr Gly Lys Tyr Tyr Ala Lys Val Thr
 420 425 430

Val Thr Gly Gly Thr Gly Lys Asp Gly Tyr Tyr Glu Val Ser Val Asp
 435 440 445

Lys Thr Asn Gly Glu Val Thr Leu Ala Gly Gly Ala Thr Ser Pro Leu
 450 455 460

Thr Gly Gly Leu Pro Ala Thr Ala Thr Glu Asp Val Lys Asn Val Gln
 465 470 475 480

Val Ala Asn Ala Asp Leu Thr Glu Ala Lys Ala Ala Leu Thr Ala Ala
 485 490 495

Gly Val Thr Gly Thr Ala Ser Val Val Lys Met Ser Tyr Thr Asp Asn
 500 505 510

Asn Gly Lys Thr Ile Asp Gly Gly Leu Ala Val Lys Val Gly Asp Asp
 515 520 525

Tyr Tyr Ser Ala Thr Gln Asn Lys Asp Gly Ser Ile Ser Ile Asn Thr
 530 535 540

Thr Lys Tyr Thr Ala Asp Asp Gly Thr Ser Lys Thr Ala Leu Asn Lys
 545 550 555 560

Leu Gly Gly Ala Asp Gly Lys Thr Glu Val Val Ser Ile Gly Gly Lys
 565 570 575

Thr Tyr Ala Ala Ser Lys Ala Glu Gly His Asn Phe Lys Ala Gln Pro
 580 585 590

Asp Leu Ala Glu Ala Ala Ala Thr Thr Thr Glu Asn Pro Leu Gln Lys
 595 600 605

Ile Asp Ala Ala Leu Ala Gln Val Asp Thr Leu Arg Ser Asp Leu Gly
 610 615 620

Ala Val Gln Asn Arg Phe Asn Ser Ala Ile Thr Asn Leu Gly Asn Thr
 625 630 635 640

Val Asn Asn Leu Thr Ser Ala Arg Ser Arg Ile Glu Asp Ser Asp Tyr
 Page 105

645

650

655

Ala Thr Glu Val Ser Asn Met Ser Arg Ala Gln Ile Leu Gln Gln Ala
 660 665 670

Gly Thr Ser Val Leu Ala Gln Ala Asn Gln Val Pro Gln Asn Val Leu
 675 680 685

Ser Leu Leu Arg
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 <211> 1722
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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 tctaaaggct acctgagtgc gctccgcaca ggatggtaca cctccgtgat caccatcgag 180
 ctcagcaata ttaaagagaa caagtgaat ggtaccgacg ctaaagtcaa acttatcaag 240
 caggaactcg acaaatataa gaacgctgtg accgagctgc agttattgat gcagagtaca 300
 cctgccacca ataacagagc taggagggag ttgcctaggt ttatgaacta cactctcaac 360
 aacgcgaaga agaccaatgt gacgctatcc aagaaacgga agaggagggt cctgggggtt 420
 cttttagggg tgggctctgc cattgcttcc ggcgtggctg tatgtaaagt tctccacctc 480
 gagggagagg ttaataagat taagtcggcc ctgctgagta ctaacaaagc agtggtgtcg 540
 ctgagtaacg gagtaagtgt gttaacattt aagggtctgg acctcaagaa ttatattgac 600
 aaacagttgc ttcctattct aaacaaacag agctgttcaa taagtaatat tgaaactggt 660
 attgagtttc agcagaagaa caacaggctt cttgagatta cacgcgagtt cagtgtcaat 720
 gccggcggtta caacaccgt gtctacctac atgctgacga attctgagct tctctctctc 780
 ataaacgaca tgcccattac gaatgaccaa aagaaactta tgtccaacaa cgtgcagatt 840
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 gtgcagctac cactctatgg tgtgattgac accccctggt ggaagctgca taccagtcca 960
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 ctctgcaacg tcgacatttt caatcctaaa tatgactgca agatcatgac cagcaagacc 1200
 gacgtctcca gtcagtaat cactagccta ggggccattg taagctgcta tggcaagacc 1260
 aagtgtactg cctctaataa gaacagaggc ataattaaga ctttttcaaa tggctgtgac 1320

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aaacaggaag	gcaaatccct	ttatgtaaag	ggcgagccca	tcataaattt	ctacgaccca	1440
cttgtgttcc	ccagtgatga	attcgatgca	tcaatctccc	aggtgaacga	aaagatcaat	1500
caatcccttg	cttttatacg	aaagtcagat	gaactcctgc	ataacgtgaa	tgctgggaaa	1560
tctacaacca	acatcatgat	cactaccatc	attattgtga	ttatcgtaat	tctgctatcc	1620
ttgattgctg	tcgggctgct	tctgtactgt	aaggccagat	cgacgcctgt	gaccctttca	1680
aaggaccaac	ttagcgggat	caataatatt	gccttttagca	at		1722

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 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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tctaaaggct	acctgagtgc gctccgcaca ggatggtaca cctccgtgat caccatcgag 180
ctcagcaata	ttaaagagaa caagtgaat ggtaccgacg ctaaagtcaa acttatcaag 240
caggaactcg	acaaatataa gaacgctgtg accgagctgc agttattgat gcagagtaca 300
cctgccacca	ataacagagc taggagggag ttgcctaggt ttatgaacta cactctcaac 360
aacgcgaaga	agaccaatgt gacgctatcc aagaaacgga agaggagggt cctgggggtt 420
cttttagggg	tgggctctgc cattgcttcc ggcgtggctg tatgtaaagt tctccacctc 480
gagggagagg	ttaataagat taagtcggcc ctgctgagta ctaacaaagc agtggtgtcg 540
ctgagtaacg	gagtaagtgt gttaacattt aagggtctgg acctcaagaa ttatattgac 600
aaacagttgc	ttcctattct aaacaaacag agctgttcaa taagtaatat tgaaactggt 660
attgagtttc	agcagaagaa caacaggctt cttgagatta cacgcgagtt cagtgtcaat 720
gccggcggtt	caacacccgt gtctacctac atgctgacga attctgagct tctctctctc 780
ataaacgaca	tgcccattac gaatgaccag aagaaactta tgtccaacaa cgtgcagatt 840
gtgcgacagc	aatcctatag cattatgtgt atcatcaagg aagagggtact cgcttatggt 900
gtgcagctac	cactctatgg tgtgattgac accccctggt ggaagctgca taccagtcca 960
ctctgcacca	ctaacacaaa ggaagggagc aatatttgcc tcactcgaac cgacaggggg 1020
tggtattgctg	ataatgcggg ctccgtgtcc ttctttccac aggctgaaac ttgtaaggta 1080
cagtcaaacc	gcgtgttctg tgatactatg aattctctga ctcttcccag cgagggtaat 1140
ctctgcaacg	tcgacatttt caatcctaaa tatgactgca agatcatgac cagcaagacc 1200
gacgtctcca	gctcagtaat cactagccta ggggccattg taagctgcta tggcaagacc 1260
aagtgtactg	cctctaataa gaacagaggc ataattaaga ctttttcaaa tggctgtgac 1320

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aaacaggaag	gcaaatccct	ttatgtaaag	ggcgagccca	tcataaattt	ctacgaccca	1440
cttgtgttcc	ccagtgatga	attcgatgca	tcaatctccc	aggtgaacga	gaagatcaat	1500
caatcccttg	cttttatacg	aaagtcagat	gaactcctgc	ataacgtgaa	tgctgggaaa	1560
tctacaacca	acatcatgat	cactaccatc	attattgtga	ttatcgtaat	tctgctatcc	1620
ttgattgctg	tcgggctgct	tctgtactgt	aaggccagat	cgacgcctgt	gaccctttca	1680
aaggaccaac	ttagcgggat	caataatatt	gccttttagca	at		1722

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 <211> 1722
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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tctaaaggct	acctgagtgc gctccgcaca ggatggtaca cctccgtgat caccatcgag 180
ctcagcaata	ttaaagagaa caagtgcaat ggtaccgacg ctaaagtcaa acttatcaag 240
caggaactcg	acaatatata gaacgctgtg accgagctgc agttattgat gcagagtaca 300
cctgccacca	ataacagagc taggagggag ttgcctaggt ttatgaacta cactctcaac 360
aacgcgaaga	aaaccaatgt gacgctatcc aagaaacgga agaggagggtt cctgggggttt 420
cttttagggg	tgggctctgc cattgcttcc ggcgtggctg tatgtaaagt tctccacctc 480
gagggagagg	ttaataagat taagtcggcc ctgctgagta ctaacaaagc agtggtgtcg 540
ctgagtaacg	gagtaagtgt gttaacattt aagggtgctgg acctcaagaa ttatattgac 600
aaacagttgc	ttcctattct aaacaaacag agctgttcaa taagtaatat tgaaactggt 660
attgagtttc	agcagaagaa caacaggctt cttgagatta cacgcgagtt cagtgtcaat 720
gccggcgtta	caacacccgt gtctacctac atgctgacga attctgagct tctctctctc 780
ataaacgaca	tgcccattac gaatgaccaa aagaaactta tgtccaacaa cgtgcagatt 840
gtgcgacagc	aatcctatag cattatgtgt atcatcaagg aagagggtact cgcttatggt 900
gtgcagctac	cactctatgg tgtgattgac accccctggt ggaagctgca taccagtcca 960
ctctgcacca	ctaacacaaa ggaagggagc aatatttgcc tcactcgaac cgacaggggg 1020
tggtattgctg	ataatgcggg ctccgtgtcc ttctttccac aggctgaaac ttgtaaggta 1080
cagtcaaacc	gcgtgttctg tgatactatg aattctctga ctcttcccag cgagggttaat 1140
ctctgcaacg	tcgacatttt caatcctaaa tatgactgca agatcatgac cagcaagacc 1200
gacgtctcca	gctcagtaat cactagccta ggggccattg taagctgcta tggcaaaacc 1260
aagtgtactg	cctctaataa gaacagaggc ataattaaaa ctttttcaaa tggctgtgac 1320

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cttgtgttcc	ccagtgatga	attcgatgca	tcaatctccc	aggtgaacga	aaagatcaat	1500
caatcccttg	cttttatacg	aaagtcagat	gaactcctgc	ataacgtgaa	tgctgggaaa	1560
tctacaacca	acatcatgat	cactaccatc	attattgtga	ttatcgtaat	tctgctatcc	1620
ttgattgctg	tcgggctgct	tctgtactgt	aaggccagat	cgacgcctgt	gaccctttca	1680
aaagaccaac	ttagcgggat	caataatatt	gccttttagca	at		1722

<210> 260
 <211> 1722
 <212> RNA
 <213> Respiratory Syncytial Virus

<400> 260	
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ugcuucgccu	ccggccaaaa uaucaccgaa gaguucuauc aguccaccug cucugccguu 120
ucuaaagguu	accugucagc ccuuagaaca gggugguaua ccucuguuau uaccauugag 180
uuguccaaca	uuuagaagaa caagugcaau ggcacagacg cuaagguuua gcucaucaag 240
caggagcucg	acaaauauaa aaugccguc acggagcugc aguuauugau gcagagcacc 300
caggcgacaa	acaaccgugc acgacgcgag cuaccccgau ucaugaacua caccucuauu 360
aaugcaaaga	agacaaaugu gacgcucucu aagaagcgca agcgucgcuu ucugggcuuu 420
cuucucgggg	uugggagcgc gaucgcaagc ggcguggcug uaucaaaagu gcuucaucuu 480
gagggagaag	ugaauaaaau caaaagugcu cugcuaucua caaacaagc cguuguauc 540
cuguccaacg	gaguguccgu gcucacgucc aaagugcuag auuugaagaa uuacaucgau 600
aagcagcugc	ucccuauugu gaacaaacaa ucauguucca ucaguaacau ugaaacaguc 660
aucgaguuuu	aacagaaaaa caauagacug cuggagauua ccagagaauu uucgguuuac 720
gccggcguga	cuaccccgug aagcaccuac auguugacaa acuccgaacu uuugucacug 780
auaaacgaua	ugccuauuac uaaugaucag aaaaaauuga uguccaauaa uguccaaauc 840
gucaggcaac	aguccuacag uaucaugucu auuauuaagg aggagguccu ugcauacgug 900
gugcaacugc	cauuauacgg agucauugau acucccgugu ggaaacucca uacaagcccc 960
cugugcacua	cuaacacuaa agagggauc aauuuuguc ucacucggac agauagaggu 1020
ugguacugug	auaaugcugg cucaguguca uucuuuccac aggcugaaac cugcaagguu 1080
cagucaaaca	ggguguuuug cgauaccaug aaucucuaa cccuccccag ugaggugaac 1140
cuguguaaag	uggauauauu caacccaag uaugauugua agaucaugac cuccaagacg 1200
gacgugagua	gcaguguuau caccuccug ggggccauug uauccugcua cggaaaaacg 1260
aaauguacug	ccucgaacaa aaauagggga aucauacaaa cuuuuaguaa uggaugcgac 1320
uacguaucua	auaaaggugu ugacacagug ucagucggca acacacugua uuacgugaau 1380
aagcaagaag	ggaagucgcu guauguacaa ggggagccua ucauuuuuuu uuaugaccca 1440

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uccacuacca	acauuaugau	aacuaccauc	aucauaguaa	uaauaguaau	uuuacugucu	1620
cugaucgcug	ugggccuguu	acuguaauugc	aaagcccgcga	guacuccugu	caccuuauca	1680
aaggaccagc	ugucugggau	aaacaacauc	gcguucucca	au		1722

<210> 261
 <211> 1722
 <212> RNA
 <213> Respiratory Syncytial Virus

<400> 261	
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ucuaaaggcu	accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
cucagcaaua	uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
caggaacucg	acaaauauaa aaacgcugug accgagcugc aguuauugau gcagaguaca 300
ccugccacca	auaacagagc uaggagggag uugccuaggu uuaugaacua cacucucaac 360
aacgcgaaaa	aaaccaaugu gacgcuauc aagaaacgga agaggagguu ccuggggguuu 420
cuuuuagggg	ugggcucugc cauugcuucc ggcguggcug uauguaaagu ucuccaccuc 480
gagggagagg	uuauaagau uaagucggcc cugcugagua cuaacaaagc aguggugucg 540
cugaguaacg	gaguaagugu guuaacauuu aaggugcugg accucaagaa uuauauugac 600
aaacaguugc	uuccuauucu aaacaaacag agcuguucaa uaaguaauau ugaaacuguu 660
auugaguuuu	agcagaagaa caacaggcuu cuugagauua cacgcgaguu cagugucaau 720
gccggcguaa	caacacccgu gucuaccuac augcugacga auucugagcu ucucucucuc 780
auaaacgaca	ugcccauuac gaaugaccaa aaaaaacuua uguccaacia cgugcagauu 840
gugcgacagc	aauccuauag cauuauugug aucaucaagg aagagguacu cgcuuauugu 900
gugcagcuac	cacucuaugg ugugauugac acccccuguu ggaagcugca uaccagucca 960
cucugcacca	cuaacacaaa ggaagggagc aaauuuugcc ucacucgaac cgacaggggg 1020
ugguauugcg	auaaugcggg cuccgugucc uucuuuccac aggcugaaac uuguaaggua 1080
cagucaaaacc	gcguguucug ugauacuaug aaucucuga cucuucccag cgagguaau 1140
cucugcaacg	ucgacauuuu caauccuaaa uaugacugca agaucaugac cagcaagacc 1200
gacgucucca	gcucaguaau cacuagccua ggggccauug uaagcugcua uggcaaaacc 1260
aaguguacug	ccucuaauaa gaacagaggc auauuuuuuu cccuuuuaaa uggcugugac 1320
uaugugucga	auaagggcgug cgacacgguc ucaguaggga auaccucua cuacguuaac 1380
aaacaggaag	gcaaaucucu uuauguaaag ggcgagccca ucauaaaauu cuacgaccca 1440
cuuguguucc	ccagugauga auucgaugca ucaaucuccc aggugaacga aaagaucuu 1500

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caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
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uugauugcug	ucgggugcgu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaagaccaac	uuagcgguau	cauaauauu	gccuuuagca	au		1722

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 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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ucuaaagguu	accugucagc ccuuagaaca gggugguaua ccucuguuau uaccauugag 180
uuguccaaca	uuagaagaa caagugcaau ggcacagacg cuaagguuaa gcucaucaag 240
caggagcucg	acaaauauaa aaaugccguc acggagcugc aguuauugau gcagagcacc 300
caggcgacaa	acaaccgugc acgacgcgag cuaccccgau ucaugaacua caccucuau 360
aaugcaaaga	agacaaaugu gacgcucucu aagaagcgca agcgucgcuu ucugggcuuu 420
cuucucgggg	uugggagcgc gaucgcaagc ggcguggcug uaucaaaagu gcuucaucuu 480
gagggagaag	ugaauaaaau caaaagugcu cugcuaucua caaacaagc cguuguauca 540
cuguccaacg	gaguguccgu gcucacgucc aaagugcuag auuugaagaa uuacaucgau 600
aagcagcugc	ucccuauugu gaacaaacaa ucauguucca ucaguaacau ugaaacaguc 660
aucgaguuuu	aacagaaaaa caauagacug cuggagauua ccagagaauu uucgguuuac 720
gccggcguga	cuaccccgug aagcaccuac auguugacaa acuccgaacu uuugucacug 780
auaaacgaua	ugccuauuac uaaugaucag aaaaauuga uguccaauaa uguccaaauc 840
gucaggcaac	aguccuacag uaucaugucu auuauuaagg aggagguccu ugcuaucgug 900
gugcaacugc	cauuauacgg agucauugau acucccgugu ggaaacucca uacaagcccc 960
cugugcacua	cuaacacuaa agagggauca aaauuuuguc ucacucggac agauagaggu 1020
ugguacugug	auaaugcugg cucaguguca uucuuuccac aggcugaaac cugcaagguu 1080
cagucaaaaca	ggguguuuug cgauaccaug aaucucuaa cccuccccag ugaggugaac 1140
cuguguaaag	uggauauauu caaccccaag uaugauugua agaucaugac cuccaagacg 1200
gacgugagua	gcaguguuau caccuccug ggggccauug uauccugcua cggaaaaacg 1260
aaauguacug	ccucgaacaa aaauagggga aucaucaaaa cuuuuaguaa uggaugcgac 1320
uacguaucua	auaaaggugu ugacacagug ucagucggca acacacugua uuacgugaau 1380
aagcaagaag	ggaagucgcu guaugucaa ggggagccua ucauuuuuuu uuaugacca 1440
cugguuuuucc	ccagcgaua guucgacgcc agcauuaguc agguuaauga gaaaaucaac 1500

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caguccuugg	cauuuauucg	uaagagugau	gaauugcucc	auaauuguaa	cgcuuguaaa	1560
uccacuacca	acauuaugau	aacuaccauc	aucauaguaa	uaauaguaau	uuuacugucu	1620
cugaucgcug	ugggccuguu	acuguaauugc	aaagcccgcga	guacuccugu	caccuuauca	1680
aaggaccagc	ugucugggau	aaacaacauc	gcguucucca	au		1722

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 <212> RNA
 <213> Artificial Sequence

<220>
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ucuaaaggcu	accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
cucagcaaua	uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
caggaacucg	acaaauauaa aaacgcugug accgagcugc aguuauugau gcagaguaca 300
ccugccacca	auaacagagc uaggagggag uugccuaggu uuaugaacua cacucucaac 360
aacgcgaaaa	aaaccaaugu gacgcuauc aagaaacgga agaggagguu ccuggggguuu 420
cuuuuagggg	ugggcucugc cauugcuucc ggcguggcug uauguaaagu ucuccaccuc 480
gagggagagg	uuauaagau uaagucggcc cugcugagua cuaacaaagc aguggugucg 540
cugaguaacg	gaguaagugu guuaacauuu aaggugcugg accucaagaa uuauauugac 600
aaacaguugc	uuccuauucu aaacaaacag agcuguucaa uaaguaauau ugaaacuguu 660
auugaguuuu	agcagaagaa caacaggcuu cuugagauua cacgcgaguu cagugucaau 720
gccggcguaa	caacacccgu gucuaccuac augcugacga auucugagcu ucucucucuc 780
auaaacgaca	ugcccauuac gaaugaccaa aaaaaacuua uguccaacia cgugcagauu 840
gugcgacagc	aauccuauag cauuauugug aucaucaagg aagagguacu cgcuuauugu 900
gugcagcuac	cacucuaugg ugugauugac acccccuguu ggaagcugca uaccagucca 960
cucugcacca	cuaacacaaa ggaagggagc aaauuuugcc ucacucgaac cgacaggggg 1020
ugguauugcg	auaaugcggg cuccgugucc uucuuuccac aggcugaaac uuguaaggua 1080
cagucaaacc	gcguguucug ugauacuaug aaucucuga cucuucccag cgagguaau 1140
cucugcaacg	ucgacauuuu caauccuaaa uaugacugca agaucaugac cagcaagacc 1200
gacgucucca	gcucaguaau cacuagccua ggggccauug uaagcugcua uggcaaaacc 1260
aaguguacug	ccucuaauaa gaacagaggc auauuuuuuu cccuuuuaaa uggcugugac 1320
uaugugucga	auaagggcgcu cgacacgguc ucaguaggga auaccucua cuacguuaac 1380
aaacaggaag	gcaaaucucu uuauguaaag ggcgagccca ucauuuuuuu cuacgaccca 1440
cuuguguucc	ccagugauga auucgaugca ucaaucuccc aggugaacga aaagaucuu 1500

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caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
ucuacaacca	acaucaugau	cacuaccauc	auuauuguga	uuaucguaau	ucugcuaucc	1620
uugauugcug	ucgggcugcu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaagaccaac	uuagcggau	cauaauauu	gccuuuagca	au		1722

<210> 264
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 <212> RNA
 <213> Artificial Sequence

<220>
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agcaaagguu	aucugagcgc uuuaagaacu ggcugguaca ccaguguuau uacuauagag 180
cugucaaaau	uuaaaaagaa uaaaugcaac gggaccgaug ccaaaguaaa auuaauaag 240
caggaauugg	acaaguauaa gaaugcagug acagaguugc agcuccugau gcagagcaca 300
caagcuacaa	acaauccgcgc ucgccagcag caacagcggg uuuuaggggu ccugcuaggg 360
guggggucag	ccauugccuc uggaguggca guguccaaag ugcugcaucu ggaaggggaa 420
guuaacaaga	uaaaauccgc acuccucagc accaauaaag ccguggucuc ccuguccaau 480
ggaguauacg	uuuugacaag caaggugcug gaccugaaga auuauauaga uaagcaguua 540
cugccaauag	ugaauaaaca gucaugcuca auuagcaaca uugagacagu uaucgaauuc 600
cagcagaaaa	auaaauaggcu ucuggaaaua acucgcgaau ucucaguaaa ugccggagug 660
accacacccg	uauccgacuua uaugcuuaca aacucugaac uguuguccuu gauuaacgau 720
augccaauaa	caaauagacca gaagaagcua augagcaaca augugcagau uguaagacag 780
cagucuuacu	caauaauguc uauaauaaaa gaggaggugu uggcauangu ggugcaacug 840
ccucucuau	gugugaucga uacuccuugc uggaaguuaac auacaucucc acuguguaca 900
acuaauacua	aggagggugag caauuuugu cugacacgca cagaucgggg uugguauugc 960
gacaacgcgg	gcagugugag cuuuuucccu caggccgaaa ccuguaaggu ucaaucuaau 1020
cggguauuuu	gcgacacaau gaacagccug acccuuccgu ccgaaguuaa uuugugcaac 1080
gucgacaucu	ucaauccuaa auaugacugc aaaaucauga cuucuaaaac cgacguaucc 1140
agcucaguga	uaacaagccu uggggcauu guaaugcugcu auggcaagac gaagugcacc 1200
gcuaguaaca	agaaccgggg gauuauuaag acuuuuucga acggaugcga uuacgucucc 1260
aacaaaggcg	ucgauacugu guccguggga aacaccucuc acuaugugaa caagcaggaa 1320
ggcaaaagcc	ucuacgucaa aggagagccu aucaucauu ucuacgaccc ucuaguauuc 1380
ccuucagacg	auuuugacgc aucauuuucc caggugaacg agaaaauaaa ucaaagcuua 1440
gccuuuaucc	gcaagaguga ugaguugcuu cacaacguca acgccggcaa aucaaccacu 1500

aau

1503

<210> 265
 <211> 1563
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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 ugcuucgcca gcggacagaa uauuacggag gaguuuuaua aaucuaaccug uagugccgug 120
 agcaaggggu accugucugc ccugaggacg ggaugguaca cauccgugau caccaucgag 180
 uugucuaaca uuaaaaagaa caagugcaac ggaacugacg ccaaggugaa gcucauuuag 240
 caagagcucg acaauauuaa gaaugcgguu acagaacuac agcuacuaau gcaguccaca 300
 caggcaacca auaaccgagc acgucagcag cagcaacgcu uccuuggcuu ccugcucggg 360
 guuggcucgg caauugcauc cggaguggcu guuuccaagg uuuugcaccu ugagggagag 420
 gucaauaaga ucaagagcgc ccuccuguca acuaauaagg ccguggucag ccuuuccaac 480
 gguguuucug uguuaaccuc aaaagugcuc gaccuuaaaa acuaauaucga uaagcagcug 540
 cugcccuaug ugaacaaaca guccuguucu aucaguaaua ucgagacagu gaucgaauuc 600
 cagcagaaga acaaucgucu gcuggaaauu acaagggagu ucagcguaaa cgcuggaguc 660
 acaacccccg uguccacuua caugcugacc aaauccgagc ugcugaguuu gauuaaugau 720
 augcccuaau cgaacgauc gaagaaacug augucgaaua auguucagau cguuaggcag 780
 cagucuuaua gcaucaugag uauuaucaaa gaggaggucc ucgccuaugu gguucagcug 840
 ccucucuacg gcguuauaga caccucaugc uggaagcuuc acaccucucc ucuguguacg 900
 accaauacaa aggagggcuc aaacauuugc cuuacccgca cagauagagg augguacugc 960
 gauaaugcug gcucuguguc uuucuuuccu caggccgaaa cauguaaggu acaguccaau 1020
 aggguauiuu gcgacaccau gaacuccua accuuaccaa gugaagugaa ccucugcaau 1080
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 aguaguguga uuaccucacu gggcgcaauc guuucaugcu augggaagac aaagugcacc 1200
 gcaagcaaca agaaucgggg caucaucaa accuucagua acggguuguga cuauguuua 1260
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 gggaaauac ucguaugugaa aggugagccg aucauuuacu uuucgaccc ucucguguuu 1380
 cccuccgaug aguucgacgc auccaucagu caggucaaug agaaaaucac ccaaucucuc 1440
 gccuucuuu gaaaaucuga cgaauuacug agugccauug gaggauauu uccggaggcu 1500
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 cua 1563

<210> 266

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<211> 1692

<212> RNA

<213> Artificial Sequence

<220>

<223> Synthetic Polynucleotide

<400> 266

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ucaaaggggu auuuauCagc acugagaacc gguugguaua ccaguguuau uacaauagag      180
cugaguaaca uaaaggagaa uaagugcaac ggcacugacg ccaaggucAA gcucauCAAA      240
caggaacucg auaaaAucaa gaacgcuguc acugaacugc agcugcugau gcaaagcacc      300
cccgccacca acaauagggc ccgcagagag cuuccuagau uuaugaacua cacucugaac      360
aacgccAAAA agaccaaugu aacacuguca aagaaacaga aacagcaggc uauugcaagc      420
gguguggcug ugucuaaagu gcugcaucuc gagggggagg ucaacaagau caaaucgcga      480
uugcucagca ccaacaaggc uguggugagc cuguccaauG gugucucagu gcucaccagc      540
aaagugcugg accugaagaa uuauauugau aagcagcugc uaccCAUagu caacaaacag      600
ucaugcucca uaucuaauau ugagacuguc aucgaguucc aacagaagaa caaucgccug      660
cuggagauua ccagggaguu cucagucAAU gccgggguca cgacacccgu uaguacuuau      720
augcuuacca acuccgagcu ucucucuUUG aucaaugaca ugccaauuac uaacgaccag      780
aagaaguuga ugucuaacaa uguacagauc guucgccagc aguccuauuc cauuaugucg      840
auuauuaaag aggagguucu ugcauacguc gugcaguugc cauuauagg agucaucgac      900
acccccugcu ggaaacugca uacgucacca uuaugcacca cgaauacaaa ggagggcagu      960
aaauuuuguc uuacacggac ugaucgaggc ugguaauugug auaacgcagg cucgguguca      1020
uucuuuccac aggcugaaac cuguaaggug caaucuaaua ggguguuuug cgauaccaug      1080
aauucucuga cucugcccag ugaggucaau uuguguaacg uggacaucuu caacccaaag      1140
uacgacugca agaucaugac aucuaagaca gaugugucau ccagcguuau cacgagccuc      1200
ggcgcuauag ucuccuguua cggcaagacc aagugcaccg cuagcaacaa gaaucgggga      1260
aucauCAAAA cUUUUucuaa cgguugugac uacgugagca acaaggggggU ggauaccguc      1320
ucagucggua acaccCUGua cuacgugaau aaacaggagg ggaagucauu guacgugaag      1380
ggugaaccua ucaucaacuu uuauGacccc cucgucuucc caucagacga guuugacgcg      1440
uccaucucuc aggugaauga gaagauuAAC cagagccugg CUUUUauccg caaaucagac      1500
gaacuacugc acaaugucaa cgcuggcaag agcacaacaa auauaaugau aacaaccauc      1560
aucaucguca uuauugugau cuuguuauca cugaucgcug uggggcuccu cUUUUauugc      1620
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gcguuuagca ac                                     1692

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<210> 267

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<211> 1539
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 267
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 ucgaaagguu accucagcgc gcuuaggaca ggaugguaua ccuccguuau cacgauugaa 180
 cugaguaaau ucaaggaaaa caaguguaac ggaacagacg ccaaggucua acuuauuaaa 240
 caagaacugg acaaguauaa gucugcagug accgaauugc agcuccugau gcagaguacc 300
 ccugcaacua acaacaaguu uuugggcuuu cugcaaggcg uggguagcgc gaucgccucc 360
 ggaaucgcgg ucuccaaagu guugcaccug gagggagaag uuaacaagau caaauccggcu 420
 cuguugagua ccaacaaggc agugguguca cugagcaacg guguaagcgu guuaacaagc 480
 aagguaauug acuuuaagaa cuauauugac aaacagcugc ucccacugcu gaacaaacag 540
 agcugcucaa ucuccaaau agagacggug auagaguucc agcaaaaaaa uauucggcuc 600
 cuugagauca cccgcgaauu cucaguuaau gccggcgua caacuccggu gcuuacauac 660
 augcugacca acucggagcu guuaucuuu auaaaugaca ugcccacac caaugaucaa 720
 aaaaaacuga ugucaauuaa cguccagaua guaagacagc agagcuacag caucaugucg 780
 auuaucaaag aggaggugcu ggcguacgug gucgagcugc ccuguaugg ggugauugac 840
 accccuuguu ggaagcugca caccuccca cuauguacua ccaauaccaa agaaggaucc 900
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 uacgauugca aaauuugac gucaaaaacc gaugucaguu caagcguuau caccagcuug 1140
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 auaauuaaga cauucagcaa uggugcgac uacguaucaa auaagggugu cgacaccguu 1260
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 gagaacgaga ucgccaggau caaaaagcuu auuggggag 1539

<210> 268
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 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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 aucacacuca gcauccuggc aaugauuuu ucaacaucucc ugaucuaugc cgcaaucaua 180
 uuuaucgccu cagcaaauc acaaguuacc ccgaccacag ccauuaucca ggacgcuaca 240
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 ccauccaacc cuuccgagau caccucuaa aucaccacca uucucgccc uacuacccc 360
 ggaguaaaga gcacucuuca gagcacaacc guuaaaacua aaaauaccac caccacucag 420
 acucagccuu cgaaaccaac gacuaaacag cggcaaaaau agccuccauc caaacgaa 480
 aacgacuuuc auuucgaagu cuuuacuuc gugccaugca guauuugcuc caauaauccu 540
 acuugcuggg cuaucugcaa gagaauccu aacaagaagc cuggaaagaa gacaacgaca 600
 aagccaacua agaagccgac acuaaagacu accaaaaag acccuaagcc gcagacuacc 660
 aagagcaagg agguuccac aaccaagccu acagaggagc cgacuauua cacaacaaag 720
 accaacauc ucaccacccu gcuuacuuc aaauacuacc gaaaccaga gcugacgucc 780
 cagauggaga cguuccauuc cacaucucc gaagggaauc cuaguccag ccaggugagc 840
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 <212> RNA
 <213> Artificial Sequence

<220>
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 aagggcuacc uuagugcauu acgaaccggg ugguaucga guguaaucac cauugagcug 180
 uccaacauc agaagaaca gugcaauagg acugaugcca aggugaaacu uaucaaaaa 240
 gagcucgaca aguauaagaa cgccgugacc gaacuacaac uccugaugca aucgacucag 300
 gcuacuaaca acagagcucg gagggagcug cccagauuca ugaauuuauac cuuaaacaac 360
 gcuaaaaaaa caaauugac ccugaguaag aagcggaac gaagguuccu gggcuuccug 420
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 ggugagguca auuagauca guccgcucuc cucucuacca acaaggcagu ggugagccug 540
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 cagcugcugc cuauugugaa uaagcauucc ugcaguauc ccaacauuga gacagugauu 660
 gaauuucagc aaaagaaca ucguuuguug gagauaaca gagaauucag uguuaauggc 720
 ggcguuacca cucccguguc gacauacug cuaacaaaau gcgagcugcu aucucuaau 780

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aggcagcagu	ccuacagcau	uauagcaua	auuaaagagg	aaguguuggc	uuacgucguc	900
cagcuuccac	uguauggcgu	gaucgauacc	ccuuguugga	agcugcauac	uucccccccuu	960
uguacaacua	auaccaaaga	agggaguaau	auaugccuca	caaggacuga	cagaggcugg	1020
uacugcgaca	acgccgggag	cgucagcuuu	uucccgagg	ccgagacaug	uaaggugcag	1080
agcaaccgug	ucuuuugcga	caccaugaau	agccugacuu	ugccaaguga	ggucaaccuu	1140
ugcaacgugg	auauuuuuua	cccuaaguac	gauuguaaga	uaaugacauc	caaaaccgau	1200
guuaguagcu	ccgugaucac	uucgcugggu	gcgauaguua	gcugcuauug	aaagacaaag	1260
uguaccgcaa	guaacaagaa	ccgcgggauu	auuaaaacau	uuagcaaugg	gugcgacuac	1320
guaucaaaaca	agggggugga	uacagucagc	gugggaaaca	cacuuuacua	cguuaacaag	1380
caggaaggga	aaucccuuuu	ugugaaggga	gaaccaauua	ucaacuuiua	ugaucuccuc	1440
guguuuuccaa	gugaugaauu	cgacgcaagc	aucucgcagg	ugaacgagaa	aaucaaucag	1500
agucuagcuu	ucauaaggaa	gucugaugaa	cugcuuagug	ccauuggcg	guacauaccg	1560
gaagccccac	gcgacgguca	ggcuuacgug	aggaaggacg	gagagugggu	ucugcugucc	1620
acuuuccuu						1629

<210> 270
 <211> 1629
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 270	
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gcuguuuuug	cuccuccuau
ggcugccgga	uaccaccggc
	60
uuugccucug	gacagaacau
uaccgaggaa	uucuaucagu
cgacuuguuc	cgagucucg
	120
aagggguacc	ugagugcccu
gcgcaccggg	ugguacacca
guguuauac	uauugagcug
	180
uccaacaaua	aagaaaauaa
guguaaugga	acugacgcga
aggugaaguu	gauaaaacag
	240
gagcuggaua	aaucacagaa
ugcagugacc	gaacugcagc
uccugaugca	guccacucca
	300
gcaacaaaua	aucgcgcgag
acgcgaacuc	ccccgcuuuu
ugaacuacac	ucugaauauu
	360
gcgaagaaaa	cgaauugugac
acuaaguaag	aaaagaaaac
ggcgauuucu	uggguuccug
	420
cucggggugg	gaucugccau
agcaagcggg	guggcgguau
guaaaguccu	ucaccuagaa
	480
ggggagguga	acaaaauuaa
gagugcccug	cugagcacca
acaaggcugu	gguuucacug
	540
ucaaaccggag	uaagcgugcu
aacauuuuaa	gucuuggacc
ugaagaauua	uauugacaag
	600
cagcuccugc	ccauucucua
caaacaguca	uguuccauua
gcaacaucga	aacagucuuu
	660
gaguuuacgc	aaaaaaacaa
ccgccuccuu	gagauuacgc
gugaguuuuc	cguaaagcuu
	720
ggagucacga	caccgguguc
cacuuacaug	cugacuaaca
gcgaacuccu	gagccuaauc
	780
aaugacaugc	ccauuacuaa
cgaccagaaa	aaauugaugu
ccaauaacgu	gcagauaugu
	840

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cgccagcaau	cuuacuccau	aaugugcauu	aucaaggagg	aaguccuggc	guacguuguu	900
cagcugccgc	uguauuggugu	gauagauacg	ccaugcugga	aacugcacac	aucccccuu	960
ugcacaacga	auacuaaaga	gggaaguaac	auuugcuuga	ccagaacaga	ucggggcugg	1020
uacugcgaca	acgcugguag	ugugucauuu	uucccccagg	cagaaacgug	uaaaguccag	1080
agcaaucgcg	uguucugcga	cacaaugaac	ucacuuacuu	ugcccucaga	ggucaauuug	1140
uguaaugugg	auaucuucaa	cccgaauac	gauuguaaga	uuauagcgag	caaaacagac	1200
gugucuucan	cagugauaac	aagucugggc	gcaauagugu	caugcuauug	uaagacuaag	1260
ugcacugccu	ccaauaaaaa	ccgcggcauc	aucaagacau	uuucaaaugg	augcgacuac	1320
gugucaaaca	agggcgucga	cacaguaagc	guugggaaca	cccuauacua	cguaacaag	1380
caggagggga	aaagccuaua	cgugaaaggc	gagccaauca	ucaauuucua	cgauccacug	1440
gucuuuccaa	gugacgaauu	ugaugccagc	auaucgcagg	ugaacgagaa	aaauaaucag	1500
ucacucgccu	ucaucaggaa	gucagaugag	cugcuguccg	ccaucggagg	auacauucca	1560
gaagccccac	gcgacggcca	ggcauacgug	cggaaggacg	gcgaauuggu	ccuuuugagc	1620
acuuuucua						1629

<210> 271
 <211> 1500
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 271	
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uucgcuucgg	gucagaauau uacagaggag uucuacaaa guacuugcuc ugcagucucc 120
aagggaauacc	uguccgcucu gcggacggga ugguauacca guguuauaac gaucgaguug 180
agcaacauca	agaagaacaa auguaaugga acagaugcca aggugaaacu gaucaaacag 240
gaguuggaua	aaauaaagaa ugcugucacc gaacugcagc uauugaugca guccacccag 300
gcuaccaaca	accggggccag gcagcaacaa cagagauuuu ugguuuucuu gcugggpcgug 360
gggucugcca	ucgcuucagg gguggccgug aguaaagucc ugcaccugga aggcgaaguc 420
aacaagauca	agucugcauu acuaaguacc aaauaaggcug uaguuaagccu guccaauggc 480
gugagugugc	uuacuucuaa gguacuggac cugaagaacu acaucgacaa gcaacuacua 540
cccauuguaa	auaagcaguc auguagcaua ucaaacaucg agacagugau cgaauuucua 600
cagaagaaua	accgggcuguu ggagauaaca cgggaguucu cuguaaaugc cggcgugacg 660
accccgugca	gcaccuacau gcucacgaau agcgaguugc uuucccugau uaaugauaug 720
ccgauuacaa	augaccagaa gaagcugaug aguaauaauug uccaaaauugu ccgucagcag 780
agcuauucga	uuauuguccau caucaaggag gaagucuuag ccuauguggu gcagcucucc 840
cucuacggag	ugauugacac accgugcugg aagcugcaca ccuccccuuu guguaacaacc 900

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aauaccaagg	aggggcucaa	caucugccuu	acuaggaccg	acaggggaug	guauugcgac	960
aacgccgggu	ccgucucauu	uuuuccucag	gcggaaaccu	guaagguaca	gucgaauca	1020
guguuuugug	acacuaugaa	cagccugacc	uugccuagcg	aggugaauca	guguaacguu	1080
gauaucuuca	acccuaagua	ugacuguaag	aucaugacuu	caaaaacuga	ugucuccuca	1140
agcgugauca	ccucuuuggg	cgccaucgug	ucaugcuacg	gaaagacgaa	gugcaccgcc	1200
ucuaacaaga	accgagggau	caucaaaaca	uucuccaau	gcugugauua	cgucaguaac	1260
aaaggugugg	acacagucuc	cgugggcaau	acguuauuu	augugaauaa	gcaggagggg	1320
aaaagucucu	augugaaggg	ugaaccgaua	aucauuuucu	acgauccuuu	gguguuucca	1380
agcgacgagu	ucgacgccuc	gaucagccag	gugaacgaga	aaaaucaacca	gucuuuggca	1440
uucauccgca	agagcgacga	gcuacugcau	aacgugaacg	caggcaagag	uacuaccaau	1500

<210> 272
 <211> 1560
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 272	
auggagacuc	ccgcucaguu guuguuccug cuacugcugu ggcugccuga uacaaccgga 60
uuugcuagug	ggcagaauau caccgaagaa uucuaucaga gcacuugcag ugcagugucc 120
aaaggauauu	ugagcgcccu gcgcacuggg ugguacacaa gugucaucac aaucgagcua 180
aguaacauua	aaaaaaacaa augcaacggg acugacgcaa aggucaaacu cauaaagcaa 240
gaacuugaca	aaauaaagaa cgcuguuaca gaguugcagc ugcuaaugca aagcacucag 300
gcuaccaaua	accgagcgag acagcagcag caacguuucc ugguuuuccu guuaggugug 360
gguagcgcaa	uugccagugg uguagccgug uccaaggugc ugcaccugga aggggaagug 420
aaauagauca	agucugcacu gcuguccacc aaauaggcgg ucguuucgcu gucuaacggc 480
gucucggucc	uaacaaguua aguucuggau uuaaagaacu auauugauaa gcaauugcug 540
ccuaucguaa	auaagcagag uugcagcauu agcaauaucg agacagugau agaauuucag 600
caaaagaaca	aucgauuacu cgaaucaca cgcgaaauca gugucaaugc cgggguuaca 660
accccugugu	cgaccuacau gcuuaccaau uccgagcuuc ugucucuau uaacgauaug 720
cccaucacga	acgaucagaa gaaacugaug ucaaaauacg uccaaauugu gcggcagcaa 780
agcuacagua	ucaugagcau caucaaagag gaggugcucg ccuauugguu ccaauugccg 840
cuauacgggg	ucauugauac acccuguugg aagcuccaua cauccccacu uuguacaacg 900
aauaccaagg	aggggucuaa cauuugucug acccggaccg acagaggcug guauugcgau 960
aaugcuggaa	gcguuaguuu cuuuccucag gcagaaacau gcaaggugca gucaaacaga 1020
guuuucugug	acaccaugaa uuuccuugacg cugccuucag aagugaauca guguaacgug 1080
gauaucuuua	auccgaagua cgauuguaaa auuaugacua gcaagacaga ugucucgucc 1140

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ucugugauca	cuagccuggg	agcgauugug	agcuguuauug	guaaaacaaa	guguacugcu	1200
agcaauaaga	acagggggau	uaucaaaacg	uucaguaacg	gcugugauua	cguauccaac	1260
aagggggugg	acaccguguc	agucgggaac	acgcucuacu	acgugaacaa	gcaggaaggu	1320
aagucgcuau	acgugaaggg	ggaacccaau	aucaauuucu	acgauccgcu	cguguuuccu	1380
agcgacgaau	ucgacgcauc	uauagccag	gugaacgaga	agaucuuca	gagucuggcc	1440
uucauccgca	aguccgacga	gcugcuuagu	gcuaucggag	guuauauccc	ugaggccccc	1500
agggacggcc	aagcguaugu	gagaaaggac	ggggaauggg	uacuguuguc	aacuuuccua	1560

<210> 273
 <211> 1536
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 273	
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uucgcaucuu	cacaaaacau cacggaagag uuuuaccaga gcacaugcuc cgcgguucucu 120
aaaggcuau	uuucugcccu gcggaucggc ugguauacca gcgucaucac cauagagcug 180
ucaaacauc	aggagaacaa guguaacggc acugacgcca aggucaagcu uauaaagcag 240
gaacuggaca	aguauaagag ugcuguuacc gagcuccagu ugcuuauugca guccaccccc 300
gcaacaaaca	auaaaauucu gggcuuucua cagggcgucg gaagcgccau cgcaagcggc 360
aucgcuguga	gcaagguguu gcaucuggag ggagagguga auaagauaaa gagugcucug 420
cuuuccacua	acaaagccgu ggugagccug agcaauaggc uaucuguucu gacuucuaaa 480
guccuggauc	ucaagaacua uaucgacaag cagcucuugc ccuauuguaa caaacagucc 540
ugcuccauuu	ccaauauuga gaccgucuu gaguuccaac agaagaauaa ccguuugcug 600
gaaauuacaa	gggaauucag uguuaaugcc gguguaacca cccugugag caccuauaug 660
cucaccaacu	cugaacugcu gagucugauu aacgauaugc ccuauacuaa ugaucagaag 720
aaacuaauga	guaacaauu ccagauaguu cggcagcagu cauauuccau uaugaguaua 780
aucaaggagg	aagugcuagc cuacguagu cagcucuccc ucuacggcg uauagacacg 840
ccauguugga	agcugcauac gaguccucug ugcacuacaa auaccaagga gggcaguaac 900
auaugcuuga	cuagaacuga uagaggcugg uacugcgaca augcaggcuc cgugucauuc 960
uuuccucucg	ccgagacgug uaaagugcag aguaacagag uguuuuguga cacaauaac 1020
ucauugaccc	ugccuagcga agugaacuua ugcaacaucg acuuuuuuua cccaaaauac 1080
gauugcaaga	uuauagaccuc uaagacugac guaucuucuu ccgucauac uucucuagga 1140
gcgaucguga	gcugcuacgg uaagacuaaa ugcacggcu gaaauaaaa uagagguauc 1200
auuaagacuu	uuaguaacgg uugcgauuu gugucuaaca agggagucga cacuguuuc 1260
gugggcaaua	cucucuacua cguaaacaaa caggagggua aaucuuuuu ugugaaaggg 1320

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gaaccca	uca	uuuuuuuu	ugacccacuu	guguuuccua	gugacgaguu	ugacgcuuca	1380
aucagucaag	ugaacgaaaa	aauuuauaggc	acgcucgcgu	uuaucaaggaa	aagcgacgag		1440
aagcugcaua	acguggaaga	uaagaucgag	gagauucucu	cgaaaauuua	ucauauagag		1500
aaugaaaucg	caagaaucaa	aaagcuuauu	ggggag				1536

<210> 274
 <211> 1632
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 274	
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ugcuucgccu	ccggggcagaa caucaccgag gaguucuacc agucuacgug cuccgcccugc 120
uccaaagguu	accuguccgc auuaaggacg gggugguaca cuuccgucau aacuaauugaa 180
cugaguaaca	uaaaaaagaa caaguguaau gggacggaug ccaaggugaa gcucaucaag 240
caagagcuug	acaaauacaa gaaugcagug acagagcucc aacuucucau gcagucuaca 300
caggccacga	auaaccgugc ccgaagagaa cugccuagau uuaugaaaua cacuuugaac 360
aacgccaaaa	agaccaacgu gacucuaagc aaaaaaagga aacggcguuu ucugggcuuu 420
cugcuggggg	uugguagcgc caucgcaucu ggcguggcag ucaguaaagu uuugcaccuu 480
gagggggagg	ucaacaaaau caagagcgcg cuguuaucaa caaacaaggc agucgugucc 540
cucuccaaug	gcgugucugu ccugaccucu aaaguacugg aucucaagaa cuauaucgac 600
aaacaacugc	uaccaauvcu cauaagcag aguugcucua uuuccaauau ugagaccgug 660
aucgaguuuu	aacagaagaa uaacagauug uuggagauca ccagggaauu cagcgucaau 720
gcaggggguga	ccacacccgu aucuaccuac augcugacca acucggaacu ccucuccuua 780
auaaacgaca	ugccuauuac uaacgacca aaaaaguuga uguccaaca uguccagauc 840
gugcgacagc	aaucuuauuc aaauaugucc auuauaaaag aggaggugcu ggcguacgua 900
gugcagcugc	ccuuuacgg agugaucgac accccaugcu ggaagcucca caccuccccc 960
cugugcacca	cuaauaccaa agaaggcagc acaucuguc ugacccguac cgaccgcgga 1020
ugguacugcg	auaauvcagg uagcgucucu uuuuuucccc aggcugaaac uugcaagguu 1080
caguccaacc	ggguauucug ugacacgaug aacagucua cccuaccuac agaggugaac 1140
cugugcaaug	uggacauuu uaaccuuaaa uaugacugua agaucaugac cuccaaaacu 1200
gacguuucca	gcagugucau aaccucacug ggcgcaauag uuucaugcua uggaaagacu 1260
aagugcacug	ccucuaacaa aaucgaggu auuauuaaga ccuuuagcaa uggcugcgau 1320
uauugcagua	acaaaggugu ugauacagug agugugggca acacauuaa cuauguuaac 1380
aagcaagaag	gcaagagccu cuaugugaag ggagaaccaa ucauuuuuu uuacgauccg 1440
cuggucuuuc	ccagcgaua guucgaugca uccaucucuc aggugaauga aaaaauuac 1500

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caaucacugg	cuuucacg	gaagagcgau	gaacugcuga	gcgccaucgg	gggauacauc	1560
ccugaagcuc	cgaggacgg	ccaagcuuau	guccgcaaag	acggagagug	gguguugcuc	1620
aguaccuucc	uc					1632

<210> 275
 <211> 1632
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

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auggaacugc	ugauucuuaa ggcgaaugcc auaaccacua ucuugaccgc aguuacuuuu 60
ugcuucgccu	cugggcagaa uauuaccgaa gaguucuacc aguccacgug cagugccgug 120
ucuaagggcu	accuuuccgc gcuucgcacu ggcugguaca cgucagucac aacgaucgaa 180
cucucuaaau	uaaaggaaaa uaaguguaac ggaacagacg cuaaggucac guuaaucaag 240
caggagcugg	acaaauauaa gaaugccgua acggagcucc agcugcucac gcagagcacg 300
ccagcuacaa	acaacagggc acgccgugag cucccccga uuaugaacua cacauugaac 360
aacgccaaag	aaacuaacgu gacuuugucc aagaagagga agcggcgauu cuuagggguu 420
cuuuuggggg	uaggcucggc gauugccagu gggguugccg uaugcaaggu gcuccaccug 480
gaaggggagg	ugaacaagau uaagucggcu cugcucagua caaacaagc ugucgucua 540
uugucaaacg	gagucagugu auugacauuu aaaguccucg accugaagaa cuauauagau 600
aaacaguuac	ucccaaucuu gaauaagcag uccuguagca ucagcaacau ugagacagug 660
aucgaguucc	agcagaagaa uaaucgccua cugcagauca ccagagaauu cucagucacu 720
gccggaguaa	ccacuccugu cagcacauac augcucacaa acucugaacu ccuaagccug 780
auuaaugaua	ugccuauac aaaugaucag aagaaacuca ugagcaauaa ugugcagauu 840
guaagacagc	agaguuauuc uauaauuguu auuauuaagg aggagguacu ggccuauug 900
guucaacuuc	cucuguaugg ggugauagau acaccaugcu ggaagcugca caccagccca 960
cuguguacga	ccaauacaaa ggagggcucc aaauuuugcu uaacacggac ugaccggggg 1020
ugguauugcg	acaaugccgg aucagucucc uucuuccccc aagcagagac cugcaaggug 1080
caguccaaua	gaguuuucug cgacacaau aacucgcuga cccuaccuag cgaaguuuac 1140
uuauugcaacg	uggauuuuu uauuccgaag uauauugua aaaucaugac uagcaaaacg 1200
gauguuagcu	ccagcguaau caccuccua ggcgcuaucg ugagcuguua uggcaagacg 1260
aagugcacug	caucuaauaa aaauaggggu auuauuuuuu ccuucagcaa uggcugcgac 1320
uauugagca	auaagggcgu ggacaccgug ucagugggaa acaccucua uauugugaac 1380
aagcaggagg	gaaaaucccu uuauguaaag ggcgaaccca uuaucuuuu cuauagcccc 1440
cugguuuucc	caagcgacga guucgacgca ucuauucuc aagugaacga gaaaaucaau 1500
cagagucuug	ccuuuauacg aaaaucggau gagcugcuuu ccgccaucgg uggcuauauc 1560

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ccagaagccc caagagacgg acaagcguac guccggaaag auggugagug gguccuccuc 1620
 ucuaccuuuc uu 1632

<210> 276
 <211> 813
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 276
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 uccuccuca ccgaggugga aacauacgug cuguccauca uaccauccgg gcccuugaaa 120
 gccgagaucg cccagagacu cgaaucugua uucgcaggaa agaacacgga uuuggaggca 180
 cuaauggaau ggcuagaagac ccguccgauc cugucuccuc ucacaaaggg gauucuugga 240
 uuugucuuua cccucaccgu cccgagcgag cgcggucucc agcgcagacg uuuuguacag 300
 aaugcacuga auggcaacgg cgaucccaau acauggauc gugcgguaaa gcuuuauaaa 360
 aagcugaaga gagaaucac uuuccauggg gcuaaagagg ugagucucuc cuauucaacc 420
 ggggcauugg ccucuugcau gggucuuua uacaaucgaa ugggcaccgu uaccaccgag 480
 gccgcauuug gucugguuug ugcuacgugc gagcaaacg cagauagcca gcaucggucc 540
 caucggcgaga uggccaccac uacgaaccu cuaauucgac augaaaucg caugguccug 600
 gcuagcacca cgcgaaggc aauggagcag auggcgggcu cuagugaaca ggcagccgag 660
 gcaauggaag uggccaauca gaccaggcag augguccaug cuaugcggac uauugguacc 720
 caccgucca gcagugcugg acugaaggau gaccuccuug agaaccugca ggcauaccag 780
 aaacgaauug gggugcaau gcagagauuc aag 813

<210> 277
 <211> 1722
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 277
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 uguuuugccu caggccagaa cauaaccgag gaguuuauc aaucuacaug cagcgcugua 120
 ucuaaaggcu accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
 cucagcaaua uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
 caggaacucg acaaaauaaa aaacgcugug accgagcugc aguuaugau gcagaguaca 300
 ccugccacca auaacagagc uaggaggag uugccuaggu uuaugaacua cacucucaac 360
 aacgcgaaaa aaaccaaugu gacgcuauc aagaaacgga agaggagguu ccugggguuu 420
 cuuuuagggg ugggcucugc cauugcuucc ggcguggcug uauguaagu ucuccaccuc 480

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gagggagagg	uuauaagau	uaagucggcc	cugcugagua	cuaacaaagc	aguggugucg	540
cugaguaacg	gaguaagugu	guuaacauuu	aaggugcugg	accucaagaa	uuauauugac	600
aaacaguugc	uuccuauucu	aaacaaacag	agcuguucaa	uaaguaauau	ugaaacuguu	660
auugaguuuc	agcagaagaa	caacaggcuu	cuugagauua	cacgcgaguu	cagugucaau	720
gccggcguaa	caacacccgu	gucuaccuac	augcugacga	auucugagcu	ucucucucuc	780
auaaacgaca	ugcccauuac	gaaugaccaa	aaaaaacuua	uguccaacia	cgugcagauu	840
gugcgacagc	aauccuauag	cauuauugugu	aucaucaagg	aagagguacu	cgcuuauugu	900
gugcagcuac	cacucuaugg	ugugauugac	acccccuguu	ggaagcugca	uaccagucca	960
cucugcacca	cuaacacaaa	ggaagggagc	aaauuuugcc	ucacucgaac	cgacaggggg	1020
ugguauugcg	auaauugcgg	cuccgugucc	uucuuuccac	aggcugaaac	uuguaaggua	1080
cagucaaacc	guguguucug	ugauacuau	aaucucugca	cucuucccag	cgagguuaau	1140
cucugcaacg	ucgacauuuu	caauccuaaa	uaugacugca	agaucaugac	cagcaagacc	1200
gacgucucca	gcucaguaau	cacuagccua	ggggccauug	uaagcugcua	uggcaaaacc	1260
aaguguacug	ccucuaauaa	gaacagaggc	auaaauaaaa	ccuuuucaaa	uggcugugac	1320
uaugugucga	auaagggcgu	cgacacgguc	ucaguaggga	auaccucua	cuacguuaac	1380
aaacaggaag	gcaaaucccu	uuauguaaa	ggcgagccca	ucauaaaauu	cuacgaccca	1440
cuuguguucc	ccagugauga	auucgaugca	ucaaucuccc	aggugaacga	aaagaucaau	1500
caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
ucuacaacca	acaucaugau	cacuaccauc	auuuuuguga	uuauuguaau	ucugcuaucc	1620
uugauugcug	ucgggcugcu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaagaccaac	uuagcgguau	cauaauauu	gccuuuagca	au		1722

<210> 278
 <211> 1722
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 278	
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uguuuugccu	caggccagaa cauaaccgag gaguuuuauc aaucuaaug cagcgugua 120
ucuaaaggcu	accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
cucagcaaua	uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
caggaacucg	acaaauauaa gaacgcugug accgagcugc aguuaauugau gcagaguaca 300
ccugccacca	auaacagagc uaggagggag uugccuaggu uuaugaacua cacucucaac 360
aacgcgaaga	agaccaaugu gacgcuauc aagaaacgga agaggagguu ccugggguuu 420
cuuuuagggg	ugggcucugc cauugcuucc ggcguggcug uauguaaagu ucuccaccuc 480

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gagggagagg	uuauaagau	uaagucggcc	cugcugagua	cuaacaaagc	aguggugucg	540
cugaguaacg	gaguaagugu	guuaacauuu	aaggugcugg	accucaagaa	uuauauugac	600
aaacaguugc	uuccuauucu	aaacaaacag	agcuguucaa	uaaguaauau	ugaaacuguu	660
auugaguuuc	agcagaagaa	caacaggcuu	cuugagauua	cacgcgaguu	cagugucaau	720
gccggcguaa	caacacccgu	gucuaccuac	augcugacga	auucugagcu	ucucucucuc	780
auaaacgaca	ugcccauuac	gaaugaccaa	aagaaacuua	uguccaacia	cgugcagauu	840
gugcgacagc	aauccuauag	cauuauugugu	aucaucaagg	aagagguacu	cgcuuauugu	900
gugcagcuac	cacucuaugg	ugugauugac	acccccuguu	ggaagcugca	uaccagucca	960
cucugcacca	cuaacacaaa	ggaagggagc	aaauuuugcc	ucacucgaac	cgacaggggg	1020
ugguauugcg	auaauugcggg	cuccgugucc	uucuuuccac	aggcugaaac	uuguaaggua	1080
cagucacacc	gcguguucug	ugauacuau	aaucucuga	cucuucccag	cgagguuaau	1140
cucugcaacg	ucgacauuuu	caauccuaaa	uaugacugca	agaucaugac	cagcaagacc	1200
gacgucucca	gcucaguaau	cacuagccua	ggggccauug	uaagcugcua	uggcaagacc	1260
aaguguacug	ccucuaauaa	gaacagaggc	auaauuaaga	ccuuuucaaa	uggcugugac	1320
uaugugucga	auaagggcgu	cgacacgguc	ucaguaggga	auaccucua	cuacguuaac	1380
aaacaggaag	gcaaucccu	uuauuaaag	ggcgagccca	ucauaaaauu	cuacgaccca	1440
cuuguguucc	ccagugauga	auucgaugca	ucaaucuccc	aggugaacga	aaagaucaau	1500
caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
ucuacaacca	acaucaugau	cacuaccauc	auuauuguga	uuauuguaau	ucugcuaucc	1620
uugauugcug	ucgggcugcu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaggaccaac	uuagcgguau	cauaauauu	gccuuuagca	au		1722

<210> 279
 <211> 1722
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 279	
auggaacugc	ucauuuugaa ggcaaacgcu aucacgacaa uacucacugc agugaccuuc 60
uguuuugccu	caggccagaa cauaaccgag gaguuuauuc aaucuaaug cagcgcugua 120
ucuaaaggcu	accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
cucagcaaua	uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
caggaacucg	acaaauauaa gaacgcugug accgagcugc aguuaauugau gcagaguaca 300
ccugccacca	auaacagagc uaggagggag uugccuaggu uuaugaacua cacucucaac 360
aacgcgaaga	agaccaaugu gacgcuauc aagaaacgga agaggagguu ccugggguuu 420
cuuuuagggg	ugggcucugc cauugcuucc ggcguggcug uauguaaagu ucuccaccuc 480

M137870026W000-SEQLIST-HJD

gagggagagg	uuauaagau	uaagucggcc	cugcugagua	cuaacaaagc	aguggugucg	540
cugaguaacg	gaguaagugu	guuaacauuu	aaggugcugg	accucaagaa	uuauauugac	600
aaacaguugc	uuccuauucu	aaacaaacag	agcuguucaa	uaaguaauau	ugaaacuguu	660
auugaguuuc	agcagaagaa	caacaggcuu	cuugagauua	cacgcgaguu	cagugucaau	720
gccggcguaa	caacacccgu	gucuaccuac	augcugacga	auucugagcu	ucucucucuc	780
auaaacgaca	ugcccauuac	gaaugaccag	aagaaacuua	uguccaacia	cgugcagauu	840
gugcgacagc	aauccuauag	cauuauugugu	aucaucaagg	aagagguacu	cgcuuauugu	900
gugcagcuac	cacucuaugg	ugugauugac	acccccuguu	ggaagcugca	uaccagucca	960
cucugcacca	cuaacacaaa	ggaagggagc	aaauuuugcc	ucacucgaac	cgacaggggg	1020
ugguauugcg	auaauugcgg	cuccgugucc	uucuuuccac	aggcugaaac	uuguaaggua	1080
cagucaaacc	guguguucug	ugauacuau	aaucucuga	cucuucccag	cgagguuaau	1140
cucugcaacg	ucgacauuuu	caauccuaaa	uaugacugca	agaucaugac	cagcaagacc	1200
gacgucucca	gcucaguaau	cacuagccua	ggggccauug	uaagcugcua	uggcaagacc	1260
aaguguacug	ccucuaauaa	gaacagaggc	auaauuaaga	ccuuuucaaa	uggcugugac	1320
uaugugucga	auaagggcgu	cgacacgguc	ucaguaggga	auaccucua	cuacguuaac	1380
aaacaggaag	gcaaaucccu	uuauuaaag	ggcgagccca	ucauaaaauu	cuacgaccca	1440
cuuguguucc	ccagugauga	auucgaugca	ucaaucuccc	aggugaacga	gaagaucaau	1500
caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
ucuacaacca	acaucaugau	cacuaccauc	auuauuguga	uuauuguaau	ucugcuaucc	1620
uugauugcug	ucgggcugcu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaggaccaac	uuagcgguau	cauaauauu	gccuuuagca	au		1722

<210> 280
 <211> 1722
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Synthetic Polynucleotide

<400> 280	
auggaacugc	ucauuuugaa ggcaaacgcu aucacgacaa uacucacugc agugaccuuc 60
uguuuugccu	caggccagaa cauaaccgag gaguuuuauc aaucuaaug cagcgugua 120
ucuaaaggcu	accugagugc gcuccgcaca ggaugguaca ccuccgugau caccaucgag 180
cucagcaaua	uuaaagagaa caagugcaau gguaccgacg cuaaagucua acuuaucaag 240
caggaacucg	acaaauuaa gaacgcugug accgagcugc aguuauugau gcagaguaca 300
ccugccacca	auaacagagc uaggagggag uugccuaggu uuaugaacua cacucuacac 360
aacgcgaaga	aaaccaaugu gacgcuauc aagaaacgga agaggagguu ccugggguuu 420
cuuuuagggg	ugggcucugc cauugcuucc ggcguggcug uauguaaagu ucuccaccuc 480

M137870026W000-SEQLIST-HJD

gagggagagg	uuauaagau	uaagucggcc	cugcugagua	cuaacaaagc	aguggugucg	540
cugaguaacg	gaguaagugu	guuaacauuu	aaggugcugg	accucaagaa	uuauauugac	600
aaacaguugc	uuccuauucu	aaacaaacag	agcuguucaa	uaaguaauau	ugaaacuguu	660
auugaguuuc	agcagaagaa	caacaggcuu	cuugagauua	cacgcgaguu	cagugucaau	720
gccggcguaa	caacacccgu	gucuaccuac	augcugacga	auucugagcu	ucucucucuc	780
auaaacgaca	ugcccauuac	gaaugaccaa	aagaaacuua	uguccaacia	cgugcagauu	840
gugcgacagc	aauccuauag	cauuauugugu	aucaucaagg	aagagguacu	cgcuuauugu	900
gugcagcuac	cacucuaugg	ugugauugac	acccccuguu	ggaagcugca	uaccagucca	960
cucugcacca	cuaacacaaa	ggaagggagc	aaauuuugcc	ucacucgaac	cgacaggggg	1020
ugguauugcg	auaauugcgg	cuccgugucc	uucuuuccac	aggcugaaac	uuguaaggua	1080
cagucaaaacc	guguguucug	ugauacuau	aaucucuga	cucuucccag	cgagguuaau	1140
cucugcaacg	ucgacauuuu	caauccuaaa	uaugacugca	agaucaugac	cagcaagacc	1200
gacgucucca	gcucaguaau	cacuagccua	ggggccauug	uaagcugcua	uggcaaaacc	1260
aaguguacug	ccucuaauaa	gaacagaggc	auaaauaaaa	ccuuuucaaa	uggcugugac	1320
uaugugucga	auaagggcgu	cgacacgguc	ucaguaggga	auaccucua	cuacguuaac	1380
aaacaggaag	gcaaaucccu	uuauguaaa	ggcgagccca	ucauaaaauu	cuacgaccca	1440
cuuguguucc	ccagugauga	auucgaugca	ucaaucuccc	aggugaacga	aaagaucaau	1500
caaucccuug	cuuuuauacg	aaagucagau	gaacuccugc	auaacgugaa	ugcugggaaa	1560
ucuacaacca	acaucaugau	cacuaccauc	auuauuguga	uuauuguaau	ucugcuaucc	1620
uugauugcug	ucgggcugcu	ucuguacugu	aaggccagau	cgacgccugu	gacccuuuca	1680
aaagaccaac	uuagcgguau	cauaauauu	gccuuuagca	au		1722

<210> 281
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 281

Met	Asp	Trp	Thr	Trp	Ile	Leu	Phe	Leu	Val	Ala	Ala	Ala	Thr	Arg	Val
1				5					10					15	

His Ser

<210> 282
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

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<400> 282

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly
20

<210> 283

<211> 24

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 283

Met Leu Gly Ser Asn Ser Gly Gln Arg Val Val Phe Thr Ile Leu Leu
1 5 10 15

Leu Leu Val Ala Pro Ala Tyr Ser
20

<210> 284

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 284

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
1 5 10 15

Ala

<210> 285

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 285

Met Trp Leu Val Ser Leu Ala Ile Val Thr Ala Cys Ala Gly Ala
1 5 10 15

<210> 286

<211> 13

<212> PRT

<213> Salmonella typhimurium

<400> 286

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Leu Gln Arg Val Arg Glu Leu Ala Val Gln Ser Ala Asn
1 5 10

<210> 287
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 287
tggagactcc cgctcagctg ctgtttttgc tcctcctatg gctgccggat accaccggc 59

<210> 288
<211> 60
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 288
auggagacuc ccgcucagcu gcuguuuuug cuccuccuau ggcugccgga uaccaccggc 60

<210> 289
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 289
Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Thr
1 5 10 15

Ala Val Thr Phe Cys
20

<210> 290
<211> 553
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 290
Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Lys Asn Lys Cys
35 40 45

M137870026W000-SEQLIST-HJD

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

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Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr
325 330 335

Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu
340 345 350

Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro
355 360 365

Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser
370 375 380

Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys
385 390 395 400

Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn
405 410 415

Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly
420 425 430

Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val
435 440 445

Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser
450 455 460

Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln
465 470 475 480

Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn
485 490 495

Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr Thr Ile Ile Ile Val
500 505 510

Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val Gly Leu Leu Leu Tyr
515 520 525

Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser Lys Asp Gln Leu Ser
530 535 540

Gly Ile Asn Asn Ile Ala Phe Ser Asn
545 550

<210> 291
<211> 553
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

M137870026W000-SEQLIST-HJD

<400> 291

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Pro
65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg Phe Met Asn Tyr
85 90 95

Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu Ser Lys Lys Arg
100 105 110

Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala
115 120 125

Ser Gly Val Ala Val Cys Lys Val Leu His Leu Glu Gly Glu Val Asn
130 135 140

Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu
145 150 155 160

Ser Asn Gly Val Ser Val Leu Thr Phe Lys Val Leu Asp Leu Lys Asn
165 170 175

Tyr Ile Asp Lys Gln Leu Leu Pro Ile Leu Asn Lys Gln Ser Cys Ser
180 185 190

Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg
195 200 205

Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr
210 215 220

Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile
225 230 235 240

Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn
245 250 255

Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Cys Ile Ile Lys
260 265 270

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Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile
 275 280 285
 Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn
 290 295 300
 Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp
 305 310 315 320
 Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr
 325 330 335
 Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu
 340 345 350
 Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro
 355 360 365
 Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser
 370 375 380
 Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys
 385 390 395 400
 Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn
 405 410 415
 Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly
 420 425 430
 Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val
 435 440 445
 Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser
 450 455 460
 Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln
 465 470 475 480
 Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn
 485 490 495
 Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr Thr Ile Ile Ile Val
 500 505 510
 Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val Gly Leu Leu Leu Tyr
 515 520 525
 Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser Lys Asp Gln Leu Ser
 530 535 540

M137870026W000-SEQLIST-HJD

Gly Ile Asn Asn Ile Ala Phe Ser Asn
545 550

<210> 292
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 292

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Lys Asn Lys Cys
35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Gln
65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Gln Gln Gln Gln Arg Phe Leu Gly Phe
85 90 95

Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys
100 105 110

Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu
115 120 125

Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu
130 135 140

Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu
145 150 155 160

Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val
165 170 175

Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu
180 185 190

Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu
195 200 205

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Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn
 210 215 220
 Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln
 225 230 235 240
 Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val
 245 250 255
 Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu
 260 265 270
 His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile
 275 280 285
 Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser
 290 295 300
 Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg
 305 310 315 320
 Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn
 325 330 335
 Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met
 340 345 350
 Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala
 355 360 365
 Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn
 370 375 380
 Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn
 385 390 395 400
 Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
 405 410 415
 Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn
 420 425 430
 Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile
 435 440 445
 Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys
 450 455 460
 Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn
 465 470 475 480

M137870026W000-SEQLIST-HJD

<210> 293
 <211> 469
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 293

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
 1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
 20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Lys Asn Lys Cys
 35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Gln
 65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Gln Gln Gln Gln Arg Phe Leu Gly Phe
 85 90 95

Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys
 100 105 110

Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu
 115 120 125

Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu
 130 135 140

Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu
 145 150 155 160

Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val
 165 170 175

Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu
 180 185 190

Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu
 195 200 205

Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn
 210 215 220

Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln
 225 230 235 240

M137870026W000-SEQLIST-HJD

Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val
245 250 255

Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu
260 265 270

His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile
275 280 285

Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser
290 295 300

Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg
305 310 315 320

Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn
325 330 335

Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met
340 345 350

Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala
355 360 365

Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn
370 375 380

Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn
385 390 395 400

Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
405 410 415

Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn
420 425 430

Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile
435 440 445

Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys
450 455 460

Ser Asp Glu Leu Leu
465

<210> 294
<211> 543
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 294

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
 1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
 20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
 35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Pro
 65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg Phe Met Asn Tyr
 85 90 95

Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu Ser Lys Lys Gln
 100 105 110

Lys Gln Gln Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His
 115 120 125

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

Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys
 145 150 155 160

Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val
 165 170 175

Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe
 180 185 190

Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val
 195 200 205

Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser
 210 215 220

Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys
 225 230 235 240

Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser
 245 250 255

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Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu
 260 265 270

Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser
 275 280 285

Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr
 290 295 300

Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe
 305 310 315 320

Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys
 325 330 335

Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn
 340 345 350

Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys
 355 360 365

Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser
 370 375 380

Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile
 385 390 395 400

Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val
 405 410 415

Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu
 420 425 430

Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp
 435 440 445

Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val
 450 455 460

Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu
 465 470 475 480

Leu Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile
 485 490 495

Thr Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala
 500 505 510

Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu
 515 520 525

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Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn
 530 535 540

<210> 295
 <211> 464
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Polypeptide

<400> 295

Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
 1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
 20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
 35 40 45

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

Tyr Lys Ser Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Pro
 65 70 75 80

Ala Thr Asn Asn Lys Phe Leu Gly Phe Leu Gln Gly Val Gly Ser Ala
 85 90 95

Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu His Leu Glu Gly Glu
 100 105 110

Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val
 115 120 125

Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu
 130 135 140

Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn Lys Gln Ser
 145 150 155 160

Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn
 165 170 175

Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val
 180 185 190

Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser
 195 200 205

Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser
 210 215 220

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Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile
 225 230 235 240

Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly
 245 250 255

Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr
 260 265 270

Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg
 275 280 285

Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Leu Ala
 290 295 300

Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn
 305 310 315 320

Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Ile Asp Ile Phe
 325 330 335

Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser
 340 345 350

Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys
 355 360 365

Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe
 370 375 380

Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser
 385 390 395 400

Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu
 405 410 415

Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe
 420 425 430

Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile
 435 440 445

Asn Gly Thr Leu Ala Phe Ile Arg Lys Ser Asp Glu Lys Leu His Asn
 450 455 460

<210> 296
 <211> 492
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

<400> 296

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
 1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
 20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Lys Asn Lys Cys
 35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Gln
 65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg Phe Met Asn Tyr
 85 90 95

Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu Ser Lys Lys Arg
 100 105 110

Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala
 115 120 125

Ser Gly Val Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn
 130 135 140

Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu
 145 150 155 160

Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn
 165 170 175

Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn Lys Gln Ser Cys Ser
 180 185 190

Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg
 195 200 205

Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr
 210 215 220

Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile
 225 230 235 240

Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn
 245 250 255

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Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys
260 265 270

Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile
275 280 285

Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn
290 295 300

Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp
305 310 315 320

Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr
325 330 335

Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu
340 345 350

Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro
355 360 365

Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser
370 375 380

Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys
385 390 395 400

Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn
405 410 415

Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly
420 425 430

Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val
435 440 445

Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser
450 455 460

Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln
465 470 475 480

Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu
485 490

<210> 297

<211> 492

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Polypeptide

M137870026W000-SEQLIST-HJD

<400> 297

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
 1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
 20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
 35 40 45

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

Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu Met Gln Ser Thr Pro
 65 70 75 80

Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg Phe Met Asn Tyr
 85 90 95

Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr Leu Ser Lys Lys Arg
 100 105 110

Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala
 115 120 125

Ser Gly Val Ala Val Cys Lys Val Leu His Leu Glu Gly Glu Val Asn
 130 135 140

Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu
 145 150 155 160

Ser Asn Gly Val Ser Val Leu Thr Phe Lys Val Leu Asp Leu Lys Asn
 165 170 175

Tyr Ile Asp Lys Gln Leu Leu Pro Ile Leu Asn Lys Gln Ser Cys Ser
 180 185 190

Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg
 195 200 205

Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr
 210 215 220

Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile
 225 230 235 240

Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn
 245 250 255

Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met Cys Ile Ile Lys
 260 265 270

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Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile
275 280 285

Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn
290 295 300

Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp
305 310 315 320

Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr
325 330 335

Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu
340 345 350

Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro
355 360 365

Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser
370 375 380

Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys
385 390 395 400

Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn
405 410 415

Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly
420 425 430

Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val
435 440 445

Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser
450 455 460

Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln
465 470 475 480

Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu
485 490

<210> 298
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 298

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

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His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile
275 280 285

Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser
290 295 300

Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg
305 310 315 320

Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn
325 330 335

Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met
340 345 350

Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala
355 360 365

Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn
370 375 380

Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn
385 390 395 400

Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
405 410 415

Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn
420 425 430

Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile
435 440 445

Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys
450 455 460

Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn
465 470 475 480

<210> 299
<211> 469
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 299

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
20 25 30

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

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Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg
305 310 315 320

Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn
325 330 335

Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met
340 345 350

Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala
355 360 365

Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn
370 375 380

Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn
385 390 395 400

Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
405 410 415

Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn
420 425 430

Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile
435 440 445

Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys
450 455 460

Ser Asp Glu Leu Leu
465

<210> 300
<211> 464
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 300

Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10 15

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
20 25 30

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile Lys Glu Asn Lys Cys
35 40 45

M137870026W000-SEQLIST-HJD

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

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Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Ile Asp Ile Phe
 325 330 335

Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp Val Ser
 340 345 350

Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys
 355 360 365

Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe
 370 375 380

Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr Val Ser
 385 390 395 400

Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu
 405 410 415

Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe
 420 425 430

Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu Lys Ile
 435 440 445

Asn Gly Thr Leu Ala Phe Ile Arg Lys Ser Asp Glu Lys Leu His Asn
 450 455 460