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(54) Title: CORONAVIRUS VACCINE

(57) Abstract: This disclosure relates to the field of RNA to prevent or treat coronavirus infection. In particular, the present disclosure relates to methods and agents for vaccination against coronavirus infection and inducing effective coronavirus antigen-specific immune responses such as antibody and/or T cell responses. Specifically, in one embodiment, the present disclosure relates to methods comprising administering to a subject RNA encoding a peptide or protein comprising an epitope of SARS-CoV-2 spike protein (S protein) for inducing an immune response against coronavirus S protein, in particular S protein of SARS-CoV-2, in the subject, i.e., vaccine RNA encoding vaccine antigen.

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Coronavirus vaccine

[0001] This disclosure relates to the field of RNA to prevent or treat coronavirus infection. In particular, the present disclosure relates to methods and agents for vaccination against coronavirus infection and inducing effective coronavirus antigen-specific immune responses such as antibody and/or T cell responses. These methods and agents are, in particular, useful for the prevention or treatment of coronavirus infection. Administration of RNA disclosed herein to a subject can protect the subject against coronavirus infection. Specifically, in one embodiment, the present disclosure relates to methods comprising administering to a subject RNA encoding a peptide or protein comprising an epitope of SARS-CoV-2 spike protein (S protein) for inducing an immune response against coronavirus S protein, in particular S protein of SARS-CoV-2, in the subject, i.e., vaccine RNA encoding vaccine antigen. Administering to the subject RNA encoding vaccine antigen may provide (following expression of the RNA by appropriate target cells) vaccine antigen for inducing an immune response against vaccine antigen (and disease-associated antigen) in the subject.

[0002] Coronaviruses are positive-sense, single-stranded RNA ((+)ssRNA) enveloped viruses that encode for a total of four structural proteins, spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N). The spike protein (S protein) is responsible for receptor-recognition, attachment to the cell, infection via the endosomal pathway, and the genomic release driven by fusion of viral and endosomal membranes. Though sequences between the different family members vary, there are conserved regions and motifs within the S protein making it possible to divide the S protein into two subdomains: S1 and S2. While the S2, with its transmembrane domain, is responsible for membrane fusion, the S1 domain recognizes the virus-specific receptor and binds to the target host cell. Within several coronavirus isolates, the receptor binding domain (RBD) was identified and a general structure of the S protein defined (Figure 1).

[0003] In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China and it became clear that a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was the underlying cause. The genetic sequence of SARS-CoV-2 became available to the WHO and public (MN908947.3) and the virus was categorized into the betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, namely the Middle East respiratory syndrome (MERS) virus.

[0004] SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

[0005] Every individual is at risk of infection as there is no pre-existing immunity to SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts. According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care. Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

[0006] The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and

subsequent multi-organ failure and death. Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

[0007] All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

[0008] In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab.

[0009] Among other things, the present disclosure provides insights into immune responses elicited by exposure to (e.g., by vaccination and/or infection) different SARS-CoV-2 variants or immunogenic polypeptides (e.g., S protein), or immunogenic fragments thereof. For example, in some embodiments, administering RNA encoding an S protein of certain Omicron variants (e.g., an S protein of a BA.4/5, XBB.1.5, XBB.1.16, XBB.2.3, and/or XBB.2.3.2 variant), or an immunogenic fragment thereof, can produce an improved immune response (including, e.g., (i) higher neutralization titers against a particular SARS-CoV-2 Omicron variant of concern (e.g., a BA.4/5, XBB.1.5, XBB.1.16, XBB.2.3, and/or XBB.2.3.2 variant) and/or (ii) broader cross-neutralization of Omicron variants of concern (e.g., higher neutralization titers against a larger number of Omicron variants of concern)) as compared to RNA encoding an S protein of a different SARS-CoV-2 strain or variant (e.g., higher neutralization titers as compared to RNA encoding an S protein of a Wuhan strain, or another SARS-CoV-2 variant of concern). In some embodiments, the present disclosure provides an insight that a bivalent coronavirus vaccine (e.g., a bivalent vaccine comprising (i) a first RNA comprising a sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.4/5 Omicron variant or an immunogenic fragment thereof, and (ii) a second RNA comprising a sequence that encodes a SARS-CoV-2 S protein of another strain or variant (e.g., a Wuhan strain, an XBB.1.5 strain, a XBB.1.16 strain, or a BQ.1.1 strain)) can provide broader cross-neutralization against SARS-CoV-2 Wuhan strain and certain variants thereof (e.g., in some embodiments variants that are prevalent and/or rapidly spreading in a relevant jurisdiction, e.g., certain Omicron variants) in certain subjects as compared to a monovalent coronavirus vaccine (e.g., a vaccine comprising RNA encoding a SARS-CoV-2 S protein of a coronavirus strain or variant thereof). The present disclosure also provides XBB-adapted monovalent vaccines (e.g., monovalent vaccines comprising an RNA that encodes a SARS-CoV-2 S protein of an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 variant) can induce (i) surprisingly high titers against XBB Omicron variants of concern (e.g., XBB.1.5 and XBB.1.15), and (ii) broad cross-neutralization of XBB variants of concern. In some embodiments, the broader cross-neutralization induced by compositions described herein can be observed in vaccine-naïve subjects. In some embodiments, such broader cross-neutralization can be observed in subjects without a previous or current coronavirus infection (e.g., a SARS-CoV-2 infection). In some embodiments, such broader cross-neutralization can be observed in subjects who previously received a SARS-CoV-2 vaccine (e.g., in some embodiments an RNA vaccine encoding a SARS-CoV-2 S protein, e.g., in some embodiments of a Wuhan strain) and/or who were previously infected with SARS-CoV-2. In some embodiments, such broader cross-neutralization can be observed in young pediatric subjects (e.g., subjects aged 6 months to less than 2 years, and/or 2 years to less than 5 years).

[0010] In some embodiments, the present disclosure provides an insight that exposure to at least two certain SARS-CoV-2 variants or immunogenic polypeptides (e.g., S protein), or immunogenic fragments thereof can result

in a synergistic improvement in immune response (e.g., higher neutralization titers, broader cross-neutralization, and/or an immune response that is less susceptible to immune escape) as compared to exposure to one SARS-CoV-2 strain and/or other combination of SARS-CoV-2 variants. In some embodiments, the present disclosure provides an insight that exposure to a SARS-CoV-2 S protein from a Wuhan strain or an immunogenic fragment thereof (e.g., by vaccination and/or infection), and exposure to a SARS-CoV-2 S protein of certain Omicron variants (specifically a BA.4/5. XBB.1.5, XBB.2.3, or XBB.2.3 variant) or an immunogenic fragment thereof (e.g., by vaccination and/or infection) can result in a synergistic improvement in immune response (e.g., higher neutralization titers, broader cross-neutralization, and/or an immune response that is less susceptible to immune escape) as compared to exposure to one SARS-CoV-2 strain and/or other combinations comprising other SARS-CoV-2 variants. In some embodiments, the present disclosure provides an insight that exposure to a SARS-CoV-2 S protein from a Wuhan strain or an immunogenic fragment thereof (e.g., by vaccination and/or infection), and exposure to a SARS-CoV-2 S protein of an Omicron BA.4 or BA.5 variant or an immunogenic fragment thereof (e.g., by vaccination and/or infection) can result in an synergistic improvement in immune response (e.g., higher neutralization titers, broader cross-neutralization, and/or an immune response that is less susceptible to immune escape) as compared to exposure to one SARS-CoV-2 strain and/or other combinations of other SARS-CoV-2 strains or variants. In some embodiments, the present disclosure provides an insight that (i) exposure to a SARS-CoV-2 S protein from a strain/variant selected from the group consisting of Wuhan strain, an alpha variant, beta variant, delta variant, Omicron BA.1, and sublineages derived from any of the aforementioned strains/variants, or immunogenic fragments thereof (e.g., by vaccination and/or infection), combined with (ii) exposure to a SARS-CoV-2 S protein from a strain/variant selected from the group consisting of Omicron BA.2, Omicron BA.4, Omicron BA.5, and sublineages derived from any of the aforementioned strains/variants, or immunogenic fragments thereof (e.g., by vaccination and/or infection) can result in a synergistic improvement in immune response (e.g., higher neutralization titers, broader cross-neutralization, and/or an immune response that is less susceptible to immune escape) as compared to exposure to one SARS-CoV-2 strain and/or other combinations of SARS-CoV-2 variants).

[0011] The present disclosure also provides significant insights into how an immune response develops in subjects following exposure to (e.g., by vaccination and/or infection) multiple, different SARS-CoV-2 strains. Among other things, disclosed herein is a finding that different combinations of SARS-CoV-2 variants can elicit different immune responses. Specifically, the present disclosure provides an insight that exposure to certain combinations of SARS-CoV-2 variants can elicit an improved immune response (e.g., higher neutralization titers, broader cross-neutralization, and/or an immune response that is less susceptible to immune escape) as compared to other combinations of SARS-CoV-2 variants. In some embodiments, an improved immune response can be produced when subjects are delivered two or more antigens (e.g., as polypeptides or RNAs encoding such polypeptides), each having few shared epitopes. In some embodiments, an improved immune response can be produced when subjects are delivered a combination of SARS-CoV-2 S proteins (e.g., as polypeptides or RNAs encoding such polypeptides) sharing no more than 50% (e.g., no more than 40%, no more than 30%, no more 20% or more) of epitopes (including, e.g., amino acid mutations) that can be bound by neutralization antibodies.

[0012] In some embodiments, the present disclosure also provides an insight that administration of multiple doses (e.g., at least 2, at least 3, at least 4, or more doses) of a coronavirus vaccine described herein (e.g., (i) a bivalent vaccine described herein such as a bivalent vaccine comprising an RNA encoding a BA.4/5 S protein and an RNA encoding an S protein of a different SARS-CoV-2 variant; or (ii) a monovalent vaccine comprising RNA encoding a SARS-CoV-2 S protein of an XBB variant (e.g., an XBB.1.5 or XBB.1.16 variant)) may provide certain beneficial effect(s) on affinity of antibodies against one or more SARS-CoV-2 strain or variants thereof. In some embodiments, such beneficial effect(s) on affinity of antibodies may be observed with respect to antibodies against

certain Omicron variants. By way of example only, in some embodiments, such beneficial effect(s) on affinity of antibodies may be observed with respect to antibodies against certain Omicron variants that share at least one or more common epitopes, for example, with a Wuhan strain.

[0013] Also disclosed herein are compositions that can produce an improved immune response (e.g., an immune response having broader cross-neutralization activity, higher neutralization titers, and/or which is less susceptible to immune escape), e.g., as compared to previously approved vaccines (e.g., previously approved RNA or protein vaccines), vaccines that deliver antigens of a Wuhan S protein, and/or vaccines that deliver antigens of other SARS-CoV-2 variants. In particular, in some embodiments, compositions described herein that comprise two or more antigens that have few shared epitopes, or nucleic acids (e.g., RNA) that encode such antigens can provide such an improved immune response. In some embodiments, such compositions deliver, as polypeptides or nucleic acids encoding such polypeptides, a combination of SARS-CoV-2 S proteins or immunogenic fragments thereof sharing no more than 50% (e.g., no more than 40%, no more than 30%, no more than 20% or more) of epitopes (including, e.g., amino acid mutations) that can be bound by neutralization antibodies. In some embodiments, such compositions comprise (a) RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, or an immunogenic fragment thereof, and (b) RNA encoding an S protein from an Omicron variant of SARS-CoV-2 (e.g., an S protein from a BA.4/5, XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant) or an immunogenic fragment thereof.

[0014] In some embodiments, a composition comprises RNA encoding an S protein from a BA.4 or BA.5 Omicron variant of SARS-CoV-2 or an immunogenic fragment thereof. In some embodiments, a composition comprise (a) RNA encoding a SARS-CoV-2 S protein from an Omicron BA.4/5 variant, and (b) RNA encoding another SARS-CoV-2 variant (e.g., an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant) or an immunogenic fragment thereof.

[0015] In some embodiments, compositions disclosed herein (e.g., monovalent compositions comprising RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant) can also induce a strong immune response (e.g.,. high neutralization titers) against certain SARS-CoV-2 variants of concern (e.g., XBB variants of concern (e.g., as described herein, including an XBB.1.5 variant, an XBB.1.16 variant, an XBB.2.3 variant, and/or an XBB.2.3.2 variant)). In some embodiments, such compositions are monovalent compositions comprising RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant. As demonstrated herein, in some embodiments, such compositions can induce surprisingly high neutralization titers against certain XBB variants of concern (including, e.g., XBB.1.5, XBB.1.16, and XBB.2.3 variants of concern). Even more surprisingly, in some embodiments, such compositions can induce neutralization titers that are higher against a given variant than a variant-matched vaccine (e.g., in some embodiments, RNA described herein comprising a nucleotide sequence that encodes an XBB.1.5 S protein, can induce neutralization titers against a XBB.1.16 variant of concern that are higher than those induced by an XBB.1.16-adapted vaccine).

[0016] SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the spike protein is considered a relevant antigen for vaccine development.

[0017] BNT162b2 (which comprises an RNA comprising SEQ ID NO: 20) is an mRNA vaccine for prevention of COVID-19 and demonstrated an efficacy of 95% or more at preventing COVID-19. The vaccine comprises a 5'capped mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The finished product is presented as a concentrate for dispersion for injection containing BNT162b2 as active substance. Other ingredients include: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-Distearoyl-sn-glycero-

3-phosphocholine (DSPC), cholesterol, and, in some embodiments, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injection.

[0018] In some embodiments, a different buffer may be used in lieu of PBS. In some embodiments, BNT162b2 is formulated in a Tris-buffered solution optionally comprising sucrose. In some embodiments, the formulation comprises ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), cholesterol, sucrose, trometamol (Tris), trometamol hydrochloride and water.

[0019] In some embodiments, the concentration of RNA in a pharmaceutical RNA preparation is about 0.1 mg/ml. In some embodiments, about 30 ug of RNA is administered by administering about 200 uL of RNA preparation.

[0020] In some embodiments, RNA in a pharmaceutical RNA preparation is diluted prior to administration (e.g., diluted to a concentration of about 0.05 mg/ml). In some embodiments, administration volumes are between about 200 µl and about 300 µl. In some embodiments, RNA in a pharmaceutical RNA preparation is formulated in about 10 mM Tris buffer, and about 10% sucrose.

[0021] In some embodiments, RNA in a pharmaceutical RNA preparation is present at a concentration of about 0.1 mg/ml, and is formulated in about 10 mM Tris buffer, and about 10% sucrose, and a dose of about 10 µg of RNA is administered by (i) diluting the pharmaceutical RNA preparation about 1:1 and (ii) administering about 200 µl of the diluted pharmaceutical RNA preparation. In some embodiments, RNA in a pharmaceutical RNA preparation is present at a concentration of about 0.1 mg/ml, and is formulated in about 10 mM Tris buffer, and about 10% sucrose and a dose of RNA of about 10 µg is administered by (i) diluting the pharmaceutical RNA preparation about 1:5.75 and (ii) administering about 200 µl of diluted pharmaceutical RNA preparation.

[0022] The amino acid sequence of the S protein encoded by BNT162b2 was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu -1": GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein). The BNT162b2 active substance consists of a single-stranded, 5'-capped codon-optimized mRNA that is translated into the spike antigen of SARS-CoV-2. The spike antigen protein sequence encoded by BNT162b2 contains two proline mutations, which stabilizes an antigenically improved pre-fusion confirmation (P2 S). BNT162b2 does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. BNT162b2 mRNA is translated into a SARS-CoV-2 S protein in host cells. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein encoded by BNT162b2 is identified as a target for neutralising antibodies against the virus and is considered a relevant vaccine component. For adult vaccine naïve subjects (i.e., subjects 16 years and older who have not previously been administered a SARS-CoV-2 vaccine), the dosing regimen of BNT162b2 approved by the FDA comprises administering intramuscularly (IM) two 30 µg doses of the diluted vaccine solution approximately 21 days apart.

[0023] The recent emergence of novel circulating variants of SARS-CoV-2 has raised significant concerns about geographic and temporal efficacy of vaccine interventions. One of the earliest variants that emerged and rapidly became globally dominant was D614G.

[0024] The alpha variant (also known as B.1.1.7, VOC202012/01, 501Y.V1 or GRY) was initially detected in the United Kingdom. The alpha variant has a large number of mutations, including several mutations in the S gene. It has been shown to be inherently more transmissible, with a growth rate that has been estimated to be 40-70% higher than other SARS-CoV-2 lineages in multiple countries (Volz et al., 2021, Nature, https://doi.org/10.1038/s41586-021-03470-x; Washington et al., 2021, Cell, https://doi.org/10.1016/j.cell.2021.03.052).

[0025] The beta variant (also known as B.1.351 or GH/501Y.V2) was first detected in South Africa. The beta variant carries several mutations in the S gene. Three of these mutations are at sites in the RBD that are associated with immune evasion: N501Y (shared with alpha) and E484K and K417N.

[0026] The gamma variant (also known as P.1 or GR/501Y.V3) was first detected in Brazil. The gamma variant carries several mutations that affect the spike protein, including two shared with beta (N501Y and E484K), as well as a different mutation at position 417 (K417T).

[0027] The delta variant (also known as B.1.617.2 or G/478K.V1) was first documented in India. The delta variant has several point mutations that affect the spike protein, including P681R (a mutation position shared with alpha and adjacent to the furin cleavage site), and L452R, which is in the RBD and has been linked with increased binding to ACE2 and neutralizing antibody resistance. There is also a deletion in the spike protein at position 156/157.

[0028] These four VOCs have circulated globally and became dominant variants in the geographic regions where they were first identified.

[0029] On 24 November 2021, the Omicron (B.1.1.529) variant was first reported to WHO from South Africa. SARS-CoV-2 Omicron and its sublineages have had a major impact on the epidemiological landscape of the COVID-19 pandemic since initial emergence in November 2021 (WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE): Classification of Omicron (B.1.1.259): SARS-CoV-2 Variant of Concern (2021); WHO Headquarters (HQ), WHO Health Emergencies Programme, Enhancing Response to Omicron SARS-CoV-2 variant: Technical brief and priority actions for Member States (2022)). Significant alterations in the spike (S) glycoprotein of the first Omicron variant BA.1 leading to the loss of many neutralizing antibody epitopes (M. Hoffmann et al., "The Omicron variant is highly resistant against antibody mediated neutralization: Implications for control of the COVID-19 pandemic", Cell 185, 447–456.e11 (2022)) rendered BA.1 capable of partially escaping previously established SARS-CoV-2 wild-type strain (Wuhan-Hu-1)-based immunity (V. Servellita, et al., "Neutralizing immunity in vaccine breakthrough infections from the SARS-CoV-2 Omicron and Delta variants", Cell 185, 1539–1548.e5 (2022); Y. Cao et al., "Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies", Nature 602, 657–663 (2022)). Hence, breakthrough infection of vaccinated individuals with Omicron are more common than with previous Variants of Concern (VOCs). While Omicron BA.1 was displaced by the BA.2 variant in many countries around the globe, other variants such as BA.1.1 and BA.3 temporarily and/or locally gained momentum but did not become globally dominant (S. Xia et al., "Origin, virological features, immune evasion and intervention of SARS-CoV-2 Omicron sublineages. Signal Transduct. Target. Ther. 7, 241 (2022); H. Gruell et al., "SARS-CoV-2 Omicron sublineages exhibit distinct antibody escape patterns, Cell Host Microbe 7, 241 (2022).). Omicron BA.2.12.1 subsequently displaced BA.2 to become dominant in the United States, whereas BA.4 and BA.5 displaced BA.2 in Europe, parts of Africa, and Asia/Pacific (H. Gruell et al., "SARS-CoV-2 Omicron sublineages exhibit distinct antibody escape patterns," Cell Host Microbe 7, 241 (2022); European Centre for Disease Prevention and Control, Weekly COVID-19 country overview -Country overview report: Week 31 2022 (2022); J. Hadfield et al., "Nextstrain: Real-time tracking of pathogen evolution," Bioinformatics 34, 4121–4123 (2018)). Currently, Omicron BA.5 is dominant globally, including in the United States (Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, August 12. https://covid.cdc.gov/coviddata-tracker (2022)).

[0030] Omicron has acquired numerous alterations (amino acid exchanges, insertions, or deletions) in the S glycoprotein, among which some are shared between all Omicron VOCs while others are specific to one or more Omicron sublineages. Antigenically, BA.2.12.1 exhibits high similarity with BA.2 but not BA.1, whereas BA.4 and BA.5 differ considerably from their ancestor BA.2 and even more so from BA.1, in line with their genealogy (A. Z.

Mykytyn et al., "Antigenic cartography of SARS-CoV-2 reveals that Omicron BA.1 and BA.2 are antigenically distinct," Sci. Immunol. 7, eabq4450 (2022).). Major differences of BA.1 from the remaining Omicron VOCs include Δ143–145, L212I, or ins214EPE in the S glycoprotein N-terminal domain and G446S or G496S in the receptor binding domain (RBD). Amino acid changes T376A, D405N, and R408S in the RBD are in turn common to BA.2 and its descendants but not found in BA.1. In addition, some alterations are specific for individual BA.2-descendant VOCs, including L452Q for BA.2.12.1 or L452R and F486V for BA.4 and BA.5 (BA.4 and BA.5 encode for the same S sequence). Most of these shared and VOC-specific alterations were shown to play an important role in immune escape from monoclonal antibodies and polyclonal sera raised against the wild-type S glycoprotein. In particular, the BA.4/BA.5-specific alterations are strongly implicated in immune escape of these VOCs (P. Wang et al., "Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 593, 130–135 (2021); Q. Wang et al., "Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4, & BA.5. Nature 608, 603–608 (2022)). As of the filing date of the present application, the XBB group of variants, resulting from a recombination of BA.10.1 and BA.2.75, are the most prevalent SARS-CoV-2 variants of concern, representing the top three most prevalent strains in the US between May 28, 2023, and June 10, 2023.

Summary

[0031] The present disclosure generally embraces immunotherapeutic treatment of a subject comprising administration of RNA, e.g., vaccine RNA, encoding an amino acid sequence, e.g., a vaccine antigen, comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, i.e., an antigenic peptide or protein. Thus, vaccine antigen comprises an epitope of SARS-CoV-2 S protein for inducing an immune response against coronavirus S protein, in particular SARS-CoV-2 S protein, in the subject. RNA encoding vaccine antigen is administered to provide (following expression of the polynucleotide by appropriate target cells) antigen for induction, i.e., stimulation, priming and/or expansion, of an immune response, e.g., antibodies and/or immune effector cells, which is targeted to target antigen (coronavirus S protein, in particular SARS-CoV-2 S protein) or a procession product thereof. In one embodiment, the immune response which is to be induced according to the present disclosure is a B cell-mediated immune response, i.e., an antibody-mediated immune response. Additionally or alternatively, in one embodiment, the immune response which is to be induced according to the present disclosure is a T cell-mediated immune response. In one embodiment, the immune response is an anti-coronavirus, in particular anti-SARS-CoV-2 immune response.

[0032] Vaccines described herein comprise as an active principle single-stranded RNA that may be translated into protein upon entering cells of a recipient. In addition to wildtype or codon-optimized sequences encoding an antigen sequence, RNA may contain one or more structural elements optimized for maximal efficacy with respect to stability and translational efficiency (e.g., 5' cap, 5' UTR, 3' UTR, poly(A)-tail, and combinations thereof). In one embodiment, RNA contains all of these elements. In one embodiment, a cap1 structure may be utilized as specific capping structure at the 5'-end of an RNA drug substance. In one embodiment, beta-S-ARCA(D1) ($m_2^{7,2'\text{-}O}$GppSpG) or $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG may be utilized as specific capping structure at the 5'-end of an RNA drug substance. As 5'-UTR sequence, the 5'-UTR sequence of the human alpha-globin mRNA, optionally with an optimized 'Kozak sequence' to increase translational efficiency (e.g., SEQ ID NO: 12) may be used. As 3'-UTR sequence, a combination of two sequence elements (FI element) derived from the "amino terminal enhancer of split" (AES) mRNA (called F) and the mitochondrial encoded 12S ribosomal RNA (called I) (e.g., SEQ ID NO: 13) placed between the coding sequence and the poly(A)-tail to assure higher maximum protein levels and prolonged persistence of the mRNA may be used. These features were identified by an *ex vivo* selection process for sequences that confer

RNA stability and augment total protein expression (see WO 2017/060314, herein incorporated by reference). Alternatively, the 3'-UTR may be two re-iterated 3'-UTRs of the human beta-globin mRNA. Additionally or alternatively, in some embodiments, a poly(A)-tail may comprise a length of at least 100 adenosine residues (including, e.g., at least 110 adenosine residues, at least 120 adenosine residues, 130 adenosine residues, or longer). In some embodiments, a poly(A)-tail may comprise a length of about 100 to about 150 adenosine residues. In some embodiments a poly(A)-tail may comprise an interrupted poly(A)-tail. For example, in some such embodiments, a poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence (of random nucleotides) and another 70 adenosine residues (e.g., SEQ ID NO: 14) may be used. This poly(A)-tail sequence was designed to enhance RNA stability and translational efficiency.

[0033] Furthermore, in some embodiments, a nucleotide sequence encoding a secretory signal peptide (sec) may be fused to antigen-encoding regions of an RNA, preferably in some embodiments in a way that the sec is translated as an N terminal tag. In one embodiment, sec corresponds to the secretory signal peptide of a SARS-CoV-2 S protein (e.g., of a Wuhan strain). In some embodiments, sequences coding for short linker peptides predominantly consisting of the amino acids glycine (G) and serine (S), as commonly used for fusion proteins, may be used as GS/Linkers between sec and an antigen.

[0034] Vaccine RNA described herein may be complexed with proteins and/or lipids, preferably lipids, to generate RNA-particles for administration. If a combination of different RNAs is used, RNAs may be complexed together or complexed separately with proteins and/or lipids to generate RNA-particles for administration.

[0035] In one aspect, the present disclosure relates to a composition or medical preparation comprising RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof.

[0036] In one embodiment, an immunogenic fragment of the SARS-CoV-2 S protein comprises the S1 subunit of the SARS-CoV-2 S protein, or the receptor binding domain (RBD) of the S1 subunit of the SARS-CoV-2 S protein.

[0037] In one embodiment, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is able to form a multimeric complex, in particular a trimeric complex. To this end, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof may comprise a domain allowing the formation of a multimeric complex, in particular a trimeric complex of the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof. In one embodiment, the domain allowing formation of a multimeric complex comprises a trimerization domain, for example, a trimerization domain as described herein, e.g., SARS-CoV-2 S protein trimerization domain. In one embodiment, trimerization is achieved by addition of a trimerization domain, e.g., a T4-fibritin-derived "foldon" trimerization domain (e.g., SEQ ID NO: 10), in particular if the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof corresponds to a portion of a SARS-CoV-2 S protein that does not comprise the SARS-CoV-2 S protein trimerization domain.

[0038] In one embodiment, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence. Those skilled in the art will appreciate that

codon optimization involves choosing between or among alternative codons encoding the same amino acid residue. Codon optimization typically includes consideration of codon(s) preferred by a particular host in which a sequence is to be expressed. In accordance with the present disclosure, in many embodiments, a preferred host is a human. In some embodiments, a preferred host may be a domestic animal. Alternatively or additionally, in some embodiments, selection between or among possible codons encoding the same amino acid may consider one or more other features such as, for example, overall G/C content (as noted above) and/or similarity to a particular reference. For example, in some embodiments of the present disclosure, a provided coding sequence that encodes a SARS-CoV-2 S protein or immunogenic variant thereof that differs in amino acid sequence from that encoded by a BNT162b2 construct described herein utilizes a codon, in at least one position of such difference, that preserves greater similarity to the BNT162b2 construct sequence relative to at least one alternative codon encoding the same amino acid at such position of difference.

[0039] In one embodiment, the RNA is a modified RNA, in particular a stabilized mRNA. In one embodiment, the RNA comprises a modified nucleoside in place of at least one uridine. In one embodiment, the RNA comprises a modified nucleoside in place of each uridine. In one embodiment, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

[0040] In one embodiment, RNA comprises a modified nucleoside in place of uridine.

[0041] In one embodiment, the modified nucleoside is selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

[0042] In one embodiment, RNA comprises a 5′ cap.

[0043] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a 5′ UTR comprising the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 12.

[0044] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a 3′ UTR comprising the nucleotide sequence of SEQ ID NO: 13, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 13.

[0045] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a poly-A sequence.

[0046] In one embodiment, the poly-A sequence comprises at least 100 nucleotides.

[0047] In one embodiment, the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 14.

[0048] In one embodiment, RNA is formulated or is to be formulated as a liquid, a solid, or a combination thereof.

[0049] In one embodiment, RNA is formulated or is to be formulated for injection.

[0050] In one embodiment, RNA is formulated or is to be formulated for intramuscular administration.

[0051] In one embodiment, RNA is formulated or is to be formulated as particles.

[0052] In one embodiment, particles are lipid nanoparticles (LNP) or lipoplex (LPX) particles.

[0053] In one embodiment, LNPs comprise ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol.

[0054] In one embodiment, RNA lipoplex particles are obtainable by mixing RNA with liposomes. In one embodiment, RNA lipoplex particles are obtainable by mixing RNA with lipids.

[0055] In one embodiment, RNA is formulated or is to be formulated as colloid. In one embodiment, RNA is formulated or is to be formulated as particles, forming the dispersed phase of a colloid. In one embodiment, 50% or more, 75% or more, or 85% or more of RNA is present in the dispersed phase. In one embodiment, RNA is formulated or is to be formulated as particles comprising RNA and lipids. In one embodiment, particles are formed by exposing RNA, dissolved in an aqueous phase, with lipids, dissolved in an organic phase. In one embodiment, the organic phase comprises ethanol. In one embodiment, particles are formed by exposing RNA, dissolved in an aqueous phase, with lipids, dispersed in an aqueous phase. In one embodiment, the lipids dispersed in an aqueous phase form liposomes.

[0056] In one embodiment, RNA is mRNA or saRNA.

[0057] In one embodiment, a composition or medical preparation is a pharmaceutical composition.

[0058] In one embodiment, a composition or medical preparation is a vaccine.

[0059] In one embodiment, a pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

[0060] In one embodiment, a composition or medical preparation is a kit.

[0061] In one embodiment, RNA and optionally the particle forming components are in separate vials.

[0062] In one embodiment, a kit further comprises instructions for use of a composition or medical preparation for inducing an immune response against coronavirus in a subject.

[0063] In one aspect, the present disclosure relates to a composition or medical preparation described herein for pharmaceutical use.

[0064] In one embodiment, a pharmaceutical use comprises inducing an immune response against coronavirus in a subject.

[0065] In one embodiment, a pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus infection.

[0066] In one embodiment, a composition or medical preparation described herein is for administration to a human.

[0067] In one embodiment, the coronavirus is a betacoronavirus.

[0068] In one embodiment, the coronavirus is a sarbecovirus.

[0069] In one embodiment, the coronavirus is SARS-CoV-2.

[0070] In one aspect, the present disclosure relates to a method of inducing an immune response against coronavirus in a subject comprising administering to the subject a composition comprising RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof.

[0071] In one embodiment, an immunogenic fragment of the SARS-CoV-2 S protein comprises the S1 subunit of the SARS-CoV-2 S protein, or the receptor binding domain (RBD) of the S1 subunit of the SARS-CoV-2 S protein.

[0072] In one embodiment, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is able to form a multimeric complex, in particular a trimeric complex. To this end, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof may comprise a domain allowing the formation of a multimeric complex, in particular a trimeric complex of the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof. In

one embodiment, the domain allowing the formation of a multimeric complex comprises a trimerization domain, for example, a trimerization domain as described herein.

[0073] In one embodiment, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

[0074] In one embodiment,

(i) the RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9; and/or

(ii) a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7.

[0075] In one embodiment, an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a secretory signal peptide.

[0076] In one embodiment, a secretory signal peptide is fused, preferably N-terminally, to a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof.

[0077] In one embodiment,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1.

[0078] In one embodiment, a composition described herein comprises an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5, XBB.1.16, BA.4/5, XBB, XBB.1, XBB.2.3, XBB.2.3.2, or BQ.1.1 Omicron variant or sublineages thereof.

[0079] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0080] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.4/5 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0081] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.2.75 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0082] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.2.75.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N.

[0083] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.4.6/BF.7 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N658S, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0084] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0085] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0086] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, E180V,

Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0087] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0088] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, G184V, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

[0089] In one embodiment, a composition described herein comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BQ.1.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

[0090] In one embodiment, a SARS-CoV-2 S protein encoded by an RNA described herein comprises one or more substitutions that stable a prefusion-confirmation. In one embodiment, the one or more substitutions that stabilize a prefusion confirmation are proline substitutions at positions corresponding to K986 and V987 of SEQ ID NO: 1.

[0091] In one embodiment, an RNA molecule comprises at least at least one modified uridine in place of a uridine. In one embodiment, an RNA molecule comprises a modified uridine in place of each uridine.

[0092] In one embodiment, an RNA molecule comprises a 5′ cap. In some embodiments, the 5‘ cap comprises (e.g., consists of) $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

[0093] In one embodiment, an RNA molecule comprises a 5′ untranslated region (UTR). In one embodiment, the 5′ UTR comprises a human alpha-globin 5′-UTR. In one embodiment, the human alpha-globin 5′ untranslated region (UTR) comprises SEQ ID NO: 12.

[0094] In one embodiment, an RNA molecule comprises a 3′ UTR. In one embodiment, the 3′ UTR comprises a first sequence from the amino terminal enhancer of split (AES) messenger RNA and a second sequence from the mitochondrial encoded 12S ribosomal RNA. In one embodiment, the 3′ UTR comprises SEQ ID NO: 13.

[0095] In one embodiment, an RNA molecule comprises a poly-A sequence of at least 100 A nucleotides. In one embodiment, the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence. In some embodiments, the poly-A sequence comprises SEQ ID NO: 14.

[0096] In one embodiment, an RNA comprises a nucleotide sequence encoding a SARS-CoV-2 S protein, wherein the sequence is codon-optimized (e.g., codon-optimized for expression in human cells) and/or which has a G/C content that is increased compared to a wild type coding sequence.

[0097] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1.5 variant, wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 158, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 159; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 161.

[0098] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron BA.4/5 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 69, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 70; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 72.

In some embodiments, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron BA.2.75 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 80, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 81; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 83.

[0099] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron BA.2.75.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 85, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 86; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 88.

[0100] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron BA.4.6/BF.7 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 90, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 91; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 93.

[0101] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 95, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 96; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 98.

[0102] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron BQ.1.1 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 100, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 101; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 103.

[0103] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1.16 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 163, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 164; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 166.

[0104] In one embodiment, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.2.3 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 168, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 169; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 171.

In some embodiments, an RNA molecule comprises a nucleotide sequence that encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.2.3.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 173, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 174; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 176.

In some embodiments, an RNA molecule is encapsulated in a lipid nanoparticle (LNP). In some embodiments, the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

[0105] In one embodiment, a composition described herein comprises a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and wherein the RNA comprises:

(a) modified uridines (e.g., modified uridines in place of all uridines);

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0106] In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 80 and comprises the nucleotide sequence of SEQ ID NO: 81 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 81, and wherein the RNA comprises:

(a) at least one modified uridine (e.g., modified uridines in place of all uridines);

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0107] In some embodiments, an RNA comprises SEQ ID NO: 83.

[0108] In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0109] In some embodiments, a composition comprises SEQ ID NO: 88.

[0110] In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 90 and comprises the nucleotide sequence of SEQ ID NO: 91 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 91, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0111] In some embodiments, an RNA comprises SEQ ID NO: 93.

In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 95 and comprises the nucleotide sequence of SEQ ID NO: 96 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 96, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0112] In some embodiments, a composition comprises an RNA comprising SEQ ID NO: 98.

In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0113] In some embodiments, a composition comprises an RNA comprising SEQ ID NO: 103.

[0114] In some embodiments, a composition comprises a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 163 and comprises the nucleotide sequence of SEQ ID NO: 164 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 164, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0115] In some embodiments, an RNA comprises SEQ ID NO: 166.

[0116] In some embodiments, a composition comprises an lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 168 and comprises the nucleotide sequence of SEQ ID NO: 169 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 169, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0117] In some embodiments, an RNA comprises SEQ ID NO: 171.

[0118] In some embodiments, a composition comprises: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 173 and comprises the nucleotide sequence of SEQ ID NO: 174 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 174, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0119] In some embodiments, an RNA comprises SEQ ID NO: 176.

[0120] In some embodiments, a composition comprises a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0121] In some embodiments, an RNA comprises SEQ ID NO: 72.

[0122] In some embodiments, a composition described herein comprises one or more additional RNA molecules, each comprising a nucleotide sequence that encodes a SARS-CoV-2 S protein of a SARS-CoV-2 variant. In some embodiments, a composition comprises one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.5. In some embodiments, the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

[0123] In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and one or more additional RNA molecules, each comprising one or more mutations associated with a SARS-CoV-2 variant that is not BA.4/5. In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

[0124] In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron BA.2.75.2 variant and one or more additional RNA molecules, each comprising one or more mutations that is associated with a SARS-CoV-2 variant that is not BA.2.75.2. In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron BA.2.75.2 variant and one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant.

[0125] In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.1.16 variant and one or more additional RNA molecules, each comprising one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.16. In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.1.16 variant and one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

[0126] In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.2.3 variant and one or more additional RNA molecules, each comprising one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3. In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.2.3 variant and one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

[0127] In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.2.3.2 variant and one or more additional RNA molecules, each comprising one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3.2. In some embodiments, a composition comprises a first RNA molecule encoding a SARS-CoV-2 S protein of an Omicron XBB.2.3.2 variant and one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

[0128] In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0129] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72.

In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0130] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

In some embodiments, described herein is a composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0131] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 101 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0132] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0133] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0134] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

[0135] In some embodiments, a composition comprises a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

[0136] In some embodiments, a composition comprises:

a first RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

a second RNA molecule that comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

[0137] In some embodiments, a composition described herein is formulated as a liquid, a solid, or a combination thereof.

[0138] In some embodiments, a composition described herein is formulated for injection. In some embodiments, a composition described herein is formulated for intramuscular administration.

[0139] In some embodiments, an RNA described herein is mRNA.

[0140] In some embodiments, an RNA described herein is saRNA.

[0141] In some embodiments, a composition described herein is a pharmaceutical composition. In some embodiments, a pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients. In some embodiments, a composition described herein is a vaccine.

[0142] In some embodiments, the present disclosure provides a method of eliciting an immune response in a subject, where the method comprising administering a composition described herein. In some embodiments, the immune response is elicited against an Omicron variant of SARS-CoV-2. In some embodiments, the immune response is elicited against a Wuhan strain, an Omicron variant, a Beta variant, an Alpha variant, and a Delta variant of SARS-CoV-2.

[0143] In some embodiments, a composition described herein is administered to a subject that has not been previously infected with and/or has not been previously administered a SARS-CoV-2 vaccine.

[0144] In some embodiments, a composition described herein is adminsitered to a subject that has previously been infected with SARS-CoV-2 and/or has been previously administered a SARS-CoV-2 vaccine.

[0145] In some embodiments, a composition described herein is adminsitered to a subject who has previously received a vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

[0146] In some embodiments, a composition described herein is adminsitered to subject who has previously been administered RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

[0147] In some embodiments, a composition described herein is adminsitered to subject who has previously been administered two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain.

[0148] In some embodiments, a composition described herein is adminsitered to subject who has previously been administered:

(i) two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., BNT162b2); and

(ii) one or more doses of a bivalent vaccine comprising:

(a) a first RNA comprising a nucleotide sequence encoding a SARS-CoV-2 S protein of a Wuhan strain; and

(b) a second RNA comprising a nucleoside sequence encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant.

[0149] In some embodiments, a composition described herein is administered to a subject who has previously been administered one or more doses of a bivalent vaccine comprising

(1) a first RNA that comprises a nucleotide sequence of that is at least 90% identical to that set forth in SEQ ID NO: 20 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical), and

(2) a second RNA that comprises a nucleotide sequence that is at least 90% identical to that set forth in SEQ ID NO: 72 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical).

[0150] In some embodiments, a composition described herein comprises about 3 μg to about 30 μg of RNA (e.g., about 3 μg, about 10 μg, or about 30 μg of RNA).

[0151] In some embodiments, a composition described herein comprises about 3 μg of RNA, and is administered to a subject who is about 6 months to less than about 5 years old.

[0152] In some embodiments, a composition described herein comprises about 10 μg of RNA, and is administered to a subject who is about 5 years old to less than about 12 years old.

[0153] In some embodiments, a composition described herein comprises about 30 μg of RNA, and is administered to a subject who is about 12 years or older.

[0154] In some embodiments, a composition described herein is co-administered with one or more vaccines against a non-SARS-CoV-2 disease (e.g., a non-SARS-CoV-2 respiratory disease). In some embodiments, the one or more vaccines against a non-SARS-CoV-2 disease comprises an influenza vaccine, an RSV vaccine, or a combination thereof.

[0155] In some embodiments, the present disclosure provides a kit comprising a composition described herein. In some embodiments the kit further comprises instructions for use of the composition to induce an immune response against coronavirus in a subject.

[0156] In some embodiments, a composition described herein is for pharmaceutical use. In some embodiments, the pharmaceutical use comprises inducing an immune response against coronavirus (e.g., a betacoronavirus, a sarbecovirus, or a SARS-CoV-2 virus) in a subject. In some embodiments, an immune response is induced in a human. In some embodiments, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus (e.g., a betacoronavirus, a sarbecovirus, or a SARS-CoV-2 virus) infection.

[0157] In some embodiments, a composition described herein is for administration to a human.

[0158] In some embodiments, a composition described herein is for pharmaceutical use. In some embodiments, the pharmaceutical use comprises inducing an immune response against coronavirus in a subject. In some embodiments, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus (e.g., a betacoronavirus, a sarbecovirus, or a SARS-CoV-2 virus) infection.

[0159] In some embodiments, described herein is the use of a composition described herein for the manufacture of a medicament for inducing an immune response against coronavirus in a subject. In some embodiments, the medicament is for therapeutic or prophylactic treatment of a coronavirus (e.g., a betacoronavirus, a sarbecovirus, or a SARS-CoV-2 virus) infection.

[0160] In some embodiments, described herein is a composition comprising an RNA molecule having:

(a) a nucleotide sequence that is at least 99% identical to SEQ ID NO: 161;

(b) a nucleotide sequence that is at least 95% identical to SEQ ID NO: 161, and which encodes a SARS-CoV-2 S protein comprising the following mutations relative to SEQ ID NO: 1: T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N,

N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, K986P, and V987P; or

(c) a nucleotide sequence as set forth in SEQ ID NO: 161; and

wherein the RNA molecule comprises:

(i) a 5′ cap; and

(ii) a modified uridine in place of each uridine.

In some embodiments, a composition comprises an RNA molecule comprising:

(i) N1-methyl-pseudouridine in place of each uridine; and

(ii) a 5′ cap that comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$;

wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP); and

wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

[0161] In some embodiments, a composition described herein comprises about 10 mM Tris buffer and about 10% sucrose.

[0162] In some embodiment, a composition comprises at least one unit dose of LNP-encapsulated RNA molecules, optionally wherein the unit dose comprises the RNA molecule in an amount of about 30 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 10 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 3 μg.

[0163] In some embodiments, a composition described herein is formulated as a multi-dose formulation in a vial.

[0164] In some embodiments, a composition described herein is for use in a method of inducing an immune response against coronavirus in a subject, said method comprising administering to a subject the composition. In some embodiments:

the subject is 12 years or older, and the composition comprises 30 μg of the RNA molecule, or

the subject is 5 years to less than 12 years old, and the composition comprises 10 μg of the RNA molecule, or

the subject is 6 months to less than 5 years old, and the composition comprises 3 μg of the RNA molecule.

[0165] In some embodiments, a composition described herein is administered in a volume of about 200 μL to 300 μL.

[0166] In some embodiments, a composition described herein is adminsitered to a subject previously administered one or more doses of a SARS-CoV-2 vaccine, preferably wherein the subject was previously administered a complete dosing regimen of a SARS-CoV-2 vaccine.

[0167] In some embodiments, a composition described herein is adminsitered to a subject previously administered a first dose and a second dose of BNT162b2, wherein the first dose and the second dose were administered about 21 days apart, and/or wherein the subject was previously administered as a booster dose a bivalent vaccine that delivers (i) a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and (ii) a SARS-CoV-2 S protein of a Wuhan strain.

[0168] In some embodiments, a composition described herein is co-administered with one or more vaccines against a non-SARS-CoV-2 disease, preferably wherein the one or more vaccines comprises an RSV vaccine, an influenza vaccine, or a combination thereof.

[0169] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant

thereof comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 12.

[0170] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 13, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 13.

[0171] In one embodiment, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a poly-A sequence.

[0172] In one embodiment, a poly-A sequence comprises at least 100 nucleotides.

[0173] In one embodiment, a poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 14.

[0174] In one embodiment, RNA is formulated as a liquid, a solid, or a combination thereof.

[0175] In one embodiment, RNA is formulated as particles.

[0176] In one embodiment, the particles are lipid nanoparticles (LNP) or lipoplex (LPX) particles.

[0177] In one embodiment, LNPs comprise ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol.

[0178] In one embodiment, RNA lipoplex particles are obtainable by mixing RNA with liposomes. In one embodiment, RNA lipoplex particles are obtainable by mixing RNA with lipids.

[0179] In one embodiment, RNA is formulated as colloid. In one embodiment, RNA is formulated as particles, forming the dispersed phase of a colloid. In one embodiment, 50% or more, 75% or more, or 85% or more of RNA are present in the dispersed phase. In one embodiment, RNA is formulated as particles comprising RNA and lipids. In one embodiment, particles are formed by exposing RNA, dissolved in an aqueous phase, with lipids, dissolved in an organic phase. In one embodiment, the organic phase comprises ethanol. In one embodiment, particles are formed by exposing RNA, dissolved in an aqueous phase, with lipids, dispersed in an aqueous phase. In one embodiment, the lipids dispersed in an aqueous phase form liposomes.

[0180] In one embodiment, a method disclosed herein is a method for vaccination against coronavirus.

[0181] In one embodiment, a method disclosed herein is a method for therapeutic or prophylactic treatment of a coronavirus infection.

[0182] In one embodiment, a subject is a human.

[0183] In one embodiment, the coronavirus is a betacoronavirus.

[0184] In one embodiment, the coronavirus is a sarbecovirus.

[0185] In one embodiment, the coronavirus is SARS-CoV-2.

[0186] In one embodiment of methods described herein, a composition described herein is administered to a subject.

[0187] In one aspect, the present disclosure relates to a composition or medical preparation described herein for use in a method described herein.

[0188] Among other things, the present disclosure teaches that a composition comprising a lipid nanoparticle encapsulated RNA encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein) can achieve detectable antibody titer against an epitope in serum within 7 days after administration to a population of adult human subjects according to a regimen that includes administration of at least one dose of the composition. Moreover, the present disclosure teaches

persistence of such antibody titer. In some embodiments, such antibody titer is increased when a modified mRNA is used, as compared with titer achieved with a corresponding unmodified mRNA.

[0189] In some embodiments, a provided regimen includes at least one dose. In some embodiments, a provided regimen includes a first dose and at least one subsequent dose. In some embodiments, the first dose is the same amount as at least one subsequent dose. In some embodiments, the first dose is the same amount as all subsequent doses. In some embodiments, the first dose is a different amount as at least one subsequent dose. In some embodiments, the first dose is a different amount than all subsequent doses. In some embodiments, a provided regimen comprises two doses. In some embodiments, a provided regimen consists of two doses.

[0190] In particular embodiments, an immunogenic composition is formulated as a single-dose in a container, e.g., a vial. In some embodiments, an immunogenic composition is formulated as a multi-dose formulation in a vial. In some embodiments, the multi-dose formulation includes at least 2 doses per vial. In some embodiments, the multi-dose formulation includes a total of 2-20 doses per vial, such as, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 doses per vial. In some embodiments, each dose in the vial is equal in volume. In some embodiments, a first dose is a different volume than a subsequent dose.

[0191] A "stable" multi-dose formulation exhibits no unacceptable levels of microbial growth, and substantially no or no breakdown or degradation of the active biological molecule component(s). As used herein, a "stable" immunogenic composition includes a formulation that remains capable of eliciting a desired immunologic response when administered to a subject.

[0192] In some embodiments, a multi-dose formulation remains stable for a specified time with multiple or repeated inoculations/insertions into the multi-dose container. For example, in some embodiments a multi-dose formulation may be stable for at least three days with up to ten usages, when contained within a multi-dose container. In some embodiments, multi-dose formulations remain stable with 2-20 inoculations/insertions.

[0193] In some embodiments, administration of a composition comprising a lipid nanoparticle encapsulated RNA (e.g., in some embodiments mRNA) encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein), e.g., according to a regimen as described herein, may result in lymphopenia in some subjects (e.g., in all subjects, in most subjects, in about 50% or fewer, in about 40% or fewer, in about 40% or fewer, in about 25% or fewer, in about 20% or fewer, in about 15% or fewer, in about 10% or fewer, in about 5% or fewer, etc). Among other things, the present disclosure teaches that such lymphopenia can resolve over time. For example, in some embodiments, lymphopenia resolves within about 14, about 10, about 9, about 8, about 7 days or less. In some embodiments, lymphopenia is Grade 3, Grade 2, or less.

[0194] Thus, among other things, the present disclosure provides compositions comprising a lipid nanoparticle encapsulated RNA (e.g., in some embodiments mRNA) encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein) that are characterized, when administered to a relevant population of adults, to display certain characteristics (e.g., achieve certain effects) as described herein. In some embodiments, provided compositions may have been prepared, stored, transported, characterized, and/or used under conditions where temperature does not exceed a particular threshold. Alternatively or additionally, in some embodiments, provided compositions may have been protected from light (e.g., from certain wavelengths) during some or all of their preparation, storage, transport, characterization, and/or use. In some embodiments, one or more features of provided compositions (e.g., RNA stability, as may be assessed, for example, by one or more of size, presence of particular moiety or modification, etc; lipid nanoparticle stability or aggregation, pH, etc) may be or have been assessed at one or more points during preparation, storage, transport, and/or use prior to administration.

[0195] Among other things, the present disclosure documents that certain provided compositions in which nucleotides within an RNA (e.g., in some embodiments mRNA) are not modified (e.g., are naturally-occurring A, U, C, G), and/or provided methods relating to such compositions, are characterized (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population), by an intrinsic adjuvant effect. In some embodiments, such a composition and/or method can induce an antibody and/or a T cell response. In some embodiments, such a composition and/or method can induce a higher T cell response, as compared to conventional vaccines (e.g., non-RNA vaccines such as protein vaccines).

[0196] Alternatively or additionally, the present disclosure documents that provided compositions (e.g., compositions comprising a lipid nanoparticle encapsulated RNA encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein)) in which nucleotides within an RNA are modified, and/or provided methods relating to such compositions, are characterized (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population), by absence of an intrinsic adjuvant effect, or by a reduced intrinsic adjuvant effect as compared with an otherwise comparable composition (or method) with unmodified results. Alternatively or additionally, in some embodiments, such compositions (or methods) are characterized in that they (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population) induce an antibody response and/or a CD4+ T cell response. Still further alternatively or additionally, in some embodiments, such compositions (or methods) are characterized in that they (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population) induce a higher CD4+ T cell response than that observed with an alternative vaccine format (e.g., a peptide vaccine). In some embodiments involving modified nucleotides, such modified nucleotides may be present, for example, in a 3′ UTR sequence, an antigen-encoding sequence, and/or a 5′UTR sequence. In some embodiments, modified nucleotides are or include one or more modified uracil residues and/or one or more modified cytosine residues.

[0197] Among other things, the present disclosure documents that provided (e.g., compositions comprising a lipid nanoparticle encapsulated RNA encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein)) and/or methods are characterized by (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population) sustained expression of an encoded polypeptide (e.g., of a SARS-CoV-2-encoded protein [such as an S protein] or portion thereof, which portion, in some embodiments, may be or comprise an epitope thereof). For example, in some embodiments, such compositions and/or methods are characterized in that, when administered to a human, they achieve detectable polypeptide expression in a biological sample (e.g., serum) from such human and, in some embodiments, such expression persists for a period of time that is at least at least 36 hours or longer, including, e.g., at least 48 hours, at least 60 hours, at least 72 hours, at least 96 hours, at least 120 hours, at least 148 hours, or longer.

[0198] Those skilled in the art, reading the present disclosure, will appreciate that it describes various RNA constructs (e.g., in some embodiments mRNA constructs) encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein)). Such person of ordinary skill, reading the present disclosure, will particularly appreciate that it describes various RNA constructs (e.g., in some embodiments mRNA constructs) encoding at least a portion of a SARS-CoV-2 S protein, for example at least an RBD portion of a SARS-CoV-2 S protein. Still further, such a person of ordinary skill, reading the present disclosure, will appreciate that it describes particular characteristics and/or advantages of RNA constructs (e.g., in some embodiments mRNA constructs) encoding at least a portion (e.g., that is or comprises an epitope) of a SARS-CoV-2-encoded polypeptide (e.g., of a SARS-CoV-2-encoded S protein). In some embodiments, an RNA construct

(e.g., in some embodiments, an mRNA construct) may encode at least one domain of a SARS-CoV-2 encoded polypeptide (e.g., one or more domains of a SARS-CoV-2 encoded polypeptide as described in WO 2021/159040, including, e.g., an N-terminal domain (NTD) of a SARS-CoV-2 Spike protein, a receptor binding domain (RBD) of a SARS- CoV-2 Spike protein, Heptapeptide repeat sequence 1 (HR1) of a SARS-CoV-2 Spike protein, Heptapeptide repeat sequence 2 (HR1) of a SARS-CoV-2 Spike protein, and/or combinations thereof). Among other things, the present disclosure particularly documents surprising and useful characteristics and/or advantages of certain RNA constructs (e.g., in some embodiments mRNA constructs) encoding a SARS-CoV-2 RBD portion and, in some embodiments, not encoding a full length SARS-CoV-2 S protein. Without wishing to be bound by any particular theory, the present disclosure suggests that provided RNA constructs (e.g., in some embodiments mRNA constructs) that encode less than a full-length SARS-CoV-2 S protein, and particularly those that encode at least an RBD portion of such SARS-CoV-2 S protein may be particularly useful and/or effective for use as or in an immunogenic composition (e.g., a vaccine), and/or for achieving immunological effects as described herein (e.g., generation of SARS-CoV-2 neutralizing antibodies, and/or T cell responses (e.g., CD4+ and/or CD8+ T cell responses)).

[0199] In some embodiments, the present disclosure provides an RNA (e.g., mRNA) comprising an open reading frame encoding a polypeptide that comprises a receptor-binding portion of a SARS-CoV-2 S protein, which RNA is suitable for intracellular expression of the polypeptide. In some embodiments, such an encoded polypeptide does not comprise the complete S protein. In some embodiments, an encoded polypeptide comprises the receptor binding domain (RBD), for example, as shown in SEQ ID NO: 5. In some embodiments, the encoded polypeptide comprises the peptide according to SEQ ID NO: 29 or 31. In some embodiments, such an RNA (e.g., mRNA) may be complexed by a (poly)cationic polymer, polyplex(es), protein(s) or peptide(s). In some embodiments, such an RNA may be formulated in a lipid nanoparticle (e.g., ones described herein). In some embodiments, such an RNA (e.g., mRNA) may be particularly useful and/or effective for use as or in an immunogenic composition (e.g., a vaccine), and/or for achieving immunological effects as described herein (e.g., generation of SARS-CoV-2 neutralizing antibodies, and/or T cell responses (e.g., CD4+ and/or CD8+ T cell responses)). In some embodiments, such an RNA (e.g., mRNA) may be useful for vaccinating humans (including, e.g., humans known to have been exposed and/or infected by SARS-CoV-2, and/or humans not known to have been exposed to SARS-CoV-2).

[0200] Those skilled in the art, reading the present disclosure, will further appreciate that it describes various mRNA constructs comprising a nucleic acid sequence that encodes a full-length SARS-CoV-2 Spike protein (e.g., including embodiments in which such encoded SARS-CoV-2 Spike protein may comprise at least one or more amino acid substitutions, e.g., proline substitutions as described herein, and/or embodiments in which the mRNA sequence is codon-optimized e.g., for mammalian, e.g., human, subjects). In some embodiments, such a full-length SARS-CoV-2 Spike protein may have an amino acid sequence that is or comprises that set forth in SEQ ID NO: 7. Still further, such a person of ordinary skill, reading the present disclosure, will appreciate, among other things, that it describes particular characteristics and/or advantages of certain mRNA constructs comprising a nucleic acid sequence that encodes a full-length SARS-CoV-2 Spike protein. Without wishing to be bound by any particular theory, the present disclosure suggests that provided mRNA constructs that encode a full-length SARS-CoV-2 S protein may be particularly useful and/or effective for use as or in an immunogenic composition (e.g., a vaccine) in particular subject population (e.g., particular age populations). For example, in some embodiments, such an mRNA composition may be particularly useful in younger (e.g., less than 25 years old, 20 years old, 18 years old, 15 years, 10 years old, or lower) subjects; alternatively or additionally, in some embodiments, such an mRNA composition may be particularly useful in elderly subjects (e.g., over 55 years old, 60 years old, 65 years old, 70 years old, 75 years old, 80 years old, 85 years old, or higher). In particular embodiments, an immunogenic composition comprising such an mRNA construct provided herein exhibits a minimal to modest increase (e.g., no

more than 30% increase, no more than 20% increase, or no more than 10% increase, or lower) in dose level and/or dose number-dependent systemic reactogenicity (e.g., fever, fatigue, headache, chills, diarrhea, muscle pain, and/or joint pain, etc.) and/or local tolerability (e.g., pain, redness, and/or swelling, etc.), at least in some subjects (e.g., in some subject age groups); in some embodiments, such reactogenicity and/or local tolerability is observed particularly, in in younger age group (e.g., less than 25 years old, 20 years old, 18 years old or lower) subjects, and/or in older (e.g., elderly) age group (e.g., 65-85 years old). In some embodiments, provided mRNA constructs that encode a full-length SARS-CoV-2 S protein may be particularly useful and/or effective for use as or in an immunogenic composition (e.g., a vaccine) for inducing SARS-CoV-2 neutralizing antibody response level in a population of subjects that are at high risk for severe diseases associated with SARS-CoV-2 infection (e.g., an elderly population, for example, 65-85 year-old group). In some embodiments, a person of ordinary skill, reading the present disclosure, will appreciate, among other things, that provided mRNA constructs that encode a full-length SARS-CoV-2 S protein, which exhibit a favorable reactogenicity profile (e.g., as described herein) in younger and elderly age populations, may be particularly useful and/or effective for use as or in an immunogenic composition (e.g., a vaccine) for achieving immunological effects as described herein (e.g., generation of SARS-CoV-2 neutralizing antibodies, and/or T cell responses (e.g., CD4+ and/or CD8+ T cell responses)). In some embodiments, the present disclosure also suggests that provided mRNA constructs that encode a full-length SARS-CoV-2 S protein may be particularly effective to protect against SARS-CoV-2 infection, as characterized by earlier clearance of SARS-CoV-2 viral RNA in non-human mammalian subjects (e.g., rhesus macaques) that were immunized with immunogenic compositions comprising such mRNA constructs and subsequently challenged by SARS-CoV-2 strain. In some embodiments, such earlier clearance of SARS-CoV-2 viral RNA may be observed in the nose of non-human mammalian subjects (e.g., rhesus macaques) that were immunized with immunogenic compositions comprising such mRNA constructs and subsequently challenged by SARS-CoV-2 strain.

[0201] In some embodiments, the present disclosure provides an RNA (e.g., mRNA) comprising an open reading frame encoding a full-length SARS-CoV-2 S protein (e.g., a full-length SARS-CoV-2 S protein with one or more amino acid substitutions), which RNA is suitable for intracellular expression of the polypeptide. In some embodiments, the encoded polypeptide comprises the amino acid sequence of SEQ ID NO:7. In some embodiments, such an RNA (e.g., mRNA) may be complexed by a (poly)cationic polymer, polyplex(es), protein(s) or peptide(s). In some embodiments, such an RNA may be formulated in a lipid nanoparticle (e.g., ones described herein).

[0202] In some embodiments, an immunogenic composition provided herein may comprise a plurality of (e.g., at least two or more, including, e.g., at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, etc.) immunoreactive epitopes of a SARS-CoV-2 polypeptide or variants thereof. In some such embodiments, such a plurality of immunoreactive epitopes may be encoded by a plurality of RNAs (e.g., mRNAs). In some such embodiments, such a plurality of immunoreactive epitopes may be encoded by a single RNA (e.g., mRNA). In some embodiments, nucleic acid sequences encoding a plurality of immunoreactive epitopes may be separated from each other in a single RNA (e.g., mRNA) by a linker (e.g., a peptide linker in some embodiments). Without wishing to be bound by any particular theory, in some embodiments, provided polyepitope immunogenic compositions (including, e.g., those that encode a full-length SARS-CoV-2 spike protein) may be particularly useful, when considering the genetic diversity of SARS-CoV-2 variants, to provide protection against numerous viral variants and/or may offer a greater opportunity for development of a diverse and/or otherwise robust (e.g., persistent, e.g., detectable about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 or more days after administration of one or more doses) neutralizing antibody and/or T cell response, and in particular a particularly robust T_H1-type T cell (e.g., CD4+ and/or CD8+ T cell) response.

[0203] In some embodiments, the present disclosure documents that provided compositions and/or methods are characterized by (e.g., when administered to a relevant population, which may in some embodiments be or comprise an adult population) in that they achieve one or more particular therapeutic outcomes (e.g., effective immune responses as described herein and/or detectable expression of encoded SARS-CoV-2 S protein or an immunogenic fragment thereof) with a single administration; in some such embodiments, an outcome may be assessed, for example, as compared to that observed in absence of RNA vaccines (e.g., mRNA vaccines) described herein. In some embodiments, a particular outcome may be achieved at a lower dose than required for one or more alternative strategies.

[0204] In some embodiments, the present disclosure provides an immunogenic composition comprising an isolated messenger ribonucleic acid (mRNA) polynucleotide, wherein the isolated mRNA polynucleotide comprises an open reading frame encoding a polypeptide that comprises a receptor-binding portion of a SARs-CoV-2 S protein, and wherein the isolated mRNA polynucleotide is formulated in at least one lipid nanoparticle. For example, in some embodiments, such a lipid nanoparticle may comprise a molar ratio of 20-60% ionizable cationic lipid, 5-25% non-cationic lipid (e.g., neutral lipid), 25-55% sterol or steroid, and 0.5-15% polymer-conjugated lipid (e.g., PEG-modified lipid). In some embodiments, a sterol or steroid included in a lipid nanoparticle may be or comprise cholesterol. In some embodiments, a neutral lipid may be or comprise 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC). In some embodiments, a polymer-conjugated lipid may be or comprise PEG2000 DMG. In some embodiments, such an immunogenic composition may comprise a total lipid content of about 1 mg to 10 mg, or 3 mg to 8 mg, or 4 mg to 6 mg. In some embodiments, such an immunogenic composition may comprise a total lipid content of about 5 mg/mL -15 mg/mL or 7.5 mg/mL- 12.5 mg/mL or 9-11 mg/mL. In some embodiments, such an isolated mRNA polynucleotide is provided in an effective amount to induce an immune response in a subject administered at least one dose of the immunogenic composition. In some embodiments, a polypeptide encoded by a provided isolated mRNA polynucleotide does not comprise the complete S protein. In some embodiments, such an isolated mRNA polynucleotide provided in an immunogenic composition is not self-replicating RNA.

[0205] In some embodiments, an immune response may comprise generation of a binding antibody titer against SARS-CoV-2 protein (including, e.g., a stabilized prefusion spike trimer in some embodiments) or a fragment thereof. In some embodiments, an immune response may comprise generation of a binding antibody titer against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. In some embodiments, a provided immunogenic composition has been established to achieve a detectable binding antibody titer after administration of a first dose, with seroconversion in at least 70% (including, e.g., at least 80%, at least 90%, at least 95% and up to 100%) of a population of subjects receiving such a provided immunogenic composition, for example, by about 2 weeks.

[0206] In some embodiments, an immune response may comprise generation of a neutralizing antibody titer against SARS-CoV-2 protein (including, e.g., a stabilized prefusion spike trimer in some embodiments) or a fragment thereof. In some embodiments, an immune response may comprise generation of a neutralizing antibody titer against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. In some embodiments, a provided immunogenic composition has been established to achieve a neutralizing antibody titer in an appropriate system (e.g., in a human infected with SARS-CoV-2 and/or a population thereof, and/or in a model system therefor). For example, in some embodiments, such neutralizing antibody titer may have been demonstrated in one or more of a population of humans, a non-human primate model (e.g., rhesus macaques), and/or a mouse model.

[0207] In some embodiments, a neutralizing antibody titer is a titer that is (e.g., that has been established to be) sufficient to reduce viral infection of B cells relative to that observed for an appropriate control (e.g., an unvaccinated control subject, or a subject vaccinated with a live attenuated viral vaccine, an inactivated viral

vaccine, or a protein subunit viral vaccine, or a combination thereof). In some such embodiments, such reduction is of at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

[0208] In some embodiments, a neutralizing antibody titer is a titer that is (e.g., that has been established to be) sufficient to reduce the rate of asymptomatic viral infection relative to that observed for an appropriate control (e.g., an unvaccinated control subject, or a subject vaccinated with a live attenuated viral vaccine, an inactivated viral vaccine, or a protein subunit viral vaccine, or a combination thereof). In some such embodiments, such reduction is of at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In some embodiments, such reduction can be characterized by assessment of SARS-CoV-2 N protein serology. Significant protection against asymptomatic infection was also confirmed by real life observations (see also: Dagan N. et al., N Engl J Med. 2021, doi: 10.1056/NEJMoa2101765, Epub ahead of print. PMID: 33626250).

[0209] In some embodiments, a neutralizing antibody titer is a titer that is (e.g., that has been established to be) sufficient to reduce or block fusion of virus with epithelial cells and/or B cells of a vaccinated subject relative to that observed for an appropriate control (e.g., an unvaccinated control subject, or a subject vaccinated with a live attenuated viral vaccine, an inactivated viral vaccine, or a protein subunit viral vaccine, or a combination thereof). In some such embodiments, such reduction is of at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

[0210] In some embodiments, induction of a neutralizing antibody titer may be characterized by an elevation in the number of B cells, which in some embodiments may include plasma cells, class-switched IgG1- and IgG2-positive B cells, and/or germinal center B cells. In some embodiments, a provided immunogenic composition has been established to achieve such an elevation in the number of B cells in an appropriate system (e.g., in a human infected with SARS-CoV-2 and/or a population thereof, and/or in a model system therefor). For example, in some embodiments, such an elevation in the number of B cells may have been demonstrated in one or more of a population of humans, a non-human primate model (e.g., rhesus macaques), and/or a mouse model. In some embodiments, such an elevation in the number of B cells may have been demonstrated in draining lymph nodes and/or spleen of a mouse model after (e.g., at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, after) immunization of such a mouse model with a provided immunogenic composition.

[0211] In some embodiments, induction of a neutralizing antibody titer may be characterized by a reduction in the number of circulating B cells in blood. In some embodiments, a provided immunogenic composition has been established to achieve such a reduction in the number of circulating B cells in blood of an appropriate system (e.g., in a human infected with SARS-CoV-2 and/or a population thereof, and/or in a model system therefor). For example, in some embodiments, such a reduction in the number of circulating B cells in blood may have been demonstrated in one or more of a population of humans, a non-human primate model (e.g., rhesus macaques), and/or a mouse model. In some embodiments, such a reduction in the number of circulating B cells in blood may have been demonstrated in a mouse model after (e.g., at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, after) immunization of such a mouse model with a provided immunogenic composition. Without wishing to be bound by theory, a reduction in circulating B cells in blood may be due to B cell homing to lymphoid compartments.

[0212] In some embodiments, an immune response induced by a provided immunogenic composition may comprise an elevation in the number of T cells. In some embodiments, such an elevation in the number of T cells may include an elevation in the number of T follicular helper (T_{FH}) cells, which in some embodiments may comprise one or more subsets with ICOS upregulation. One of skilled in the art will understand that proliferation of T_{FH} in germinal centres is integral for generation of an adaptive B-cell response, and also that in humans, T_{FH} occurring

in the circulation after vaccination is typically correlated with a high frequency of antigen-specific antibodies. In some embodiments, a provided immunogenic composition has been established to achieve such an elevation in the number of T cells (e.g., T_{FH} cells) in an appropriate system (e.g., in a human infected with SARS-CoV-2 and/or a population thereof, and/or in a model system therefor). For example, in some embodiments, such an elevation in the number of T cells (e.g., T_{FH} cells) may have been demonstrated in one or more of a population of humans, a non-human primate model (e.g., rhesus macaques), and/or a mouse model. In some embodiments, such an elevation in the number of T cells (e.g., e.g., T_{FH} cells) may have been demonstrated in draining lymph nodes, spleen, and/or blood of a mouse model after (e.g., at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, after) immunization of such a mouse model with a provided immunogenic composition.

[0213] In some embodiments, a protective response against SARS-CoV-2 induced by a provided immunogenic composition has been established in an appropriate model system for SARS-CoV-2. For example, in some embodiments, such a protective response may have been demonstrated in an animal model, e.g., a non-human primate model (e.g., rhesus macaques) and/or a mouse model. In some embodiments, a non-human primate (e.g., rhesus macaque) or a population thereof that has/have received at least one immunization with a provided immunogenic composition is/are challenged with SARS-CoV-2, e.g., through intranasal and/or intratracheal route. In some embodiments, such a challenge may be performed several weeks (e.g., 5-10 weeks) after at least one immunization (including, e.g., at least two immunizations) with a provided immunogenic composition. In some embodiments, such a challenge may be performed when a detectable level of a SARS-CoV-2 neutralizing titer (e.g., antibody response to SARS-CoV-2 spike protein and/or a fragment thereof, including, e.g., but not limited to a stabilized prefusion spike trimer, S-2P, and/or antibody response to receptor-binding portion of SARS-CoV-2) is achieved in non-human primate(s) (e.g., rhesus macaque(s)) that has received at least one immunization (including, e.g., at least two immunizations) with a provided immunogenic composition. In some embodiments, a protective response is characterized by absence of or reduction in detectable viral RNA in bronchoalveolar lavage (BAL) and/or nasal swabs of challenged non-human primate(s) (e.g., rhesus macaque(s)). In some embodiments, immunogenic compositions described herein may have been characterized in that a larger percent of challenged animals, for example, non-human primates in a population (e.g., rhesus macaques), that have received at least one immunization (including, e.g., at least two immunizations) with a provided immunogenic composition display absence of detectable RNA in their BAL and/or nasal swab, as compared to a population of non-immunized animals, for example, non-human primates (e.g., rhesus macaques). In some embodiments, immunogenic compositions described herein may have been characterized in that challenged animals, for example, non-human in a population (e.g., rhesus macaques), that have received at least one immunization (including, e.g., at least two immunizations) with a provided immunogenic composition may show clearance of viral RNA in nasal swab no later than 10 days, including, e.g., no later than 8 days, no later than 6 days, no later than 4 days, etc., as compared to a population of non-immunized animals, for example, non-human primates (e.g., rhesus macaques).

[0214] In some embodiments, immunogenic compositions described herein when administered to subjects in need thereof do not substantially increase the risk of vaccine-associated enhanced respiratory disease. In some embodiments, such vaccine-associated enhanced respiratory disease may be associated with antibody-dependent enhancement of replication and/or with vaccine antigens that induced antibodies with poor neutralizing activity and Th2-biased responses. In some embodiments, immunogenic compositions described herein when administered to subjects in need thereof do not substantially increase the risk of antibody-dependent enhancement of replication.

[0215] In some embodiments, a single dose of an RNA composition (e.g., mRNA formulated in lipid nanoparticles) can induce a therapeutic antibody response in less than 10 days of vaccination. In some embodiments, such a therapeutic antibody response may be characterized in that when such an RNA vaccine can induce production of about 10-100 ug/mL IgG measured at 10 days after vaccination at a dose of 0.1 to 10 ug or 0.2- 5 ug in an animal model. In some embodiments, such a therapeutic antibody response may be characterized in that such an RNA vaccine induces about 100-1000 ug/mL IgG measured at 20 days of vaccination at a dose of 0.1 to 10 ug or 0.2- 5 ug in an animal model. In some embodiments, a single dose may induce a pseudovirus-neutralization titer, as measured in an animal model, of 10-200 pVN50 titer 15 days after vaccination. In some embodiments, a single dose may induce a pseudovirus-neutralization titer, as measured in an animal model, of 50-500 pVN50 titer 15 days after vaccination.

[0216] In some embodiments, a single dose of an RNA composition (e.g., mRNA composition) can expand antigen-specific CD8 and/or CD4 T cell response by at least at 50% or more (including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or more), as compared to that observed in absence of such an RNA construct encoding a SARS-COV2 immunogenic protein or fragment thereof (e.g., spike protein and/or receptor binding domain). In some embodiments, a single dose of an RNA composition can expand antigen-specific CD8 and/or CD4 T cell response by at least at 1.5-fold or more (including, e.g., at least 2-fold, at least 3-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1000-fold, or more), as compared to that observed in absence of such an RNA construct encoding a SARS-COV2 immunogenic protein or fragment thereof (e.g., spike protein and/or receptor binding domain).

[0217] In some embodiments, a regimen (e.g., a single dose of an mRNA composition) can expand T cells that exhibit a Th1 phenotype (e.g., as characterized by expression of IFN-gamma, IL-2, IL-4, and/or IL-5) by at least at 50% or more (including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or more), as compared to that observed in absence of such an mRNA construct encoding a SARS-COV2 immunogenic protein or fragment thereof (e.g., spike protein and/or receptor binding domain). In some embodiments, a regimen (e.g., a single dose of an mRNA composition) can expand T cells that exhibit a Th1 phenotype (e.g., as characterized by expression of IFN-gamma, IL-2, IL-4, and/or IL-5), for example by at least at 1.5-fold or more (including, e.g., at least 2-fold, at least 3-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1000-fold, or more), as compared to that observed in absence of such an mRNA construct encoding a SARS-COV2 immunogenic protein or fragment thereof (e.g., spike protein and/or receptor binding domain). In some embodiments, a T-cell phenotype may be or comprise a Th1-dominant cytokine profile (e.g., as characterized by INF-gamma positive and/or IL-2 positive), and/or no by or biologically insignificant IL-4 secretion.

[0218] In some embodiments, a regimen as described herein (e.g., one or more doses of an mRNA composition) induces and/or achieves production of RBD-specific CD4+ T cells. Among other things, the present disclosure documents that mRNA compositions encoding an RBD-containing portion of a SARS-CoV-2 spike protein (e.g., and not encoding a full-length SARS-CoV-2 spike protein) may be particularly useful and/or effective in such induction and/or production of RBD-specific CD4+ T cells. In some embodiments, RBD-specific CD4+ T-cells induced by an mRNA composition described herein (e.g., by an mRNA composition that encodings an RBD-containing-portion of a SARS-CoV-2 spike protein and, in some embodiments not encoding a full-length SARS-CoV-2 spike protein) demonstrate a Th1-dominant cytokine profile (e.g., as characterized by INF-gamma positive and/or IL-2 positive), and/or by no or biologically insignificant IL-4 secretion.

[0219] In some embodiments, characterization of CD4+ and/or CD8+ T cell responses (e.g., described herein) in subjects receiving RNA compositions (e.g., as described herein) may be performed using ex vivo assays using PBMCs collected from the subjects.

[0220] In some embodiments, immunogenicity of RNA (e.g., mRNA) compositions described herein may be assessed by one of or more of the following serological immunongenicity assays: detection of IgG, IgM, and/or IgA to SARS-CoV-2 S protein present in blood samples of a subject receiving a provided RNA composition, and/or neutralization assays using SARS-CoV-2 pseudovirus and/or a wild-type SARS-CoV-2 virus.

[0221] In some embodiments, an RNA composition (e.g., as described herein) provide a relatively low adverse effect (e.g., Grade 1-Grade 2 pain, redness and/or swelling) within 7 days after vaccinations at a dose of 10 ug – 100 ug or 1 ug-50 ug. In some embodiments, RNA compositions (e.g., as described herein) provide a relatively low observation of systemic events (e.g., Grade 1-Grade 2 fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain, medication, and combinations thereof) within 7 days after vaccinations at a dose of 10 ug – 100 ug.

[0222] In some embodiments, RNA (e.g., mRNA) compositions are characterized in that when administered to subjects at 10-100 ug dose or 1 ug-50 ug, IgG directed to a SARS-CoV2 immunogenic protein or fragment thereof (e.g., spike protein and/or receptor binding domain) may be produced at a level of 100-100,000 U/mL or 500-50,000 U/mL 21 days after vaccination.

[0223] In some embodiments, an RNA (e.g., mRNA) encodes a natively-folded trimeric receptor binding protein of SARS-CoV-2. In some embodiments, an RNA (e.g., mRNA) encodes a variant of such receptor binding protein such that the encoded variant binds to ACE2 at a Kd of 10 pM or lower, including, e.g., at a Kd of 9 pM, 8 pM, 7 pM, 6 pM, 5 pM, 4 pM, or lower. In some embodiments, an RNA (e.g., mRNA) encodes a variant of such receptor binding protein such that the encoded variant binds to ACE2 at a Kd of 5 pM. In some embodiments, an RNA (e.g., mRNA) encodes a trimeric receptor binding portion of SARS-CoV-2 that comprises an ACE2 receptor binding site. In some embodiments, an RNA (e.g., mRNA) comprises a coding sequence for a receptor-binding portion of SARS-CoV-2 and a trimerization domain (e.g., a natural trimerization domain (foldon) of T4 fibritin) such that the coding sequence directs expression of a trimeric protein that has an ACE2 receptor binding site and binds ACE2. In some embodiments, an RNA (e.g., mRNA) encodes a trimeric receptor binding portion of SARS-CoV-2 or a variant thereof such that its Kd is smaller than that for a monomeric receptor-binding domain (RBD) of SARS-CoV-2. For example, in some embodiments, an RNA (e.g., mRNA) encodes a trimeric receptor binding portion of SARS-CoV-2 or a variant thereof such that its Kd is at least 10-fold (including, e.g., at least 50-fold, at least 100-fold, at least 500-fold, at least 1000-fold, etc.) smaller than that for a RBD of SARS-CoV-2.

[0224] In some embodiments, a trimer receptor binding portion of SARS-CoV-2 encoded by an RNA (e.g., as described herein) may be determined to have a size of about 3-4 angstroms when it is complexed with ACE2 and B^0AT1 neutral amino acid transporter in a closed conformation, as characterized by electron cryomicroscopy (cryoEM). In some embodiments, geometric mean SARS-CoV-2 neutralizing titer that characterizes and/or is achieved by an RNA composition or method as described herein can reach at least 1.5-fold, including, at least 2-fold, at least 2.5-fold, at least 3-fold, or higher, that of a COVID-19 convalescent human panel (e.g., a panel of sera from COVID-19 convalescing humans obtained 20-40 days after the onset of symptoms and at least 14 days after the start of asymptomatic convalescence.

[0225] In some embodiments, RNA compositions as provided herein may be characterized in that subjects who have been treated with such compositions (e.g., with at least one dose, at least two doses, etc) may show reduced and/or more transient presence of viral RNA in relevant site(s) (e.g., nose and/or lungs, etc, and/or any other tissue susceptible to infection) as compared with an appropriate control (e.g., an established expected level for a comparable subject or population not having been so treated and having been exposed to virus under reasonably comparable exposure conditions).

[0226] In some embodiments, the RBD antigen expressed by an mRNA construct (e.g., as described herein) can be modified by addition of a T4-fibritin-derived "foldon" trimerization domain, for example, to increase its immunogenicity.

[0227] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that certain local reactions (e.g., pain, redness, and/or swelling, etc.) and/or systemic events (e.g., fever, fatigue, headache, etc.) may appear and/or peak at Day 2 after vaccination. In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that certain local reactions (e.g., pain, redness, and/or swelling, etc.) and/or systemic events (e.g., fever, fatigue, headache, etc.) may resolve by Day 7 after vaccination.

[0228] In some embodiments, RNA compositions (e.g., mRNA) and/or methods described herein are characterized in that no Grade 1 or greater change in routine clinical laboratory values or laboratory abnormalities are observed in subjects receiving RNA compositions (e.g., as described herein). Examples of such clinical laboratory assays may include lymphocyte count, hematological changes, etc.

[0229] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that by 21 days after a first dose (e.g., 10-100 ug inclusive or 1 ug-50 ug inclusive), geometric mean concentrations (GMCs) of IgG directed to a SARS-CoV-2 S polypeptide or an immunogenic fragment thereof (e.g., RBD) may reach 200-3000 units/mL or 500-3000 units/mL or 500-2000 units/mL, compared to 602 units/mL for a panel of COVID-19 convalescent human sera. In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that by 7 days after a second dose (e.g., 10-30 ug inclusive; or 1 ug-50 ug inclusive), geometric mean concentrations (GMCs) of IgG directed to a SARS-CoV-2 spike polypeptide or an immunogenic fragment thereof (e.g., RBD) may increase by at least 8-fold or higher, including, e.g., at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, or higher. In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that by 7 days after a second dose (e.g., 10-30 ug inclusive; or 1 ug-50 ug inclusive), geometric mean concentrations (GMCs) of IgG directed to a SARS-CoV-2 S polypeptide or an immunogenic fragment thereof (e.g., RBD) may increase to 1500 units/mL to 40,000 units/mL or 4000 units/mL to 40,000 units/mL. In some embodiments, antibody concentrations described herein can persist to at least 20 days or longer, including, e.g., at least 25 days, at least 30 days, at least 35 days, at least 40 days, at least 45 days, at least 50 days, after a first dose, or at least 10 days or longer, including, e.g., at least 15 days, at least 20 days, at least 25 days, or longer, after a second dose. In some embodiments, antibody concentrations can persist to 35 days after a first dose, or at least 14 days after a second dose.

[0230] In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that when measured at 7 days after a second dose (e.g., 1-50 ug inclusive), GMC of IgG directed to a SARS-CoV-2 S polypeptide or an immunogenic fragment thereof (e.g., RBD) is at least 30% higher (including, e.g., at least 40% higher, at least 50% higher, at least 60%, higher, at least 70% higher, at least 80% higher, at least 90% higher, at least 95 % higher, as compared to antibody concentrations observed in a panel of COVID-19 convalescent human serum. In many embodiments, geometric mean concentration (GMC) of IgG described herein is GMCs of RBD-binding IgG.

[0231] In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that when measured at 7 days after a second dose (e.g., 10-50 ug inclusive), GMC of IgG directed to a SARS-CoV-2 S polypeptide or an immunogenic fragment thereof (e.g., RBD) is at least 1.1-fold higher (including, e.g., at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold higher, at least 7-fold higher, at least 8-fold higher, at least 9-fold higher, at least 10-fold higher, at least 15-fold higher, at least 20-fold higher,

at least 25-fold higher, at least 30-fold higher), as compared to antibody concentrations observed in a panel of COVID-19 convalescent human serum, In many embodiments, geometric mean concentration (GMC) of IgG described herein is GMCs of RBD-binding IgG.

[0232] In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that when measured at 21 days after a second dose, GMC of IgG directed to a SARS-CoV-2 S polypeptide or an immunogenic fragment thereof (e.g., RBD) is at least 5-fold higher (including, e.g., at least 6-fold higher, at least 7-fold higher, at least 8-fold higher, at least 9-fold higher, at least 10-fold higher, at least 15-fold higher, at least 20-fold higher, at least 25-fold higher, at least 30-fold higher), as compared to antibody concentrations observed in a panel of COVID-19 convalescent human serum, In many embodiments, geometric mean concentration (GMC) of IgG described herein is GMCs of RBD-binding IgG.

[0233] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that an increase (e.g., at least 30%, at least 40%, at least 50%, or more) in SARS-CoV-2 neutralizing geometric mean titers (GMTs) is observed 21 days after a first dose. In some embodiments, RNA (e.g., mRNA) compositions described herein are characterized in that a substantially greater serum neutralizing GMTs are achieved 7 days after subjects receive a second dose (e.g., 10 μg-30 μg inclusive), reaching 150-300, compared to 94 for a COVID-19 convalescent serum panel.

[0234] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that 7 days after administration of the second dose, the protective efficacy is at least 60%, e.g., at least 70%, at least 80%, at least 90, or at least 95%. In one embodiment, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that 7 days after administration of the second dose, the protective efficacy is at least 70%. In one embodiment, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that 7 days after administration of the second dose, the protective efficacy is at least 80%. In one embodiment, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that 7 days after administration of the second dose, the protective efficacy is at least 90%. In one embodiment, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that 7 days after administration of the second dose, the protective efficacy is at least 95%.

[0235] In some embodiments, an RNA composition provided herein is characterized in that it induces an immune response against SARS-CoV-2 after at least 7 days after a dose (e.g., after a second dose). In some embodiments, an RNA composition provided herein is characterized in that it induces an immune response against SARS-CoV-2 in less than 14 days after a dose (e.g., after a second dose). In some embodiments, an RNA composition provided herein is characterized in that it induces an immune response against SARS-CoV-2 after at least 7 days after a vaccination regimen. In some embodiments, a vaccination regimen comprises a first dose and a second dose. In some embodiments, a first dose and a second dose are administered by at least 21 days apart. In some such embodiments, an immune response against SARS-CoV-2 is induced at least after 28 days after a first dose.

[0236] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that geometric mean concentration (GMCs) of antibodies directed to a SARS-CoV-2 spike polypeptide or an immunogenic fragment thereof (e.g., RBD), as measured in serum from subjects receiving RNA (e.g., mRNA) compositions of the present disclosure (e.g., at a dose of 10-30 ug inclusive), is substantially higher than in a convalescent serum panel (e.g., as described herein). In some embodiments where a subject may receive a second dose (e.g., 21 days after 1 first dose), geometric mean concentration (GMCs) of antibodies directed to a SARS-CoV-2 spike polypeptide or an immunogenic fragment thereof (e.g., RBD), as measured in serum from the subject, may be 8.0-fold to 50-fold higher than a convalescent serum panel GMC. In some embodiments where a

subject may receive a second dose (e.g., 21 days after 1 first dose), geometric mean concentration (GMCs) of antibodies directed to a SARS-CoV-2 spike polypeptide or an immunogenic fragment thereof (e.g., RBD), as measured in serum from the subject, may be at least 8.0-fold or higher, including, e.g., at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 60-fold or higher, as compared to a convalescent serum panel GMC.

[0237] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that the SARS-CoV-2 neutralizing geometric mean titer, as measured at 28 days after a first dose or 7 days after a second dose, may be at least 1.5-fold or higher (including, e.g., at least 2-fold, at least 2.5-fold, at least 3-fold, at least 3.5-fold or higher), as compared to a neutralizing GMT of a convalescent serum panel.

[0238] In some embodiments, a regimen administered to a subject may be or comprise a single dose. In some embodiments, a regimen administered to a subject may comprise a plurality of doses (e.g., at least two doses, at least three doses, or more). In some embodiments, a regimen administered to a subject may comprise a first dose and a second dose, which are given at least 2 weeks apart, at least 3 weeks apart, at least 4 weeks apart, or more. In some embodiments, such doses may be at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, or more apart. In some embodiments, doses may be administered days apart, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 ,10, 11, 12, 13, 14, 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, 60 or more days apart. In some embodiments, doses may be administered about 1 to about 3 weeks apart, or about 1 to about 4 weeks apart, or about 1 to about 5 weeks apart, or about 1 to about 6 weeks apart, or about 1 to more than 6 weeks apart. In some embodiments, doses may be separated by a period of about 7 to about 60 days, such as for example about 14 to about 48 days, etc. In some embodiments, a minimum number of days between doses may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more. In some embodiments, a maximum number of days between doses may be about 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, or fewer. In some embodiments, doses may be about 21 to about 28 days apart. In some embodiments, doses may be about 19 to about 42 days apart. In some embodiments, doses may be about 7 to about 28 days apart. In some embodiments, doses may be about 14 to about 24 days. In some embodiments, doses may be about 21 to about 42 days.

[0239] In some embodiments, particularly for compositions established to achieve elevated antibody and/or T-cell titres for a period of time longer than about 3 weeks – e.g., in some embodiments, a provided composition is established to achieve elevated antibody and/or T-cell titres (e.g., specific for a relevant portion of a SARS-CoV-2 spike protein) for a period of time longer than about 3 weeks; in some such embodiments, a dosing regimen may involve only a single dose, or may involve two or more doses, which may, in some embodiments, be separated from one another by a period of time that is longer than about 21 days or three weeks. For example, in some such embodiments, such period of time may be about 4 weeks, 5 weeks, 6 weeks 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 wees, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks or more, or about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10, months, 11 months, 12 months or more, or in some embodiments about a year or more.

[0240] In some embodiments, a first dose and a second dose (and/or other subsequent dose) may be administered by intramuscular injection. In some embodiments, a first dose and a second dose may be administered in the deltoid muscle. In some embodiments, a first dose and a second dose may be administered in the same arm. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular

injection) as a series of two doses (e.g., 0.3 mL each) 21 days part. In some embodiments, each dose is about 30 ug. In some embodiments, each dose may be higher than 30 ug, e.g., about 40 ug, about 50 ug, about 60 ug. In some embodiments, each dose may be lower than 30 ug, e.g., about 20 ug, about 10 ug, about 5 ug, etc. In some embodiments, each dose is about 3 ug or lower, e.g., about 1 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 16 or older (including, e.g., 16-85 years). In some such embodiments, an RNA composition (e.g., mRNA) described herein is administered to subjects of age 18-55. In some such embodiments, an RNA composition (e.g., mRNA) described herein is administered to subjects of age 56-85. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular injection) as a single dose.

[0241] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that RBD-specific IgG (e.g., polyclonal response) induced by such RNA compositions and/or methods exhibit a higher binding affinity to RBD, as compared to a reference human monoclonal antibody with SARS-CoV-2 RBD-binding affinity (e.g., CR3022 as described in J. ter Meulen et al., PLOS Med. 3, e237 (2006).)

[0242] In particular embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that sera of vaccinated subjects display neutralizing activity against SARs-CoV-2 spike variant "B.1.1.28".

[0243] In particular embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that sera of vaccinated subjects display neutralizing activity against SARs-CoV-2 spike variant "B.1.1.248".

[0244] In particular embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that sera of vaccinated subjects display neutralizing activity against SARs-CoV-2 spike variant "501.V2".

[0245] In particular embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that sera of vaccinated subjects display neutralizing activity against SARs-CoV-2 spike variant "B.1.1.248".

[0246] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein are characterized in that sera of vaccinated subjects display neutralizing activity against SARs-CoV-2 spike variant of the Omicron (B.1.1.529) variant. Omicron (B.1.1.529) variant is a variant of SARS-CoV-2 which was detected in South Africa. Multiple Omicron variants or sublineages have arisen, including e.g., the BA.1, BA.2, BA.2.12.1, BA.3, BA.4, BA.5, BA.2.75, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, and XBB.2.3.2 sublineages. As used herein, unless otherwise specified, "Omicron variant" refers to the first disclosed Omicron variant (BA.1) or any variant thereof that has since arisen (e.g., Omicron variants described herein).

[0247] SARs-CoV-2 spike proteins encoded by RNA described herein may or may not include a D614G mutation as compared to SEQ ID NO: 1.

[0248] In some embodiments, SARS-CoV-2 spike proteins encoded by RNA described herein comprise a mutation in a furin cleavage site (e.g., in some embodiments residues 682-685 of SEQ ID NO: 1). In some embodiments, SARS-CoV-2 spike proteins encoded by RNA described herein comprise a mutation in the furin cleavage site that prevents cleavage by a furin protease (e.g., a human furin protease). In some embodiments, a SARS-CoV-2 protein described herein comprises a furin mutation disclosed in WO2021163365 or WO2021243122 (e.g., a GSAS mutation), the contents of both of which are incorporated by reference herein in their entirety.

[0249] In some embodiments, RNA (e.g., mRNA) compositions and/or methods described herein can provide protection against SARS-CoV-2 and/or decrease severity of SARS-CoV-2 infection in at least 50% of subjects receiving such RNA compositions and/or methods.

[0250] In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 18-55. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 56-85. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include older subjects (e.g., over age 60, 65, 70, 75, 80, 85, etc, for example subjects of age 65-85). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 18-85. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 18 or younger. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 12 or younger. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include subjects of age 10 or younger. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include adolescent populations (e.g., individuals approximately 12 to approximately 17 years of age). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include pediatric populations (e.g., as described herein). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include infants (e.g., less than 1 year old). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein do not include infants (e.g., less than 1 year) whose mothers have received such RNA (e.g., mRNA) compositions described herein during pregnancy. Without wishing to be bound by any particular theory, a rat study has suggested that a SARS-CoV-2 neutralizing antibody response induced in female rats given such RNA compositions during pregnancy can pass onto fetuses. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein include infants (e.g., less than 1 year) whose mothers did not receive such RNA compositions described herein during pregnancy. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include pregnant women; in some embodiments, infants whose mothers were vaccinated during pregnancy (e.g., who received at least one dose, or alternatively only who received both doses), are not vaccinated during the first weeks, months, or even years (e.g., 1, 2, 3, 4, 5, 6, 7, 8 weeks or more, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 months or more, or 1, 2, 3, 4, 5 years or more) post-birth. Alternatively or additionally, in some embodiments, infants whose mothers were vaccinated during pregnancy (e.g., who received at least one dose, or alternatively only who received both doses), receive reduced vaccination (e.g., lower doses and/or smaller numbers of administrations – e.g., boosters – and/or lower total exposure over a given period of time) after birth, for example during the first weeks, months, or even years (e.g., 1, 2, 3, 4, 5, 6, 7, 8 weeks or more, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 months or more, or 1, 2, 3, 4, 5 years or more) post-birth or may need reduced vaccination (e.g., lower doses and/or smaller numbers of administrations – e.g., boosters – over a given period of time). In some embodiments, compositions as provided herein are administered to populations that do not include pregnant women.

[0251] In some particular embodiments, compositions as provided herein are administered to pregnant women according to a regimen that includes a first dose administered after about 24 weeks of gestation (e.g., after about 22, 23, 24, 25, 26, 27, 28 or more weeks of gestation); in some embodiments, compositions as provided herein are administered to pregnant women according to a regimen that includes a first dose administered before about 34 weeks of gestation (e.g., before about 30, 31, 32, 33, 34, 35, 36, 37, 38 weeks of gestation). In some embodiments, compositions as provided herein are administered to pregnant women according to a regimen that includes a first dose administered after about 24 weeks (e.g., after about 27 weeks of gestation, e.g., between about 24 weeks and 34 weeks, or between about 27 weeks and 34 weeks) of gestation and a second dose administered about 21 days later; in some embodiments both doses are administered prior to delivery. Without

wishing to be bound by any particular theory, it is proposed that such a regimen (e.g., involving administration of a first dose after about 24 weeks, or 27 weeks of gestation and optionally before about 34 weeks of gestation), and optionally a second dose within about 21 days, ideally before delivery, may have certain advantages in terms of safety (e.g., reduced risk of premature delivery or of fetal morbidity or mortality) and/or efficacy (e.g., carryover vaccination imparted to the infant) relative to alternative dosing regimens (e.g., dosing at any time during pregnancy, refraining from dosing during pregnancy, and/or dosing later in pregnancy for example so that only one dose is administered during gestation. In some embodiments, infants born of mothers vaccinated during pregnancy, e.g., according to a particular regimen as described herein, may not need further vaccination, or may need reduced vaccination (e.g., lower doses and/or smaller numbers of administrations – e.g., boosters –, and/or lower overall exposure over a given period of time), for a period of time (e.g., as noted herein) after birth.

[0252] In some embodiments, compositions as provided herein are administered to populations in which women are advised against becoming pregnant for a period of time after receipt of the vaccine (e.g., after receipt of a first dose of the vaccine, after receipt of a final dose of the vaccine, etc.); in some such embodiments, the period of time may be at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks or more, or may be at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, or more.

[0253] In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include one or more populations with one or more particularly high risk conditions or history, e.g., as noted herein. For example, in some embodiments, populations to be treated with RNA compositions described herein may include subjects whose profession and/or environmental exposure may dramatically increase their risk of getting SARS-CoV-2 infection (including, e.g., but not limited to mass transportation, prisoners, grocery store workers, residents in long-term care facilities, butchers or other meat processing workers, healthcare workers, and/or first responders, e.g., emergency responders). In particular embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include healthcare workers and/or first responders, e.g., emergency responders. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include those with a history of smoking or vaping (e.g., within 6 months, 12 months or more, including a history of chronic smoking or vaping). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include certain ethnic groups that have been determined to be more susceptible to SARS-CoV-2 infection.

[0254] In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include certain populations with a blood type that may have been determined to more susceptible to SARS-CoV-2 infection. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include immunocompromised subjects (e.g., those with HIV/AIDS; cancer patients (e.g., receiving antitumor treatment); patients who are taking certain immunosuppressive drugs (e.g., transplant patients, cancer patients, etc.); autoimmune diseases or other physiological conditions expected to warrant immunosuppressive therapy (e.g., within 3 months, within 6 months, or more); and those with inherited diseases that affect the immune system (e.g., congenital agammaglobulinemia, congenital IgA deficiency)). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include those with an infectious disease. For example, in some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include those infected with human immunodeficiency virus (HIV) and/or a hepatitis virus (e.g., HBV, HCV). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include those with underlying medical conditions. Examples of such underlying medical conditions may include, but are not limited to hypertension, cardiovascular disease, diabetes, chronic

respiratory disease, e.g., chronic pulmonary disease, asthma, etc., cancer, and other chronic diseases such as, e.g., lupus, rheumatoid arthritis, chronic liver diseases, chronic kidney diseases (e.g., Stage 3 or worse such as in some embodiments as characterized by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73m^2). In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include overweight or obese subjects, e.g., specifically including those with a body mass index (BMI) above about 30 kg/m^2. In some embodiments, populations to be treated with RNA (e.g., mRNA) compositions described herein may include subjects who have prior diagnosis of COVID-19 or evidence of current or prior SARS-CoV-2 infection, e.g., based on serology or nasal swab. In some embodiments, populations to be treated include white and/or non-Hispanic/non-Latino.

[0255] In some embodiments, certain RNA (e.g., mRNA) compositions described herein may be selected for administration to Asian populations (*e.g.*, Chinese populations), or in particular embodiments to older Asian populations (*e.g.*, 60 years old or over, e.g., 60-85 or 65-85 years old).

[0256] In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to and/or assessed in subject(s) who have been determined not to show evidence of prior infection, and/or of present infection, before administration; in some embodiments, evidence of prior infection and/or of present infection, may be or include evidence of intact virus, or any viral nucleic acid, protein, lipid etc. present in the subject (e.g., in a biological sample thereof, such as blood, cells, mucus, and/or tissue), and/or evidence of a subject's immune response to the same. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to and/or assessed in subject(s) who have been determined to show evidence of prior infection, and/or of present infection, before administration; in some embodiments, evidence of prior infection and/or of present infection, may be or include evidence of intact virus, or any viral nucleic acid, protein, lipid etc. present in the subject (e.g., in a biological sample thereof, such as blood, cells, mucus, and/or tissue), and/or evidence of a subject's immune response to the same. In some embodiments, a subject is considered to have a prior infection based on having a positive N-binding antibody test result or positive nucleic acid amplification test (NAAT) result on the day of Dose 1.

[0257] In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject who has been informed of a risk of side effects that may include one or more of, for example: chills, fever, headache, injection site pain, muscle pain, tiredness; in some embodiments, an RNA (e.g., mRNA) composition is administered to a subject who has been invited to notify a healthcare provider if one or more such side effects occurs, is experienced as more than mild or moderate, persists for a period of more than a day or a few days, or if any serious or unexpected event is experienced that the subject reasonably considers may be associated with receipt of the composition. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject who has been invited to notify a healthcare provider of particular medical conditions which may include, for example, one or more of allergies, bleeding disorder or taking a blood thinner medication, breastfeeding, fever, immunocompromised state or taking medication that affects the immune system, pregnancy or plan to become pregnant, etc. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject who has been invited to notify a healthcare provider of having received another COVID-19 vaccine. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject not having one of the following medical conditions: experiencing febrile illness, receiving immunosuppressant therapy, receiving anticoagulant therapy, suffering from a bleeding disorder (e.g., one that would contraindicate intramuscular injection), or pregnancy and/or breastfeeding/lactation. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject not having received another COVID-19 vaccine. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to

a subject who has not had an allergic reaction to any component of the RNA (e.g., mRNA) composition. Examples of such allergic reaction may include, but are not limited to difficulty breathing, swelling of fact and/or throat, fast heartbeat, rash, dizziness and/or weakness. In some embodiments, an RNA (e.g., mRNA) composition as provided herein is administered to a subject who received a first dose and did not have an allergic reaction (e.g., as described herein) to the first dose. In some embodiments where allergic reaction occurs in subject(s) after receiving a dose of an RNA (e.g., mRNA) composition as provided herein, such subject(s) may be administered one or more interventions such as treatment to manage and/or reduce symptom(s) of such allergic reactions, for example, fever-reducing and/or anti-inflammatory agents.

[0258] In some embodiments, a subject who has received at least one dose of an RNA (e.g., mRNA) composition as provided herein is informed of avoiding being exposed to a coronavirus (e.g., SARS-CoV-2) unless and until several days (e.g., at least 7 days, at least 8 days, 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, etc.) have passed since administration of a second dose. For example, a subject who has received at least one dose of an RNA (e.g., mRNA) composition as provided herein is informed of taking precautionary measures against SARS-CoV-2 infection (e.g., remaining socially distant, wearing masks, frequent hand-washing, etc.) unless and until several days (e.g., at least 7 days, at least 8 days, 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, etc.) have passed since administration of a second dose. Accordingly, in some embodiments, methods of administering an RNA (e.g., mRNA) composition as provided herein comprise administering a second dose of such an RNA (e.g., mRNA) composition as provided herein to a subject who received a first dose and took precautionary measures to avoid being exposed to a coronavirus (e.g., SARS-CoV-2).

[0259] In some embodiments, RNA (e.g., mRNA) compositions described herein may be delivered to a draining lymph node of a subject in need thereof, for example, for vaccine priming. In some embodiments, such delivery may be performed by intramuscular administration of a provided RNA (e.g., mRNA) composition.

[0260] In some embodiments, different particular RNA (e.g., mRNA) compositions may be administered to different subject population(s); alternatively or additionally, in some embodiments, different dosing regimens may be administered to different subject populations. For example, in some embodiments, RNA (e.g., mRNA) compositions administered to particular subject population(s) may be characterized by one or more particular effects (e.g., incidence and/or degree of effect) in those subject populations. In some embodiments, such effect(s) may be or comprise, for example titer and/or persistence of neutralizing antibodies and/or T cells (e.g., T_H1-type T cells such as $CD4^+$ and/or $CD8^+$ T cells), protection against challenge (e.g., via injection and/or nasal exposure, etc), incidence, severity, and/or persistence of side effects (e.g., reactogenicity), etc.

[0261] In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to reduce COVID-19 incidence per 1000 person-years, e.g., based on a laboratory test such as nucleic acid amplification test (NAAT). In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to reduce COVID-19 incidence per 1000 person-years based on a laboratory test such as nucleic acid amplification test (NAAT) in subjects receiving at least one dose of a provided RNA (e.g., mRNA) composition with no serological or virological evidence (e.g., up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection. In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to reduce confirmed severe COVID-19 incidence per 1000 person-years. In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to reduce confirmed severe COVID-19 incidence per 1000 person-years in subjects receiving at least one dose of a provided RNA (e.g., mRNA) composition with no serological or virological evidence of past SARS-CoV-2 infection.

[0262] In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to produce neutralizing antibodies directed to a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD) as measured in serum from a subject that achieves or exceeds a reference level (e.g., a reference level determined based on human SARS-CoV-2 infection/COVID-19 convalescent sera) for a period of time and/or induction of cell-mediated immune response (e.g., a T cell response against SARS-CoV-2), including, e.g., in some embodiments induction of T cells that recognize at least one or more MHC-restricted (e.g., MHC class I-restricted) epitopes within a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD) for a period of time. In some such embodiments, the period of time may be at least 2 months, 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months or longer. In some embodiments, one or more epitopes recognized by vaccine-induced T cells (e.g., CD8+ T cells) may be presented on a MHC class I allele that is present in at least 50% of subjects in a population, including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more; in some such embodiments, the MHC class I allele may be HLA-B*0702, HLA-A*2402, HLA-B*3501, HLA-B*4401, or HLA-A*0201. In some embodiments, an epitope may comprise HLA-A*0201 YLQPRTFLL; HLA-A*0201 RLQSLQTYV; HLA-A*2402 QYIKWPWYI; HLA-A*2402 NYNYLYRLF; HLA-A*2402 KWPWYIWLGF; HLA-B*3501 QPTESIVRF; HLA-B*3501 IPFAMQMAY; or HLA-B*3501 LPFNDGVYF.

[0263] In some embodiments, efficacy is assessed as COVID-19 incidence per 1000 person-years in individuals without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen; alternatively or additionally, in some embodiments, efficacy is assessed as COVID-19 incidence per 1000 person-years in subjects with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen. In some such embodiments, such incidence is of COVID-19 cases confirmed within a specific time period after the final vaccination dose (e.g., a first dose in a single-dose regimen; a second dose in a two-dose regimen, etc); in some embodiments, such time period may be within (i.e., up to and including 7 days) a particular number of days (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 days or more). In some embodiments, such time period may be within 7 days or within 14 days or within 21 days or within 28 days. In some embodiments, such time period may be within 7 days. In some embodiments, such time period may be within 14 days.

[0264] In some embodiments (e.g., in some embodiments of assessing efficacy), a subject is determined to have experienced COVID-19 infection if one or more of the following is established: detection of SARS-CoV-2 nucleic acid in a sample from the subject, detection of antibodies that specifically recognize SARS-CoV-2 (e.g., a SARS-Co-V-2 spike protein), one or more symptoms of COVID-19 infection, and combinations thereof. In some such embodiments, detection of SARS-CoV-2 nucleic acid may involve, for example, NAAT testing on a mid-turbinatae swap sample. In some such embodiments, detection of relevant antibodies may involve serological testing of a blood sample or portion thereof. In some such embodiments, symptoms of COVID-19 infection may be or include: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting and combinations thereof. In some such embodiments, symptoms of COVID-19 infection may be or include: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, vomiting, fatigue, headache, nasal congestion or runny nose, nausea, and combinations thereof. In some such embodiments, a subject is determined to have experienced COVID-19 infection if such subject both has experienced one such symptom and also has received a positive test for SARS-CoV-2 nucleic acid or antibodies, or both. In some such embodiments, a subject is determined to have experienced COVID-19 infection if such subject both has experienced

one such symptom and also has received a positive test for SARS-CoV-2 nucleic acid. In some such embodiments, a subject is determined to have experienced COVID-19 infection if such subject both has experienced one such symptom and also has received a positive test for SARS-CoV-2 antibodies.

[0265] In some embodiments (e.g., in some embodiments of assessing efficacy), a subject is determined to have experienced severe COVID-19 infection if such subject has experienced one or more of: clinical signs at rest indicative or severe systemic illness (e.g., one or more of respiratory rate at greater than or equal to 30 breaths per minute, heart rate at or above 125 beats per minute, SpO_2 less than or equal to 93% on room air at sea level or a PaO_2/FiO_2 below 300 m Hg), respiratory failure (e.g., one or more of needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, ECMO), evidence of shock (systolic blood pressure below 90 mm Hg, diastolic blood pressure below 60mm Hg, requiring vasopressors), significant acute renal, hepatic, or neurologic dysfunction, admission to an intensive care unit, death, and combinations thereof.

[0266] In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to reduce the percentage of subjects reporting at least one of the following: (i) one or more local reactions (e.g., as described herein) for up to 7 days following each dose; (ii) one or more systemic events for up to 7 days following each dose; (iii) adverse events (e.g., as described herein) from a first dose to 1 month after the last dose; and/or (iv) serious adverse events (e.g., as described herein) from a first dose to 6 months after the last dose.

[0267] In some embodiments, one or more subjects who have received an RNA (e.g., mRNA) composition as described herein may be monitored (e.g., for a period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 days or more, including, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks or more, including for example 1, 2, 3, 4, 5, 6, 7, 8, 9 ,10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 months or more, including for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 years or more) to assess, for example, presence of an immune response to component(s) of the administered composition, evidence of exposure to and/or immune response to SARS-CoV-2 or another coronavirus, evidence of any adverse event, etc. In some embodiments, monitoring may be via tele-visit. Alternatively or additionally, in some embodiments, monitoring may be in-person.

[0268] In some embodiments, a treatment effect conferred by one or more RNA (e.g., mRNA) compositions described herein may be characterized by (i) a SARS-CoV-2 anti-S1 binding antibody level above a pre-determined threshold; (ii) a SARS-CoV-2 anti-RBD binding antibody level above a pre-determined threshold; and/or (iii) a SARS-CoV-2 serum neutralizing titer above a threshold level, e.g., at baseline, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and/or 24 months after completion of vaccination. In some embodiments, anti-S1 binding antibody and/or anti-RBD binding antibody levels and/or serum neutralizing titers may be characterized by geometric mean concentration (GMC), geometric mean titer (GMT), or geometric mean fold-rise (GMFR).

[0269] In some embodiments, a treatment effect conferred by one or more RNA (e.g., mRNA) compositions described herein may be characterized in that percentage of treated subjects showing a SARS-CoV-2 serum neutralizing titer above a pre-determined threshold, e.g., at baseline, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and/or 24 months after completion of vaccination, is higher than the percentage of non-treated subjects showing a SARS-CoV-2 serum neutralizing titer above such a pre-determined threshold (e.g., as described herein). In some embodiments, a serum neutralizing titer may be characterized by geometric mean concentration (GMC), geometric mean titer (GMT), or geometric mean fold-rise (GMFR).

[0270] In some embodiments, a treatment effect conferred by one or more RNA (e.g., mRNA) compositions described herein may be characterized by detection of SARS-CoV-2 NVA-specific binding antibody.

[0271] In some embodiments, a treatment effect conferred by one or more RNA (e.g., mRNA) compositions described herein may be characterized by SARS-CoV-2 detection by nucleic acid amplification test.

[0272] In some embodiments, a treatment effect conferred by one or more RNA (e.g., mRNA) compositions described herein may be characterized by induction of cell-mediated immune response (e.g., a T cell response against SARS-CoV-2), including, e.g., in some embodiments induction of T cells that recognize at least one or more MHC-restricted (e.g., MHC class I-restricted) epitopes within a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD). In some embodiments, one or more epitopes recognized by vaccine-induced T cells (e.g., CD8+ T cells) may be presented on a MHC class I allele that is present in at least 50% of subjects in a population, including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more; in some such embodiments, the MHC class I allele may be HLA-B*0702, HLA-A*2402, HLA-B*3501, HLA-B*4401, or HLA-A*0201. In some embodiments, an epitope may comprise HLA-A*0201 YLQPRTFLL; HLA-A*0201 RLQSLQTYV; HLA-A*2402 QYIKWPWYI; HLA-A*2402 NYNYLYRLF; HLA-A*2402 KWPWYIWLGF; HLA-B*3501 QPTESIVRF; HLA-B*3501 IPFAMQMAY; or HLA-B*3501 LPFNDGVYF.

[0273] In some embodiments, primary vaccine efficacy (VE) of one or more RNA (e.g., mRNA) compositions described herein may be established when there is sufficient evidence (posterior probability) that either primary VE1 or both primary VE1 and primary VE2 are >30% or higher (including, e.g., greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 95%, greater than 96%, greater than 97%, greater than 98%, or higher), wherein primary VE is defined as primary VE = 100 × (1 – IRR); and IRR is calculated as the ratio of COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. Primary VE1 represents VE for prophylactic RNA (e.g., mRNA) compositions described herein against confirmed COVID-19 in participants without evidence of infection before vaccination, and primary VE2 represents VE for prophylactic RNA (e.g., mRNA) compositions described herein against confirmed COVID-19 in all participants after vaccination. In some embodiments, primary VE1 and VE2 can be evaluated sequentially to control the overall type I error of 2.5% (hierarchical testing). In some embodiments where one or more RNA (e.g., mRNA) compositions described herein are demonstrated to achieve primary VE endponts as discussed above, secondary VE endpoints (e.g., confirmed severe COVID-19 in participants without evidence of infection before vaccination and confirmed severe COVID-19 in all participants) can be evaluated sequentially, e.g., by the same method used for the primary VE endpoint evaluation (hierarchical testing) as discussed above. In some embodiments, evaluation of primary and/or secondary VE endpoints may be based on at least 20,000 or more subjects (e.g., at least 25,000 or more subjects) randomized in a 1:1 ratio to the vaccine or placebo group, e.g., based on the following assumptions: (i) 1.0% illness rate per year in the placebo group, and (ii) 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection.

[0274] In some embodiments, one or more RNA (e.g., mRNA) compositions described herein may be administered according to a regimen established to achieve maintenance and/or continued enhancement of an immune response. For example, in some embodiments, an administration regimen may include a first dose optionally followed by one or more subsequent doses; in some embodiments, need for, timing of, and/or magnitude of any such subsequent dose(s) may be selected to maintain, enhance, and/or modify one or more immune responses or features thereof. In some embodiments, number, timing, and/or amount(s) of dose(s) have been established to be effective when administered to a relevant population. In some embodiments, number, timing and/or amount(s) of dose(s) may be adjusted for an individual subject; for example, in some embodiments, one or more features of an immune response in an individual subject may be assessed at least once (and optionally more than once, for example multiple times, typically spaced apart, often at pre-selected intervals) after receipt of a first dose. For example, presence of antibodies, B cells, and/or T cells (e.g., $CD4^+$ and/or $CD8^+$ T cells), and/or of cytokines secreted thereby and/or identity of and/or extent of responses to particular antigen(s) and/or epitope(s)

may be assessed. In some embodiments, need for, timing of, and/or amount of a subsequent dose may be determined in light of such assessments.

[0275] As noted hereinabove, in some embodiments, one or more subjects who have received an RNA (e.g., mRNA) composition as described herein may be monitored (e.g., for a period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 days or more, including, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks or more, including for example 1, 2, 3, 4, 5, 6, 7, 8, 9 ,10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 months or more, including for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 years or more) from receipt of any particular dose to assess, for example, presence of an immune response to component(s) of the administered composition, evidence of exposure to and/or immune response to SARS-CoV-2 or another coronavirus, evidence of any adverse event, etc, including to perform assessment of one or more of presence of antibodies, B cells, and/or T cells (e.g., $CD4^+$ and/or $CD8^+$ T cells), and/or of cytokines secreted thereby and/or identity of and/or extent of responses to particular antigen(s) and/or epitope(s) may be assessed. Administration of a composition as described herein may be in accordance with a regimen that includes one or more such monitoring steps.

[0276] For example, in some embodiments, need for, timing of, and/or amount of a second dose relative to a first dose (and/or of a subsequent dose relative to a prior dose) is assessed, determined, and/or selected such that administration of such second (or subsequent) dose achieves amplification or modification of an immune response (e.g., as described herein) observed after the first (or other prior) dose. In some embodiments, such amplification of an immune response (e.g., ones described herein) may be at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or higher, as compared to the level of an immune response observed after the first dose. In some embodiments, such amplification of an immune response may be at least 1.5 fold, at least 2-fold, 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, at least 10-fold, at least 20-fold, at least 30-fold, or higher, as compared to the level of an immune response observed after the first dose.

[0277] In some embodiments, need for, timing of, and/or amount of a second (or subsequent) dose relative to a first (or other prior) dose is assessed, determined, and/or selected such that administration of the later dose extends the durability of an immune response (e.g., as described herein) observed after the earlier dose; in some such embodiments, the durability may be extended by at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, or longer. In some embodiments, an immune response observed after the first dose may be characterized by production of neutralizing antibodies directed to a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD) as measured in serum from a subject and/or induction of cell-mediated immune response (e.g., a T cell response against SARS-CoV-2), including, e.g., in some embodiments induction of T cells that recognize at least one or more MHC-restricted (e.g., MHC class I-restricted) epitopes within a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD). In some embodiments, one or more epitopes recognized by vaccine-induced T cells (e.g., CD8+ T cells) may be presented on a MHC class I allele that is present in at least 50% of subjects in a population, including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more; in some such embodiments, the MHC class I allele may be HLA-B*0702, HLA-A*2402, HLA-B*3501, HLA-B*4401, or HLA-A*0201. In some embodiments, an epitope may comprise HLA-A*0201 YLQPRTFLL; HLA-A*0201 RLQSLQTYV; HLA-A*2402 QYIKWPWYI; HLA-A*2402 NYNYLYRLF; HLA-A*2402 KWPWYIWLGF; HLA-B*3501 QPTESIVRF; HLA-B*3501 IPFAMQMAY; or HLA-B*3501 LPFNDGVYF.

[0278] In some embodiments, need for, timing of, and/or amount of a second dose relative to a first dose (or other subsequent dose relative to a prior dose) is assessed, determined and/or selected such that administration of such second (or subsequent) dose maintains or exceeds a reference level of an immune response; in some such

embodiments, the reference level is determined based on human SARS-CoV-2 infection/COVID-19 convalescent sera and/or PBMC samples drawn from subjects (e.g., at least a period of time such as at least 14 days or longer, including, e.g., 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 25 days, 30 days, 35 days, 40 days, 45 days, 50 days, 55 days, 60 days, or longer, after PCR-confirmed diagnosis when the subjects were asymptomatic. In some embodiments, an immune response may be characterized by production of neutralizing antibodies directed to a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD) as measured in serum from a subject and/or induction of cell-mediated immune response (e.g., a T cell response against SARS-CoV-2), including, e.g., in some embodiments induction of T cells that recognize at least one or more MHC-restricted (e.g., MHC class I-restricted) epitopes within a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD). In some embodiments, one or more epitopes recognized by vaccine-induced T cells (e.g., CD8+ T cells) may be presented on a MHC class I allele that is present in at least 50% of subjects in a population, including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more; in some such embodiments, the MHC class I allele may be HLA-B*0702, HLA-A*2402, HLA-B*3501, HLA-B*4401, or HLA-A*0201. In some embodiments, an epitope may comprise HLA-A*0201 YLQPRTFLL; HLA-A*0201 RLQSLQTYV; HLA-A*2402 QYIKWPWYI; HLA-A*2402 NYNYLYRLF; HLA-A*2402 KWPWYIWLGF; HLA-B*3501 QPTESIVRF; HLA-B*3501 IPFAMQMAY; or HLA-B*3501 LPFNDGVYF.

[0279] In some embodiments, determination of need for, timing of, and/or amount of a second (or subsequent) dose may include one or more steps of assessing, after (e.g., 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 days or longer after) a first (or other prior) dose, presence and/or expression levels of neutralizing antibodies directed to a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD) as measured in serum from a subject and/or induction of cell-mediated immune response (e.g., a T cell response against SARS-CoV-2), including, e.g., in some embodiments induction of T cells that recognize at least one or more MHC-restricted (e.g., MHC class I-restricted) epitopes within a SARS-CoV-2 spike polypeptide and/or an immunogenic fragment thereof (e.g., RBD). In some embodiments, one or more epitopes recognized by vaccine-induced T cells (e.g., CD8+ T cells) may be presented on a MHC class I allele that is present in at least 50% of subjects in a population, including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more; in some such embodiments, the MHC class I allele may be HLA-B*0702, HLA-A*2402, HLA-B*3501, HLA-B*4401, or HLA-A*0201. In some embodiments, an epitope may comprise HLA-A*0201 YLQPRTFLL; HLA-A*0201 RLQSLQTYV; HLA-A*2402 QYIKWPWYI; HLA-A*2402 NYNYLYRLF; HLA-A*2402 KWPWYIWLGF; HLA-B*3501 QPTESIVRF; HLA-B*3501 IPFAMQMAY; or HLA-B*3501 LPFNDGVYF.

[0280] In some embodiments, a kit as provided herein may comprise a real-time monitoring logging device, which, for example in some embodiments, is capable of providing shipment temperatures, shipment time and/or location.

[0281] In some embodiments, an RNA (e.g., mRNA) composition as described herein may be shipped, stored, and/or utilized, in a container (such as a vial or syringe), e.g., a glass container (such as a glass vial or syringe), which, in some embodiments, may be a single-dose container or a multi-dose container (e.g., may be arranged and constructed to hold, and/or in some embodiments may hold, a single dose, or multiple doses of a product for administration). In some embodiments, a multi-dose container (such as a multi-dose vial or syringe) may be arranged and constructed to hold, and/or may hold 2, 3, 4, 5, 6, 7, 8, 9, 10 or more doses; in some particular embodiments, it may be designed to hold and/or may hold 5 doses. In some embodiments, a single-dose or multi-dose container (such as a single-dose or multi-dose vial or syringe) may be arranged and constructed to hold and/or may hold a volume or amount greater than the indicated number of doses, e.g., in order to permit some loss in transfer and/or administration. In some embodiments, an RNA (e.g., mRNA) composition as described herein may

be shipped, stored, and/or utilized, in a preservative-free glass container (e.g., a preservative-free glass vial or syringe, e.g., a single-dose or multi-dose preservative-free glass vial or syringe). In some embodiments, an RNA (e.g., mRNA) composition as described herein may be shipped, stored, and/or utilized, in a preservative-free glass container (e.g., a preservative-free glass vial or syringe, e.g., a single-dose or multi-dose preservative-free glass vial or syringe) that contains a frozen liquid, e.g., in some embodiments 0.45 ml of frozen liquid (e.g., including 5 doses). In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a vial or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature below room temperature, at or below 4 °C, at or below 0 °C, at or below -20 °C, at or below -60 °C, at or below -70 °C, at or below -80 °C , at or below -90 °C, etc. In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a viral or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature between -80°C and -60°C and in some embodiments protected from light. In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a viral or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature below about 25°C, and in some embodiments protected from light. In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a viral or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature below about 5°C (e.g., below about 4°C), and in some embodiments protected from light. In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a viral or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature below about -20°C, and in some embodiments protected from light. In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a viral or syringe) in which it is disposed, is shipped, stored, and/or utilized may be maintained at a temperature above about -60°C (e.g., in some embodiments at or above about -20°C, and in some embodiments at or above about 4-5°C, in either case optionally below about 25°C), and in some embodiments protected from light, or otherwise without affirmative steps (e.g., cooling measures) taken to achieve a storage temperature materially below about -20°C.

[0282] In some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a vial or syringe) in which it is disposed is shipped, stored, and/or utilized together with and/or in the context of a thermally protective material or container and/or of a temperature adjusting material. For example, in some embodiments, an RNA (e.g., mRNA) composition as described herein and/or a container (e.g., a vial or syringe) in which it is disposed is shipped, stored, and/or utilized together with ice and/or dry ice and/or with an insulating material. In some particular embodiments, a container (e.g., a vial or syringe) in which an RNA (e.g., mRNA) composition is disposed is positioned in a tray or other retaining device and is further contacted with (or otherwise in the presence of) temperature adjusting (e.g., ice and/or dry ice) material and/or insulating material. In some embodiments, multiple containers (e.g., multiple vials or syringes such as single use or multi-use vials or syringes as described herein) in which a provided RNA (e.g., mRNA) composition is disposed are co-localized (e.g., in a common tray, rack, box, etc.) and packaged with (or otherwise in the presence of) temperature adjusting (e.g., ice and/or dry ice) material and/or insulating material. To give but one example, in some embodiments, multiple containers (e.g., multiple vials or syringes such as single use or multi-use vials or syringes as described herein) in which an RNA (e.g., mRNA) composition is disposed are positioned in a common tray or rack, and multiple such trays or racks are stacked in a carton that is surrounded by a temperature adjusting material (e.g., dry ice) in a thermal (e.g., insulated) shipper. In some embodiments, temperature adjusting material is replenished periodically (e.g., within 24 hours of arrival at a site, and/or every 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, etc.). Preferably, re-entry into a thermal shipper should be infrequent, and desirably should not

occur more than twice a day. In some embodiments, a thermal shipper is re-closed within 5, 4, 3, 2, or 1 minute, or less, of having been opened. In some embodiments, a provided RNA (e.g., mRNA) composition that has been stored within a thermal shipper for a period of time, optionally within a particular temperature range remains useful. For example, in some embodiments, if a thermal shipper as described herein containing a provided RNA (e.g., mRNA) composition is or has been maintained (e.g., stored) at a temperature within a range of about 15 °C to about 25 °C, the RNA (e.g., mRNA) composition may be used for up to 10 days; that is, in some embodiments, a provided RNA (e.g., mRNA) composition that has been maintained within a thermal shipper, which thermal shipper is at a temperature within a range of about 15 °C to about 25 °C, for a period of not more than 10 days is administered to a subject. Alternatively or additionally, in some embodiments, if a provided RNA (e.g., mRNA) composition is or has been maintained (e.g., stored) within a thermal shipper, which thermal shipper has been maintained (e.g., stored) at a temperature within a range of about 15 °C to about 25 °C, it may be used for up to 10 days; that is, in some embodiments, a provided RNA (e.g., mRNA) composition that has been maintained within a thermal shipper, which thermal shipper has been maintained at a temperature within a range of about 15 °C to about 25 °C for a period of not more than 10 days is administered to a subject.

[0283] In some embodiments, a provided RNA (e.g., mRNA) composition is shipped and/or stored in a frozen state. In some embodiments, a provided RNA (e.g., mRNA composition is shipped and/or stored as a frozen suspension, which in some embodiments does not contain preservative. In some embodiments, a frozen RNA (e.g., mRNA) composition is thawed. In some embodiments, a thawed RNA (e.g., mRNA) composition (e.g., a suspension) may contain white to off-white opaque amorphous particles. In some embodiments, a thawed RNA (e.g., mRNA) composition may be used for up to a small number (e.g., 1, 2, 3, 4, 5, or 6) of days after thawing if maintained (e.g., stored) at a temperature at or below room temperature (e.g., below about 30 °C, 25 °C, 20 °C, 15 °C, 10 °C, 8 °C, 4 °C, etc). In some embodiments, a thawed RNA (e.g., mRNA) composition may be used after being stored (e.g., for such small number of days) at a temperature between about 2 °C and about 8 °C; alternatively or additionally, a thawed RNA (e.g., mRNA) composition may be used within a small number (e.g., 1, 2, 3, 4, 5, 6) of hours after thawing at room temperature. Thus, in some embodiments, a provided RNA (e.g., mRNA) composition that has been thawed and maintained at a temperature at or below room temperature, and in some embodiments between about 2 °C and about 8 °C, for not more than 6, 5, 4, 3, 2, or 1 days is administered to a subject. Alternatively or additionally, in some embodiments, a provided RNA (e.g., mRNA) composition that has been thawed and maintained at room temperature for not more than 6, 5, 4, 3, 2, or 1 hours is administered to a subject. In some embodiments, a provided RNA (e.g., mRNA) composition is shipped and/or stored in a concentrated state. In some embodiments, such a concentrated composition is diluted prior to administration. In some embodiments, a diluted composition is administered within a period of about 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 hour(s) post-dilution; in some embodiments, such administration is within 6 hours post-dilution. Thus, in some embodiments, diluted preparation of a provided RNA (e.g., mRNA) composition is administered to a subject within 6 hours post-dilution (e.g., as described herein after having been maintained at an appropriate temperature, e.g., at a temperature below room temperature, at or below 4 °C, at or below 0 °C, at or below -20 °C, at or below -60 °C, at or below -70 °C, at or below - 80 °C, etc, and typically at or above about 2 °C, for example between about 2 °C and about 8 °C or between about 2 °C and about 25 °C). In some embodiments, unused composition is discarded within several hours (e.g., about 10, about 9, about 8, about 7, about 6, about 5 or fewer hours) after dilution; in some embodiments, unused composition is discarded within 6 hours of dilution.

[0284] In some embodiments, an RNA (e.g., mRNA) composition that is stored, shipped or utilized (e.g., a frozen composition, a liquid concentrated composition, a diluted liquid composition, etc.) may have been maintained at a temperature materially above -60°C for a period of time of at least 1, 2, 3, 4, 5, 6, 7 days or more, or at least

1, 2, 3, 4, 5, 6, 7, 8, 9, 10 weeks or more, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or more; in some such embodiments, such composition may have been maintained at a temperature at or above about -20°C for such period of time, and/or at a temperature up to or about 4-5°C for such period of time, and/or may have been maintained at a temperature above about 4-5°C, and optionally about 25°C for a period of time up that is less than two (2) months and/or optionally up to about one (1) month. In some embodiments, such composition may not have been stored, shipped or utilized (or otherwise exposed to) a temperature materially above about 4-5°C, and in particular not at or near a temperature of about 25°C for a period of time as long as about 2 weeks, or in some embodiments 1 week. In some embodiments, such composition may not have been stored, shipped or utilized (or otherwise exposed to) a temperature materially above about -20°C, and in particular not at or near a temperature of about 4-5°C for a period of time as long as about 12 months, 11 months, 10 months, 9 months, 8 months, 7 months, 6 months, 5 months, 4 months, 3 months, 2 months, or, in some embodiments, for a period of time as long as about 8 weeks or 6 weeks or materially more than about 2 months or, in some embodiments, 3 months or, in some embodiments 4 months.

[0285] In some embodiments, an RNA (e.g., mRNA) composition that is stored, shipped or utilized (e.g., a frozen composition, a liquid concentrated composition, a diluted liquid composition, etc.) may be protected from light. In some embodiments, one or more steps may be taken to reduce or minimize exposure to light for such compositions (e.g., which may be disposed within a container such as a vial or a syringe). In some embodiments, exposure to direct sunlight and/or to ultraviolent light is avoided. In some embodiments, a diluted solution may be handled and/or utilized under normal room light conditions (e.g., without particular steps taken to minimize or reduce exposure to room light). It should be understood that strict adherence to aseptic techniques is desirable during handling (e.g., diluting and/or administration) of an RNA (e.g., mRNA) composition as described herein. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered (e.g., is not injected) intravenously. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered (e.g., is not injected) intradermally. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered (e.g., is not injected) subcutaneously. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered (e.g., is not injected) any of intravenously, intradermally, or subcutaneously. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered to a subject with a known hypersensitivity to any ingredient thereof. In some embodiments, a subject to whom an RNA (e.g., mRNA) composition has been administered is monitored for one or more signs of anaphylaxis. In some embodiments, a subject to whom an RNA (e.g., mRNA) composition is administered had previously received at least one dose of a different vaccine for SARS-CoV-2; in some embodiments, a subject to whom an RNA (e.g., mRNA) composition is administered had not previously received a different vaccine for SARS-CoV-2. In some embodiments, a subject's temperature is taken promptly prior to administration of an RNA (e.g., mRNA) composition (e.g., shortly before or after thawing, dilution, and/or administration of such composition); in some embodiments, if such subject is determined to be febrile, administration is delayed or canceled. In some embodiments, an RNA (e.g., mRNA) composition as described herein is not administered to a subject who is receiving anticoagulant therapy or is suffering from or susceptible to a bleeding disorder or condition that would contraindicate intramuscular injection. In some embodiments, an RNA (e.g., mRNA) composition as described herein is administered by a healthcare professional who has communicated with the subject receiving the composition information relating to side effects and risks. In some embodiments, an RNA (e.g., mRNA) composition as described herein is administered by a healthcare professional who has agreed to submit an adverse event report for any serious adverse events, which may include for example one or more of death, development of a disability or congenital anomaly/birth defect (e.g., in a child of the subject), in-patient hospitalization (including prolongation of an existing hospitalization), a life-

threatening event, a medical or surgical intervention to prevent death, a persistent or significant or substantial disruption of the ability to conduct normal life functions; or another important medical event that may jeopardize the individual and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

[0286] In some embodiments, provided RNA compositions are administered to a population of individuals under 18 years of age, or under 17 years of age, or under 16 years of age, or under 15 years of age, or under 14 years of age, or under 13 years of age, for example according to a regimen established to have a rate of incidence for one or more of the local reaction events indicated below that does not exceed the rate of incidence indicated below:

- pain at the injection site (75% after a first dose and/or a second dose, and/or a lower incidence after a second dose, e.g., 65% after a second dose);
- redness at the injection site (less than 5% after a first dose and/or a second dose); and/or
- swelling at the injection site (less than 5% after a first dose and/or a second dose).

[0287] In some embodiments, provided RNA compositions are administered to a population of individuals under 18 years of age, or under 17 years of age, or under 16 years of age, or under 15 years of age, or under 14 years of age, or under 13 years of age, for example according to a regimen established to have a rate of incidence for one or more of the systemic reaction events indicated below that does not exceed the rate of incidence indicated below:

- fatigue (55% after a first dose and/or a second dose);
- headache (50% after a first dose and/or a second dose);
- muscle pain (40% after a first dose and/or a second dose);
- chills (40% after a first dose and/or a second dose);
- joint pain (20% after a first dose and/or a second dose);
- fever (25% after a first dose and/or a second dose);
- vomiting (10% after a first dose and/or a second dose); and/or
- diarrhea (10% after a first dose and/or a second dose).

[0288] In some embodiments, medication that alleviates one or more symptoms of one or more local reaction and/or systemic reaction events (e.g., described herein) are administered to individuals under 18 years of age, or under 17 years of age, or under 16 years of age, or under 15 years of age, or under 14 years of age, or under 13 years of age who have been administered with provided RNA compositions and have experienced one or more of the local and/or systemic reaction events (e.g., described herein). In some embodiments, antipyretic and/or pain medication can be administered to such individuals.

Brief description of the drawings

[0289] **Fig. 1. Schematic overview of the S protein organization of the SARS-CoV-2 S protein.** The sequence within the S1 subunit consists of the signal sequence (SS) and the receptor binding domain (RBD) which is the key subunit within the S protein which is relevant for binding to the human cellular receptor ACE2. The S2 subunit contains the S2 protease cleavage site (S2') followed by a fusion peptide (FP) for membrane fusion, heptad repeats (HR1 and HR2) with a central helix (CH) domain, the transmembrane domain (TM) and a cytoplasmic tail (CT).

[0290] **Fig. 2. General structure of certain RNA constructs.** Schematic illustration of the general structure of RNA drug substances with 5'-cap, 5'- and 3'-untranslated regions, coding sequences with intrinsic secretory signal peptide as well as GS-linker, and poly(A)-tail. Please note that the individual elements are not

drawn exactly true to scale compared to their respective sequence lengths. GS = Glycine-serine linker; UTR = Untranslated region; Sec = Secretory signal peptide; RBD = Receptor Binding Domain.

[0291] Fig. 3. General structure of certain RNA constructs. Schematic illustration of the general structure of RNA vaccines with 5'-cap, 5'- and 3'-untranslated regions, coding sequences of the Venezuelan equine encephalitis virus (VEEV) RNA-dependent RNA polymerase replicase and the SARS-CoV-2 antigen with intrinsic secretory signal peptide as well as GS-linker, and poly(A)-tail. Please note that the individual elements are not drawn exactly true to scale compared to their respective sequence lengths. UTR = Untranslated region; Sec = Secretory signal peptide; RBD = Receptor Binding Domain; GS = Glycine-serine linker.

[0292] Fig. 4. CD8+ T cell epitopes in BNT162b2 vaccine remain largely unaffected by Omicron BA.1 variant mutations. Shown is the number of previously identified MHC-I epitopes affected in various variants of concern (VOCs). Approximately 80% of previously identified CD8+ epitopes are not affected by the mutations in the BA.1 Omicron variant, suggesting that two doses of BNT162b2 may still induce protection against severe disease.

[0293] Fig. 5. Analysis of HLA class I T cell epitopes conservation between the Wuhan and Omicron BA.1 variants. HLA class I restricted Spike protein epitopes with T cell reactivity identified based on their recognition by CD8+ T cells and reported in IEDB (n=244) are plotted by their position (top row) along the Spike protein (bottom row). Epitope indications are positioned by the amino acid position of the center of the epitope; epitopes conserved in both variants are marked in light grey (n=208); while epitopes spanning an Omicron BA.1 mutation site are marked dark grey (n=36). NTD=N-terminal domain; RBD=Receptor-binding domain; FCS=Furin cleavage site. The S1 and S2 regions of the Spike protein are indicated.

[0294] Fig. 6. Schematics of an exemplary vaccination regimen.

[0295] Fig. 7. Sequences of RBDs of SARS-COV-2 Wuhan strain and variants thereof. Variant-specific amino acid alterations are indicated in bold red font, with the original Wuhan amino acid highlighted in bold blue font.

[0296] Fig. 8. Alterations on the spike glycoprotein amino acid sequence of SARS-CoV-2 Omicron sub-lineages. Amino acid positions, amino acid descriptions (one letter code) and types of mutations (substitutions, deletions, insertions) are indicated. White letters in boxes indicate the amino acid substitution per sub-lineage; Δ, deletion; ins, insertion; NTD, N-terminal domain; RBD, receptor-binding domain.

[0297] Fig. 9. T cell epitope and B cell epitope retention in the S protein of certain SARS-CoV-2 variants of concern. All potential T cell epitopes were retrieved from the Immune Epitope Database (IEDB) on November 11, 2022, and the percentages of unaltered S protein linear T cell epitopes (as compared to epitopes present in BNT162b2 – 100%) present in each variant strain were calculated. Percentages of unaltered B cell neutralization epitopes (NTD and RBD) present in each variant strain compared to BNT162b2 were estimated by an automated Early Warning System (described in Beguir, Karim, et al., "Early computational detection of potential high risk SARS-CoV-2 variants," bioRxiv (2021)). (A) Radar chart and (B) line plot analysis of T-cell and neutralizing B cell epitope conservedness in the S protein across SARS-CoV-2 variants of concern. Percent unaltered T cell

epitopes andpercent unaltered B cell neutralization epitopes are shown. In (B) numbers on top corresponding to each variant represent number of mutations in spike protein comparing to Wuhan strain. Variants are ranked in ascending order in terms of mutation number.

[0298] Fig. 10. Experimental design to test immune responses induced by monovalent and bivalent variant-adapted vaccines in SARS-CoV-2-naive subjects. Mice were split into 7 groups, comprising 5 mice each, and administered two doses of one of the compositions indicated in the Figure. „BNT162b2" refers to a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain. „Bivalent B2+BA.4/5" refers to a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. „modRNA BA.4/5" refers to a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. „modRNA BQ.1.1" refers to a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an BQ.1.1 variant. „modRNA XBB" refers to a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an XBB variant. „modRNA BA.2.75.2" refers to a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an BA.2.75.2 variant. As shown in the figure, 1 µg of vaccine was administered in each dose (1 µg of a single RNA in the case of a monovalent vaccine and 0.5 µg of two RNAs in the case of a bivalent vaccine). Vaccines were adminsitered on days 0 and 21. Sera samples were collected on days 0, 14, 21, and 35. At day 35, mice were sacrificed and the experiment concluded.

[0299] Fig. 11. Neutralization titers induced by variant-adapted monovalent and bivalent vaccines in SARS-CoV-2 naive mice. Shown are pseudovirus neutralization titers collected from the experiment summarized in Fig. 10 (titers collected on sera samples collected 14 days after administering a second dose of vaccine). Pseudovirus neutralization titers were collected against Wuhan strain and the indicated SARS-CoV-2 variants for each of the mouse groups. Shown above each bar are pseudovirus neutralization titers. „BNT162b2^{2}" refers to mice administered two doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain. „(Bivalent b2 + BA.4/5)^{2}" refers to mice administered two doses of a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. „BA.4/5^{2}" refers to mice administered two doses of RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. „BQ.1.1^{2}" refers to mice administered two doses of RNA encoding a SARS-CoV-2 S protein of a BQ.1.1 variant. „XBB^{2}" refers to mice administered two doses of RNA encoding a SARS-CoV-2 S protein of a XBB variant. „BA.2.75.2^{2}" refers to mice administered two doses of RNA encoding a SARS-CoV-2 S protein of a BA.2.75.2 variant.

[0300] Fig. 12. Neutralization antibody titers induced by one or two doses of a bivalent (Omicron BA.4/5 + Wuhan) RNA composition in vaccine naive mice. Shown are pseudovirus neutralization titers against a Wuhan strain and various SARS-CoV-2 variants of concern in mice administered: (i) two doses of an RNA that encodes a SARS-CoV-2 S protein of a Wuhan strain („BNT162b2^{2}"), (ii) two doses of a bivalent RNA composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant („(Bivalent b2 +BA.4/5)^{2}"), or (iii) a first dose of an RNA that encodes a SARS-CoV-2 S protein of a Wuhan strain and a second dose of a bivalent RNA composition that comprises a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant („BNT162b2/Bivalent (b2+BA.4/5)"). (A) Shows neutralization titers collected 42 days after a second dose of vaccine, (B) shows neutralization titers collected 70 days after a second dose of vaccine,

and (C) shows neutralization titers collected 14 days after a second dose of vaccine. In each figure, neutralization titers for a collection of SARS-CoV-2 strains and variants is shown (indicated on the x-axis). Neutralization titer values are shown above each bar graph.

[0301] Fig. 13. Experimental design to characterize immune responses induced by bivalent and trivalent variant-adapted vaccines in SARS-CoV-2-naive mice. Mice were split into 8 groups, comprising 5 mice each, and administered two doses of one of the compositions indicated in the Figure. „Bivalent BNT162b2+BA.4/5" refers to a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. „Bivalent BNT162b2+BA.4/5 + BQ.1.1" refers to a trivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain, a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, and a third RNA encoding an S protein of a BQ.1.1 variant. „Bivalent BNT162b2+BA.4/5+XBB" refers to a trivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain, a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, and a third RNA encoding an S protein of an XBB variant. „Bivalent BNT162b2+BA.4/5+BA2.75.2" refers to a trivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain, a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, and a third RNA encoding an S protein of a BA.2.75.2 variant. „BA.4/5+ BQ.1.1" refers to a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an BQ.1.1 variant. „BA.4/5 + XBB" refers to a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and a second RNA encoding a SARS-CoV-2 S protein of an XBB variant. „BA.4/5+ BA.2.75.2" refers to a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and a second RNA encoding a SARS-CoV-2 S protein of a BA.75.2 variant. 1 µg of total RNA was administered in each dose (0.5 µg of each RNA for a bivalent vaccine and 0.33 µg of each RNA for a trivalent vaccine). Vaccines were administered on days 0 and 21. Sera samples were collected on days 0, 14, 21, and 35. On day 35, mice were sacrificed and the experiment was concluded.

[0302] Fig. 14. Neutralization titers induced by variant-adapted bivalent and trivalent vaccines in SARS-CoV-2 naive mice. Shown are pseudovirus neutralization titers collected from the mouse experiment summarized in Fig. 13 (titers from sera samples collected 14 days after administering a second dose of vaccine). Pseudovirus neutralization titers were collected against Wuhan strain and various variants of concern for each of the mouse groups. Pseudovirus neutralization titer values are shown above each bar.

[0303] Fig. 15. Experimental design for a study to characterize immune responses induced by variant-adapted vaccines in SARS-CoV-2 vaccine-experienced mice. Mice are split into 9 groups, each of which is administered a first dose of an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2) and a second dose of a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-COV-2 S protein of an Omicron BA.4/5 variant (BNT162b2 + BA.4/5). Following the second dose, mice are administered a composition comprising an RNA encoding a SARS-CoV-2 S protein of a strain or variant or combination of strains/variants, as indicated in the Figure. The first and second doses are administered 21 days apart, and the third dose is administered about 70 days after the third dose. 119 days after administering the first dose, mice are sacrificed and the experiment concluded.

[0304] Fig. 16. Experimental design for a study to characterize variant-adapted vaccines in SARS-CoV-2 vaccine-experienced mice. Mice are split into 6 groups, each of which is administered a first and a second dose of an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2), followed by a third dose of a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of a BA.4/5 Omicron variant (BNT162b2 + BA.4/5). Following the third dose, mice are administered a composition comprising an RNA encoding an SARS-CoV-2 S protein of a variant or strain or combination of strains/variants, as indicated in the Figure. The first and second doses are administered 21 days apart, the third dose is administered 70 days after the third dose, and the 4th dose is administered 21 days after the third dose. 126 days after administering the first dose, mice are sacrificed and the experiment concluded.

[0305] Fig. 17. Exemplary experimental protocol for testing variant-adapted vaccines as a primary series in mice. Two doses of a monovalent or bivalent vaccine composition comprising mRNA(s) encoding the SARS-CoV-2 S protein(s) of the strains/variants indicated in the figure were administered to mice 21 days apart. „WT" corresponds to mRNA encoding a SARS-CoV-2 S protein from a Wuhan strain. Indicated in the figure is the mass of RNA (µg) administered to mice.

[0306] Fig. 18. A monovalent XBB.1.5-adapted vaccine, as a primary series, elicits higher neutralization titers against XBB.1.5 than a bivalent Wuhan + BA.4/5 vaccine. Shown are results collected in performing the experiment summarized in Figure 74. (A) shows pseudovirus neutralization titers of serum samples collected at Day 35 of the experiment summarized in Figure 74. (B) Lists values neutralization titer values for the bar graph shown in panel (A).

[0307] Fig. 19. Exemplary experimental protocol for testing variant-adapted vaccines as a fourth booster dose in mice. „BNT162b2 WT" corresponds to a monovalent mRNA vaccine encoding a SARS-CoV-2 S protein of a Wuhan strain, „BNT162b2 Bivalent WT + BA.4/5" corresponds to a bivalent vaccine comprising an RNA encoding an S protein of a Wuhan strain and an RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. On day 134, mice were administered a monovalent or bivalent vaccine encoding one of the strains, variants, or combinations indicated in the figure. On days 134 and 160, blood samples were collected (represented by the testtube racks).

[0308] Fig. 20. An XBB.1.5-adapted booster vaccine elicits the highest neutralization titers against an XBB.1.5 and XBB.1.6 pseudovirus. Shown are results collected in performing the experiment summarized in Figure 76. (A) shows neutralization titers collected for a panel of pseudoviruses (indicated in the figure legend). X-axis indicates vaccine administered. Titers collected at day 160. (B) shows neutralization titer values for the bar graph shown in panel (A). (C) Shows geometric mean ratios (GMR) of neutralization titers induced by the indicated vaccine relative to neutralization titers induced by a bivalent vaccine comprising an RNA encoding a SARS-CoV-2 S protein from a Wuhan strain (WT in the figure) and an RNA encoding a SARS-CoV-2 S protein from an Omicron BA.4/5 variant (GMR values calculated using neutralization titers at day 160). (D) provides GMR values for the bar graph shown in panel (C). (E) Shows GMR values comparing neutralization titers induced by the indicated vaccines relative to neutralization titers at day 135 (pre dose 4). (F) shows GMR values for the graph shown in panel (E). (G) shows neutralization titers against further SARS-CoV-2 variants (including XBB.2.3).

[0309] **Fig. 21. Certain variant-adapted vaccines induce a neutralization response against Omicron XBB variants in vaccine-naïve mice.** A summary of the experimental protocol is depicted at the top of the figure (syringes indicate days on which candidate vaccines were administered and the droplet indicates a day on which blood was collected). Vaccine naïve mice were administered two doses of the indicated candidate vaccines. Four weeks after receiving a second dose of vaccine, mice were bled and neutralization titers collected. As shown in the figure, neutralization titers were induced against each of the variants tested, with a monovalent XBB.1.5-adapted vaccine inducing the highest neutralization titers against each of the XBB variants tested.

[0310] **Fig. 22. Certain variant-adapted vaccines induce a neutralization response against Omicron XBB variants in vaccine-experienced mice.** A summary of the experimental protocol is depicted at the top of the figure (syringes indicate days on which candidate vaccines were administered and the droplet indicates a day on which blood was collected). Mice were administered two doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (WT), followed by a dose of a candidate vaccine. Two weeks after receiving a dose of candidate vaccine, mice were bled and neutralization titers collected. As shown in the figure, neutralization titers were induced against each of the variants tested, with a monovalent XBB.1.5-adapted vaccine inducing the highest neutralization titers against each of the XBB variants tested.

Detailed description

[0311] Although the present disclosure is described in detail below, it is to be understood that this disclosure is not limited to the particular methodologies, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present disclosure which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0312] Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", H.G.W. Leuenberger, B. Nagel, and H. Kölbl, Eds., Helvetica Chimica Acta, CH-4010 Basel, Switzerland, (1995).

[0313] The practice of the present disclosure will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, cell biology, immunology, and recombinant DNA techniques which are explained in the literature in the field (cf., e.g., Molecular Cloning: A Laboratory Manual, 2nd Edition, J. Sambrook et al. eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor 1989).

[0314] In the following, the elements of the present disclosure will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional embodiments. The variously described examples and embodiments should not be construed to limit the present disclosure to only the explicitly described embodiments. This description should be understood to disclose and encompass embodiments which combine the explicitly described embodiments with any number of the disclosed elements. Furthermore, any permutations and combinations of all described elements should be considered disclosed by this description unless the context indicates otherwise.

[0315] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the present disclosure was not entitled to antedate such disclosure.

Definitions

[0316] In the following, definitions will be provided which apply to all aspects of the present disclosure. The following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

[0317] The term "about" means approximately or nearly, and in the context of a numerical value or range set forth herein in one embodiment means ± 20%, ± 10%, ± 5%, or ± 3% of the numerical value or range recited or claimed.

[0318] The terms "a" and "an" and "the" and similar reference used in the context of describing the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it was individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), provided herein is intended merely to better illustrate the disclosure and does not pose a limitation on the scope of the claims. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the disclosure.

[0319] Unless expressly specified otherwise, the term "comprising" is used in the context of the present document to indicate that further members may optionally be present in addition to the members of the list introduced by "comprising". It is, however, contemplated as a specific embodiment of the present disclosure that the term "comprising" encompasses the possibility of no further members being present, i.e., for the purpose of this embodiment "comprising" is to be understood as having the meaning of "consisting of" or "consisting essentially of".

[0320] Terms such as "reduce", "decrease", "inhibit" or "impair" as used herein relate to an overall reduction or the ability to cause an overall reduction, preferably of at least 5%, at least 10%, at least 20%, at least 50%, at least 75% or even more, in the level. These terms include a complete or essentially complete inhibition, i.e., a reduction to zero or essentially to zero.

[0321] Terms such as "increase", "enhance" or "exceed" preferably relate to an increase or enhancement by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 80%, at least 100%, at least 200%, at least 500%, or even more.

[0322] According to the present disclosure, the term "peptide" comprises oligo- and polypeptides and refers to substances which comprise about two or more, about 3 or more, about 4 or more, about 6 or more, about 8 or more, about 10 or more, about 13 or more, about 16 or more, about 20 or more, and up to about 50, about 100 or about 150, consecutive amino acids linked to one another via peptide bonds. The term "protein" or "polypeptide" refers to large peptides, in particular peptides having at least about 150 amino acids, but the terms "peptide", "protein" and "polypeptide" are used herein usually as synonyms.

[0323] A "therapeutic protein" has a positive or advantageous effect on a condition or disease state of a subject when provided to the subject in a therapeutically effective amount. In one embodiment, a therapeutic protein has curative or palliative properties and may be administered to ameliorate, relieve, alleviate, reverse, delay onset of or lessen the severity of one or more symptoms of a disease or disorder. A therapeutic protein may have prophylactic properties and may be used to delay the onset of a disease or to lessen the severity of such disease or pathological condition. The term "therapeutic protein" includes entire proteins or peptides, and can also refer to therapeutically active fragments thereof. It can also include therapeutically active variants of a protein. Examples

of therapeutically active proteins include, but are not limited to, antigens for vaccination and immunostimulants such as cytokines.

[0324] "Fragment", with reference to an amino acid sequence (peptide or protein), relates to a part of an amino acid sequence, i.e. a sequence which represents the amino acid sequence shortened at the N-terminus and/or C-terminus. A fragment shortened at the C-terminus (N-terminal fragment) is obtainable e.g. by translation of a truncated open reading frame that lacks the 3'-end of the open reading frame. A fragment shortened at the N-terminus (C-terminal fragment) is obtainable e.g. by translation of a truncated open reading frame that lacks the 5'-end of the open reading frame, as long as the truncated open reading frame comprises a start codon that serves to initiate translation. A fragment of an amino acid sequence comprises e.g. at least 50 %, at least 60 %, at least 70 %, at least 80%, at least 90% of the amino acid residues from an amino acid sequence. A fragment of an amino acid sequence preferably comprises at least 6, in particular at least 8, at least 12, at least 15, at least 20, at least 30, at least 50, or at least 100 consecutive amino acids from an amino acid sequence.

[0325] By "variant" herein is meant an amino acid sequence that differs from a parent amino acid sequence by virtue of at least one amino acid modification. The parent amino acid sequence may be a naturally occurring or wild type (WT) amino acid sequence, or may be a modified version of a wild type amino acid sequence. Preferably, the variant amino acid sequence has at least one amino acid modification compared to the parent amino acid sequence, e.g., from 1 to about 20 amino acid modifications, and preferably from 1 to about 10 or from 1 to about 5 amino acid modifications compared to the parent.

[0326] By "wild type" or "WT" or "native" herein is meant an amino acid sequence that is found in nature, including allelic variations. A wild type amino acid sequence, peptide or protein has an amino acid sequence that has not been intentionally modified.

[0327] In some embodiments, the present disclosure refers to a SARS-CoV-2 variant that is prevalent and/or rapidly spreading in a relevant jurisdiction. In some embodiments, such variants may be identified based on publicly available data (e.g., data provided in the GISAID Initiative database: https://www.gisaid.org, and/or data provided by the World Health Organization WHO (e.g., as provided at https://www.who.int/activities/tracking-SARS-CoV-2-variants). In some embodiments, such a variant refers to a variant disclosed herein.

[0328] For the purposes of the present disclosure, "variants" of an amino acid sequence (peptide, protein or polypeptide) comprise amino acid insertion variants, amino acid addition variants, amino acid deletion variants and/or amino acid substitution variants. The term "variant" includes all mutants, splice variants, posttranslationally modified variants, conformations, isoforms, allelic variants, species variants, and species homologs, in particular those which are naturally occurring. The term "variant" includes, in particular, fragments of an amino acid sequence.

[0329] Amino acid insertion variants comprise insertions of single or two or more amino acids in a particular amino acid sequence. In the case of amino acid sequence variants having an insertion, one or more amino acid residues are inserted into a particular site in an amino acid sequence, although random insertion with appropriate screening of the resulting product is also possible. Amino acid addition variants comprise amino- and/or carboxy-terminal fusions of one or more amino acids, such as 1, 2, 3, 5, 10, 20, 30, 50, or more amino acids. Amino acid deletion variants are characterized by the removal of one or more amino acids from the sequence, such as by removal of 1, 2, 3, 5, 10, 20, 30, 50, or more amino acids. The deletions may be in any position of the protein. Amino acid deletion variants that comprise the deletion at the N-terminal and/or C-terminal end of the protein are also called N-terminal and/or C-terminal truncation variants. Amino acid substitution variants are characterized by at least one residue in the sequence being removed and another residue being inserted in its place. Preference is given to the modifications being in positions in the amino acid sequence which are not conserved between homologous proteins or peptides and/or to replacing amino acids with other ones having similar properties.

Preferably, amino acid changes in peptide and protein variants are conservative amino acid changes, i.e., substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. In one embodiment, conservative amino acid substitutions include substitutions within the following groups:

glycine, alanine;
valine, isoleucine, leucine;
aspartic acid, glutamic acid;
asparagine, glutamine;
serine, threonine;
lysine, arginine; and
phenylalanine, tyrosine.

[0330] Preferably the degree of similarity, preferably identity between a given amino acid sequence and an amino acid sequence which is a variant of said given amino acid sequence will be at least about 60%, 70%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. The degree of similarity or identity is given preferably for an amino acid region which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% or about 100% of the entire length of the reference amino acid sequence. For example, if the reference amino acid sequence consists of 200 amino acids, the degree of similarity or identity is given preferably for at least about 20, at least about 40, at least about 60, at least about 80, at least about 100, at least about 120, at least about 140, at least about 160, at least about 180, or about 200 amino acids, in some embodiments continuous amino acids. In some embodiments, the degree of similarity or identity is given for the entire length of the reference amino acid sequence. The alignment for determining sequence similarity, preferably sequence identity can be done with art known tools, preferably using the best sequence alignment, for example, using Align, using standard settings, preferably EMBOSS::needle, Matrix: Blosum62, Gap Open 10.0, Gap Extend 0.5.

[0331] "Sequence similarity" indicates the percentage of amino acids that either are identical or that represent conservative amino acid substitutions. "Sequence identity" between two amino acid sequences indicates the percentage of amino acids that are identical between the sequences. "Sequence identity" between two nucleic acid sequences indicates the percentage of nucleotides that are identical between the sequences.

[0332] The terms "% identical", "% identity" or similar terms are intended to refer, in particular, to the percentage of nucleotides or amino acids which are identical in an optimal alignment between the sequences to be compared. Said percentage is purely statistical, and the differences between the two sequences may be but are not necessarily randomly distributed over the entire length of the sequences to be compared. Comparisons of two sequences are usually carried out by comparing the sequences, after optimal alignment, with respect to a segment or "window of comparison", in order to identify local regions of corresponding sequences. The optimal alignment for a comparison may be carried out manually or with the aid of the local homology algorithm by Smith and Waterman, 1981, Ads App. Math. 2, 482, with the aid of the local homology algorithm by Neddleman and Wunsch, 1970, J. Mol. Biol. 48, 443, with the aid of the similarity search algorithm by Pearson and Lipman, 1988, Proc. Natl Acad. Sci. USA 88, 2444, or with the aid of computer programs using said algorithms (GAP, BESTFIT, FASTA, BLAST

P, BLAST N and TFASTA in Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.). In some embodiments, percent identity of two sequences is determined using the BLASTN or BLASTP algorithm, as available on the United States National Center for Biotechnology Information (NCBI) website (e.g., at blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE_TYPE=BlastSearch&BLAST_SPEC=blast2seq&LINK_LOC=align2seq). In some embodiments, the algorithm parameters used for BLASTN algorithm on the NCBI website include: (i) Expect Threshold set to 10; (ii) Word Size set to 28; (iii) Max matches in a query range set to 0; (iv) Match/Mismatch Scores set to 1, -2; (v) Gap Costs set to Linear; and (vi) the filter for low complexity regions being used. In some embodiments, the algorithm parameters used for BLASTP algorithm on the NCBI website include: (i) Expect Threshold set to 10; (ii) Word Size set to 3; (iii) Max matches in a query range set to 0; (iv) Matrix set to BLOSUM62; (v) Gap Costs set to Existence: 11 Extension: 1; and (vi) conditional compositional score matrix adjustment.

[0333] Percentage identity is obtained by determining the number of identical positions at which the sequences to be compared correspond, dividing this number by the number of positions compared (e.g., the number of positions in the reference sequence) and multiplying this result by 100.

[0334] In some embodiments, the degree of similarity or identity is given for a region which is at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% or about 100% of the entire length of the reference sequence. For example, if the reference nucleic acid sequence consists of 200 nucleotides, the degree of identity is given for at least about 100, at least about 120, at least about 140, at least about 160, at least about 180, or about 200 nucleotides, in some embodiments continuous nucleotides. In some embodiments, the degree of similarity or identity is given for the entire length of the reference sequence.

[0335] Homologous amino acid sequences exhibit according to the present disclosure at least 40%, in particular at least 50%, at least 60%, at least 70%, at least 80%, at least 90% and preferably at least 95%, at least 98 or at least 99% identity of the amino acid residues.

[0336] The amino acid sequence variants described herein may readily be prepared by the skilled person, for example, by recombinant DNA manipulation. The manipulation of DNA sequences for preparing peptides or proteins having substitutions, additions, insertions or deletions, is described in detail in Sambrook et al. (1989), for example. Furthermore, the peptides and amino acid variants described herein may be readily prepared with the aid of known peptide synthesis techniques such as, for example, by solid phase synthesis and similar methods.

[0337] In one embodiment, a fragment or variant of an amino acid sequence (peptide or protein) is preferably a "functional fragment" or "functional variant". The term "functional fragment" or "functional variant" of an amino acid sequence relates to any fragment or variant exhibiting one or more functional properties identical or similar to those of the amino acid sequence from which it is derived, i.e., it is functionally equivalent. With respect to antigens or antigenic sequences, one particular function is one or more immunogenic activities displayed by the amino acid sequence from which the fragment or variant is derived. The term "functional fragment" or "functional variant", as used herein, in particular refers to a variant molecule or sequence that comprises an amino acid sequence that is altered by one or more amino acids compared to the amino acid sequence of the parent molecule or sequence and that is still capable of fulfilling one or more of the functions of the parent molecule or sequence, e.g., inducing an immune response. In one embodiment, the modifications in the amino acid sequence of the parent molecule or sequence do not significantly affect or alter the characteristics of the molecule or sequence. In different embodiments, the function of the functional fragment or functional variant may be reduced but still significantly present, e.g., immunogenicity of the functional variant may be at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the parent molecule or sequence. However, in other embodiments, immunogenicity of the functional fragment or functional variant may be enhanced compared to the parent molecule or sequence.

[0338] An amino acid sequence (peptide, protein or polypeptide) "derived from" a designated amino acid sequence (peptide, protein or polypeptide) refers to the origin of the first amino acid sequence. Preferably, the amino acid sequence which is derived from a particular amino acid sequence has an amino acid sequence that is identical, essentially identical or homologous to that particular sequence or a fragment thereof. Amino acid sequences derived from a particular amino acid sequence may be variants of that particular sequence or a fragment thereof. For example, it will be understood by one of ordinary skill in the art that the antigens suitable for use herein may be altered such that they vary in sequence from the naturally occurring or native sequences from which they were derived, while retaining the desirable activity of the native sequences.

[0339] As used herein, an "instructional material" or "instructions" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of the compositions and methods of the present disclosure. The instructional material of the kit of the present disclosure may, for example, be affixed to a container which contains the compositions of the present disclosure or be shipped together with a container which contains the compositions. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compositions be used cooperatively by the recipient.

[0340] "Isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated", but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated". An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

[0341] The term "recombinant" in the context of the present disclosure means "made through genetic engineering". Preferably, a "recombinant object" such as a recombinant nucleic acid in the context of the present disclosure is not occurring naturally.

[0342] The term "naturally occurring" as used herein refers to the fact that an object can be found in nature. For example, a peptide or nucleic acid that is present in an organism (including viruses) and can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally occurring.

[0343] "Physiological pH" as used herein refers to a pH of about 7.5.

[0344] The term "genetic modification" or simply "modification" includes the transfection of cells with nucleic acid. The term "transfection" relates to the introduction of nucleic acids, in particular RNA, into a cell. For purposes of the present disclosure, the term "transfection" also includes the introduction of a nucleic acid into a cell or the uptake of a nucleic acid by such cell, wherein the cell may be present in a subject, e.g., a patient. Thus, according to the present disclosure, a cell for transfection of a nucleic acid described herein can be present *in vitro* or *in vivo*, e.g. the cell can form part of an organ, a tissue and/or an organism of a patient. According to the disclosure, transfection can be transient or stable. For some applications of transfection, it is sufficient if the transfected genetic material is only transiently expressed. RNA can be transfected into cells to transiently express its coded protein. Since the nucleic acid introduced in the transfection process is usually not integrated into the nuclear genome, the foreign nucleic acid will be diluted through mitosis or degraded. Cells allowing episomal amplification of nucleic acids greatly reduce the rate of dilution. If it is desired that the transfected nucleic acid actually remains in the genome of the cell and its daughter cells, a stable transfection must occur. Such stable transfection can be achieved by using virus-based systems or transposon-based systems for transfection. Generally, nucleic acid encoding antigen is transiently transfected into cells. RNA can be transfected into cells to transiently express its coded protein.

[0345] The term "seroconversion" includes a ≥4-fold rise from before vaccination to 1-month post Dose 2.

Coronavirus

[0346] Coronaviruses are enveloped, positive-sense, single-stranded RNA ((+) ssRNA) viruses. They have the largest genomes (26–32 kb) among known RNA viruses and are phylogenetically divided into four genera (α, β, γ, and δ), with betacoronaviruses further subdivided into four lineages (A, B, C, and D). Coronaviruses infect a wide range of avian and mammalian species, including humans. Some human coronaviruses generally cause mild respiratory diseases, although severity can be greater in infants, the elderly, and the immunocompromised. Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), belonging to betacoronavirus lineages C and B, respectively, are highly pathogenic. Both viruses emerged into the human population from animal reservoirs within the last 15 years and caused outbreaks with high case-fatality rates. The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes atypical pneumonia (coronavirus disease 2019; COVID-19) has raged in China since mid-December 2019, and has developed to be a public health emergency of international concern. SARS-CoV-2 (MN908947.3) belongs to betacoronavirus lineage B. It has at least 70% sequence similarity to SARS-CoV.

[0347] In general, coronaviruses have four structural proteins, namely, envelope (E), membrane (M), nucleocapsid (N), and spike (S). The E and M proteins have important functions in the viral assembly, and the N protein is necessary for viral RNA synthesis. The critical glycoprotein S is responsible for virus binding and entry into target cells. The S protein is synthesized as a single-chain inactive precursor that is cleaved by furin-like host proteases in the producing cell into two noncovalently associated subunits, S1 and S2. The S1 subunit contains the receptor-binding domain (RBD), which recognizes the host-cell receptor. The S2 subunit contains the fusion peptide, two heptad repeats, and a transmembrane domain, all of which are required to mediate fusion of the viral and host-cell membranes by undergoing a large conformational rearrangement. The S1 and S2 subunits trimerize to form a large prefusion spike.

[0348] The S precursor protein of SARS-CoV-2 can be proteolytically cleaved into S1 (685 aa) and S2 (588 aa) subunits. The S1 subunit comprises the receptor-binding domain (RBD), which mediates virus entry into sensitive cells through the host angiotensin-converting enzyme 2 (ACE2) receptor.

Antigen

[0349] The present disclosure comprises the use of RNA encoding an amino acid sequence comprising SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof. Thus, the RNA encodes a peptide or protein comprising at least an epitope SARS-CoV-2 S protein or an immunogenic variant thereof for inducing an immune response against coronavirus S protein, in particular SARS-CoV-2 S protein in a subject. The amino acid sequence comprising SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof (i.e., the antigenic peptide or protein) is also designated herein as "vaccine antigen", "peptide and protein antigen", "antigen molecule" or simply "antigen". The SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is also designated herein as "antigenic peptide or protein" or "antigenic sequence".

[0350] The SARS-CoV-2 coronavirus full length spike (S) protein from the first detected SARS-CoV-2 strain (referred to as the Wuhan strain herein) consists of 1273 amino acids and has the amino acid sequence according to SEQ ID NO: 1:

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGT
NGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYH

KNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQ
GFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDC
ALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVAD
YSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWN
SNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYR
VVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQT
LEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAE
HVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPV
SMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFN
FSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTS
ALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKL
QDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRAS
ANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPRE
GVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDV
DLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCM
TSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT (SEQ ID NO: 1)

[0351] For purposes of the present disclosure, the above sequence is considered the wildtype or Wuhan SARS-CoV-2 S protein amino acid sequence. Unless otherwise indicated, position numberings in a SARS-CoV-2 S protein given herein are in relation to the amino acid sequence according to SEQ ID NO: 1. One of skill in the art reading the present disclosure will understand the corresponding positions in SARS-CoV-2 S protein variants based on the position numbering relative to the amino acid sequence of SEQ ID NO: 1.

[0352] In specific embodiments, full length spike (S) protein encoded by an RNA described herein can be modified in such a way that the prototypical prefusion conformation is stabilized. Certain mutations that stabilize a prefusion confirmation are known in the art, e.g., as disclosed in WO 2021243122 A2 and Hsieh, Ching-Lin, et al. ("Structure-based design of prefusion-stabilized SARS-CoV-2 spikes," Science 369.6510 (2020): 1501-1505), the contents of each which are incorporated by reference herein in their entirety. In some embodiments, a SARS-CoV-2 S protein may be stabilized by introducing one or more proline mutations. In some embodiments, a SARS-CoV-2 S protein comprises a proline substitution at positions corresponding to residues 986 and/or 987 of SEQ ID NO: 1. In some embodiments, a SARS-CoV-2 S protein comprises a proline substitution at one or more positions corresponding to residues 817, 892, 899, and 942 of SEQ ID NO: 1. In some embodiments, a SARS-CoV-2 S protein comprises a proline substitution at positions corresponding to each of residues 817, 892, 899, and 942 of SEQ ID NO: 1. In some embodiments, a SARS-CoV-2 S protein comprises a proline substitution at positions corresponding to each of residues 817, 892, 899, 942, 986, and 987 of SEQ ID NO: 1.

[0353] In some embodiments, stabilization of the prefusion conformation may be obtained by introducing two consecutive proline substitutions at residues 986 and 987 in the full length spike protein. Specifically, spike (S) protein stabilized protein variants are obtained in a way that the amino acid residue at position 986 is exchanged to proline and the amino acid residue at position 987 is also exchanged to proline. In one embodiment, a SARS-CoV-2 S protein variant wherein the prototypical prefusion conformation is stabilized comprises the amino acid sequence shown in SEQ ID NO: 7:

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHV
SGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPF
LGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPI

NLVRDLPQGFSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNE
NGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYA
WNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYN
YKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPL
QSYGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPF
QQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPT
WRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAE
NSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVE
QDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDI
AARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQ
NVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRL
DPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQ
SAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVS
GNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNL
NESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEP
VLKGVKLHYT (SEQ ID NO: 7)

[0354] Those skilled in the art are aware of various spike variants, and/or resources that document them. For example, the following strains, their SARS-CoV-2 S protein amino acid sequences and, in particular, modifications thereof compared to wildtype SARS-CoV-2 S protein amino acid sequence, e.g., as compared to SEQ ID NO: 1, are useful herein.

B.1.1.7 ("Variant of Concern 202012/01" (VOC-202012/01)

[0355] B.1.1.7 (the "alpha variant") is a variant of SARS-CoV-2 which was first detected in October 2020 during the COVID-19 pandemic in the United Kingdom from a sample taken the previous month, and it quickly began to spread by mid-December. It is correlated with a significant increase in the rate of COVID-19 infection in United Kingdom; this increase is thought to be at least partly because of change N501Y inside the spike glycoprotein's receptor-binding domain, which is needed for binding to ACE2 in human cells. The B.1.1.7 variant is defined by 23 mutations: 13 non-synonymous mutations, 4 deletions, and 6 synonymous mutations (i.e., there are 17 mutations that change proteins and six that do not). The spike protein changes in B.1.1.7 include deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H.

B.1.351 (501.V2)

[0356] B.1.351 lineage (the "Beta variant") and colloquially known as South African COVID-19 variant, is a variant of SARS-CoV-2. Preliminary results indicate that this variant may have an increased transmissibility. The B.1.351 variant is defined by multiple spike protein changes including: L18F, D80A, D215G, deletion 242-244, R246I, K417N, E484K, N501Y, D614G and A701V. There are three mutations of particular interest in the spike region of the B.1.351 genome: K417N, E484K, N501Y.

B.1.1.298 (Cluster 5)

[0357] B.1.1.298 was discovered in North Jutland, Denmark, and is believed to have been spread from minks to humans via mink farms. Several different mutations in the spike protein of the virus have been confirmed. The specific mutations include deletion 69–70, Y453F, D614G, I692V, M1229I, and optionally S1147L.

P.1 (B.1.1.248)

[0358] Lineage B.1.1.248 (the "gamma variant"), known as the Brazil(ian) variant, is one of the variants of SARS-CoV-2 which has been named P.1 lineage. P.1 has a number of S-protein modifications [L18F, T20N, P26S,

D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F] and is similar in certain key RBD positions (K417, E484, N501) to variant B.1.351 from South Africa.

B.1.427/B.1.429 (CAL.20C)

[0359] Lineage B.1.427/B.1.429 (the "epsilon variant"), also known as CAL.20C, is defined by the following modifications in the S-protein: S13I, W152C, L452R, and D614G of which the L452R modification is of particular concern. CDC has listed B.1.427/B.1.429 as "variant of concern".

B.1.525

[0360] B.1.525 (the "eta variant") carries the same E484K modification as found in the P.1, and B.1.351 variants, and also carries the same ΔH69/ΔV70 deletion as found in B.1.1.7, and B.1.1.298. It also carries the modifications D614G, Q677H and F888L.

B.1.526

[0361] B.1.526 (the "iota variant") was detected as an emerging lineage of viral isolates in the New York region that shares mutations with previously reported variants. The most common sets of spike mutations in this lineage are L5F, T95I, D253G, E484K, D614G, and A701V.

[0362] The following table shows an overview of exemplary SARS-CoV-2 strains which are or have been VOI/VOC.

Table 1: Overview of certain circulating SARS-CoV-2 strains which have been/are VOI/VOC

Lineage	Amino acid substitution							
				M1229I			
	V1176F						
		D1118H					
	T1027I						
		S982A					
						F888L	
		T716I					
			A701V				A701V
				I692V			
		P681H					
						Q677H	
	H655Y						
P.1 (BRA)	D614G	D614G	D614G	D614G	D614G	D614G	D614G
		A570D					
	N501Y	N501Y	N501Y				
	E484K		E484K			E484K	E484K
				Y453F			
					L452R		
	K417T		K417N				
							D253G
			R246I				
			Δ242/243/244				
			D215G				
	R190S						
					W152C		
		Δ144					
	D138Y						
							T95I
			D80A				
		Δ69/70		Δ69/70		Δ69/70	
	P26S						
	T20N						
	L18F		L18F				
					S131		
							L5F

1.1.529

[0377] B.1.529 ("Omicron variant") was first detected in South Africa in November 2021. Omicron multiplies around 70 times faster than Delta variants, and quickly became the dominant strain of SARS-CoV-2 worldwide. Since its initial detection, a number of Omicron sublineages have arisen. Listed below are Omicron variants of concern, along with certain characteristic mutations associated with the S protein of each. The S protein of BA.4 and BA.5 have the same set of characteristic mutations, which is why the below table has a single row for "BA.4 or BA.5", and why the present disclosure refers to a "BA.4/5" S protein in some embodiments. Similarly, the S proteins of the BA.4.6 and BF.7 Omicron variants have the same set of characteristic mutations, which is why the below table has a single row for "BA.4.6 or BF.7").

Table 2: Characteristic mutations of certain Omicron variants of concern

Variant	Exemplary characteristic mutations
BA.1	A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
BA.2	T19I, Δ24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
BA.2.12.1	T19I, Δ24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452Q, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, S704L, N764K, D796Y, Q954H, N969K
BA.4 or BA.5	T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
BA.2.75	T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
BA.2.75.2	T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N
BJ.1	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, S477N, T478K, V483A, E484A, F490V, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, G798D, Q954H, N969K, and S1003I
BA.4.6 or BF.7	T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N658S, N679K, P681H, N764K, D796Y, Q954H, and N969K

XBB	Characteristic mutations (1): T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R,Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K Characteristic mutations (2): T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.1	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.1.5	Characteristic mutations (1): T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K Characteristic mutations (2): T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.2	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.1.3	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, A484T, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.1.16	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, E180V, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K

BA.2.3.20	T19I, Δ24-26, A27S, G142D, M153T, N164K, V213G, H245N, G257D, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444R, E484R N450D, L452M, N460K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
BQ.1.1	T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
CH.1.1	T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, G446S, L452R, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N
XBB.2.3	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K
XBB.2.3.2	T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, G184V, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K

[0378] In some embodiments, RNA described herein comprises a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of an Omicron variant (e.g., one or more (e.g., all of the) mutations associated with a given Omicron variant in Table 2). In some embodiments, such RNA further comprise one or more mutations that stabilize the S protein in a pre-fusion confirmation (e.g., in some embodiments, such RNA further comprises proline residues at positions corresponding to residues 986 and 987 of SEQ ID NO: 1). In some embodiments, an RNA comprises a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) listed in Table 2. In some such embodiments, an RNA comprises a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations from each of two or more variants listed in Table 2. In some embodiments, an RNA comprises a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations (e.g., all of the mutations) identified in Table 2 as being characteristic of a certain Omicron variant (e.g., in some embodiments, an RNA comprises a nucleotide sequence encoding a SARS-CoV-2 S protein comprising each of the mutations listed in Table 2 as being characteristic of an Omicron BA.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.2.75.1, BA.4.6, BQ.1.1, XBB, XBB.1, XBB.2, XBB.1.3, XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 variant).

[0379] In some embodiments, an RNA disclosed herein comprises a nucleotide sequence that encodes an immunogenic fragment of a SARS-Cov-2 S protein (e.g., the RBD), which comprises one or more mutations that are characteristic of a SARS-CoV-2 variant (e.g., an Omicron variant described herein). For example, in some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an S protein of a SARS-CoV-2 variant

(e.g., a region of the S protein corresponding to amino acids 327 to 528 of SEQ ID NO: 1, and comprising one or more mutations that are characteristic of a variant of concern that lie within this region of the S protein).

[0380] In some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an XBB.1.5 SARS-CoV-2 variant, wherein (i) the RBD comprises amino acids 323 to 524 of SEQ ID NO: 158 or an amino acid sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to SEQ ID NO: 158 and/or (ii) the RNA comprises nucleotides 967 to 1572 of SEQ ID NO: 160 or a nucleotide sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to nucleotides 967 to 1572 of SEQ ID NO: 160.

[0381] In some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an XBB.1.16 SARS-CoV-2 variant, wherein (i) the RBD comprises amino acids 323 to 524 of SEQ ID NO: 163 or an amino acid sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to SEQ ID NO: 163 and/or (ii) the RNA comprises nucleotides 967 to 1572 of SEQ ID NO: 165 or a nucleotide sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to nucleotides 967 to 1572 of SEQ ID NO: 165.

[0382] In some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an XBB.2.3 SARS-CoV-2 variant, wherein (i) the RBD comprises amino acids 323 to 524 of SEQ ID NO: 168 or an amino acid sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to SEQ ID NO: 168 and/or (ii) the RNA comprises nucleotides 967 to 1572 of SEQ ID NO: 170 or a nucleotide sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to nucleotides 967 to 1572 of SEQ ID NO: 170.

[0383] In some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an XBB.2.3.2 SARS-CoV-2 variant, wherein (i) the RBD comprises amino acids 323 to 524 of SEQ ID NO: 173 or an amino acid sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to SEQ ID NO: 173 and/or (ii) the RNA comprises nucleotides 967 to 1572 of SEQ ID NO: 175 or a nucleotide sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to nucleotides 967 to 1572 of SEQ ID NO: 175.

[0384] In some embodiments, an RNA comprises a nucleotide sequence encoding the RBD of an XBB.1.16 SARS-CoV-2 variant, wherein (i) the amino acid sequence of the RBD comprises amino acids 323 to 524 of SEQ ID NO: 163 and/or (ii) the RNA comprises a nucleotide sequence that is at least 70% (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%) identical to nucleotides 967 to 1572 of SEQ ID NO: 165.

[0385] In some embodiments, an RNA encodes a SARS-CoV-2 S protein comprising a subset of the mutations listed in Table 2. In some embodiments, an RNA encodes a SARS-CoV-2 S protein comprising the mutations listed in Table 2 that are most prevalent in a certain variant (e.g., mutations that have been detected in at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of sequences collected to date for a given variant). Mutation prevalence can be determined, e.g., based on published sequences (e.g., sequences that are collected and made available to the public by GISAID).

[0386] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations that are characteristic of a BA.4/5 variant. In some embodiments, the one or more mutations

characteristic of a BA.4/5 variant include T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations that are characteristic of a BA.4/5 variant and excludes R408S. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.4/5 variant and excludes R408S.

[0387] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) mutations characteristic of a BA.2.75 variant. In some embodiments, the one or more mutations characteristic of a BA.2.75 variant include T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H D614G, H655Y, N679K, P681H, N764K, Q954H, and N969K, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.2.75 variant, and which excludes N354D. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.2.75 variant, and which excludes D796Y. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.2.75 variant, and which excludes D796Y and N354D.

[0388] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.2.75.2 variant. In some embodiments, the one or more mutations characteristic of a BA.2.75.2 variant include T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.2.75.2 variant, and which excludes R346T.

[0389] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.4.6 or BF.7 variant. In some embodiments, the one or more mutations characteristic of a BA.4.6 or BF.7 variant include T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.4.6 or BF.7 variant, and which exclude R408S. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.4.6 or BF.7 variant, and which exclude N658S. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BA.4.6 or BF.7 variant, and which exclude N658S and R408S.

[0390] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB variant. In some embodiments, the one or more mutations

characteristic of an Omicron XBB variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, the one or more mutations characteristic of an Omicron XBB variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0391] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1 variant. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1 variant include G252V. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of an Omicron XBB.1 variant and which exclude Q493R. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of an Omicron XBB variant and which exclude Q493R and G252V.

[0392] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.2 variant. In some embodiments, the one or more mutations characteristic of an Omicron XBB.2 variant include D253G. In some embodiments, the one or more mutations characteristic of an Omicron-XBB.2 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0393] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.2.3 variant (e.g., as listed in the above Table 2). In some embodiments, the one or more mutations characteristic of an Omicron XBB.2.3 variant include one or more mutations characteristic of an XBB variant and one or more of D253G, F486P, and P521S. In some embodiments, the one or more mutations characteristic of an Omicron XBB.2.3 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0394] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.2.3.2 variant (e.g., as listed in the above Table 2). In some embodiments, the one or more mutations characteristic of an Omicron XBB.2.3.2 variant include one or more mutations characteristic of an XBB variant and one or more of G184V, D253G, F486P, and P521S. In some embodiments, the one or more mutations characteristic of an Omicron XBB.2.3 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, G184V, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0395] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1.3 variant. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.3 variant include G252V and A484T. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.3 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, A484T, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0396] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1.5 variant. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.5 variant include F486P. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.5 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, S486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.5 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0397] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB.1.16 variant. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.16 variant include E180V and K478R. In some embodiments, the one or more mutations characteristic of an Omicron XBB.1.16 variant include T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, S486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof.

[0398] In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations that are characteristic of a BQ.1.1 variant. In some embodiments, the one or more mutations characteristic of a BQ.1.1 variant include T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N463K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K, or any combination thereof. In some embodiments, RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations (including, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) that are characteristic of a BQ.1.1 variant.

[0399] In one embodiment, the vaccine antigen described herein comprises, consists essentially of or consists of a spike protein (S) of SARS-CoV-2, a variant thereof, or an immunogenic fragment thereof (e.g., but not limited to RBD).

[0400] In one embodiment, a vaccine antigen comprises the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7. In one embodiment, a vaccine antigen comprises the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7.

[0401] In one embodiment, RNA encoding a vaccine antigen (i) comprises the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7. In one embodiment, RNA encoding a vaccine antigen (i) comprises the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7.

[0402] In one embodiment, the vaccine antigen comprises, consists essentially of or consists of SARS-CoV-2 spike S1 fragment (S1) (the S1 subunit of a spike protein (S) of SARS-CoV-2), a variant thereof, or a fragment thereof.

[0403] In one embodiment, a vaccine antigen comprises, consists essentially of or consists of the receptor binding domain (RBD) of the S1 subunit of a spike protein (S) of SARS-CoV-2, a variant thereof, or a fragment thereof. The amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, a variant thereof, or a fragment thereof is also referred to herein as "RBD" or "RBD domain".

[0404] In one embodiment, a vaccine antigen comprises the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, or an immunogenic fragment of the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1. In one embodiment, a vaccine antigen comprises the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1.

Signal Peptides

[0405] According to certain embodiments, a signal peptide is fused, either directly or through a linker, to a SARS-CoV-2 S protein, a variant thereof, or a fragment thereof, i.e., the antigenic peptide or protein. Accordingly, in one embodiment, a signal peptide is fused to the above described amino acid sequences derived from SARS-CoV-2 S protein or immunogenic fragments thereof (antigenic peptides or proteins) comprised by the vaccine antigens described above.

[0406] Such signal peptides are sequences, which typically exhibit a length of about 15 to 30 amino acids and are preferably located at the N-terminus of the antigenic peptide or protein, without being limited thereto. Signal peptides as defined herein preferably allow the transport of the antigenic peptide or protein as encoded by the RNA into a defined cellular compartment, preferably the cell surface, the endoplasmic reticulum (ER) or the endosomal-lysosomal compartment. In one embodiment, the signal peptide sequence as defined herein includes, without being limited thereto, the signal peptide sequence of SARS-CoV-2 S protein, in particular a sequence comprising the amino acid sequence of amino acids 1 to 16 or 1 to 19 of SEQ ID NO: 1 or a functional variant thereof.

[0407] In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity

to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1. In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1.

[0408] In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1. In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1.

[0409] In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1. In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1.

[0410] In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 1 to 57 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 57 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 1 to 57 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 57 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1. In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 1 to 57 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 1.

[0411] In some embodiments, a signal peptide sequence as defined herein includes, without being limited thereto, the signal peptide sequence of an immunoglobulin, e.g., the signal peptide sequence of an immunoglobulin heavy chain variable region, wherein the immunoglobulin may be human immunoglobulin. In particular, in some embodiments the signal peptide sequence as defined herein includes a sequence comprising the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31 or a functional variant thereof.

[0412] In some embodiments, a signal peptide sequence is functional in mammalian cells.

[0413] In some embodiments, a utilized signal sequence is "intrinsic" in that it is, in nature, associated with (e.g., linked to) the encoded polypeptide.

[0414] In some embodiments, a utilized signal sequence is heterologous to the encoded polypeptide – e.g., is not naturally part of a polypeptide (e.g., protein) whose sequences are included in the encoded polypeptide.

[0415] In some embodiments, signal peptides are sequences, which are typically characterized by a length of about 15 to 30 amino acids.

[0416] In many embodiments, signal peptides are positioned at the N-terminus of an encoded polypeptide as described herein, without being limited thereto. In some embodiments, signal peptides preferably allow the transport of the polypeptide encoded by RNAs of the present disclosure with which they are associated into a defined cellular compartment, preferably the cell surface, the endoplasmic reticulum (ER) or the endosomal-lysosomal compartment.

[0417] In some embodiments, a signal sequence is selected from an S1S2 signal peptide (aa 1-19), an immunoglobulin secretory signal peptide (aa 1-22), an HSV-1 gD signal peptide (MGGAAARLGAVILFVVIVGLHGVRSKY), an HSV-2 gD signal peptide (MGRLTSGVGTAALLVVAVGLRVVCA); a human SPARC signal peptide, a human insulin isoform 1 signal peptide, a human albumin signal peptide, etc. Those skilled in the art will be aware of other secretory signal peptides such as, for example, as disclosed in WO2017/081082 (e.g., SEQ ID NOs: 1-1115 and 1728, or fragments variants thereof) and WO2019008001.

[0418] In some embodiments, an RNA sequence encodes an epitope that may comprise or otherwise be linked to a signal sequence (e.g., secretory sequence), such as those listed in Table A, or at least a sequence having 1, 2, 3, 4, or 5 amino acid differences relative thereto. In some embodiments, a signal sequence such as MFVFLVLLPLVSSQCVNLT, or at least a sequence having 1, 2, 3, 4, or at the most 5 amino acid differences relative thereto is utilized. In some embodiments, a sequence such as MFVFLVLLPLVSSQCVNLT, or a sequence having 1, 2, 3, 4, or at the most 5 amino acid differences relative thereto, is utilized.

[0419] In some embodiments, a signal sequence is selected from those included in the Table A below and/or those encoded by the sequences in Table B below:

Table A: Exemplary signal sequences

SEQ ID NO:	Signal	Sequence (Amino Acid)
105	HSV-1 gD SP	MGGAAARLGAVILFVVIVGLHGVRSKY
106	HSV-2 gD SP	MGRLTSGVGTAALLVVAVGLRVVCA
107	HSV-2	MGRLTSGVGTAALLVVAVGLRVVCAKYA
108	SARS-CoV-2-S	MFVFLVLLPLVSSQCVNLT
109	human Ig heavy chain signal peptide (huSec)	MDWIWRILFLVGAATGAHSQM
110	HuIgGk signal peptide	METPAQLLFLLLLWLPDTTG
111	IgE heavy chain epsilon-1signal peptide	MDWTWILFLVAAATRVHS
112	Japanese encephalitis PRM signal sequence	MLGSNSGQRVVFTILLLLVAPAYS

113	VSVg protein signal sequence	MKCLLYLAFLFIGVNCA
114		MDWTWILFLVAAATRVHS
115		ETPAQLLFLLLLWLPDTTG
116		MLGSNSGQRVVFTILLLLVAPAYS
117		MKCLLYLAFLFIGVNCA
118		MWLVSLAIVTACAGA
119		MFVFLVLLPLVSSQC

Table B: Exemplary nucleotide sequences encoding signal sequences

SEQ ID NO:	Signal	Sequence (Nucleotide)
120	HSV-1 gD SP wild-type	ATGGGGGGGGCTGCCGCCAGGTTGGGGGCCGTGATTTTGTTTGTCGTCATAGTGGGCC TCCATGGGGTCCGCAGCAAATAT
121	HSV-1 gD SP optimized nucleotide sequence	ATGggaggagccGCCGCCagactgggaGCCGTGatcctgttcgtggtgatcGTGggactgCATggagtg agaAGCaagtac
122	SARS-CoV-2-S	ATGTTTGTGTTTCTTGTGCTGCTGCCTCTTGTGTCTTCTCAGTGTGTGAATTTGACA
123	human Ig heavy chain signal peptide (huSec)	ATGGATTGGATTTGGAGAATCCTGTTCCTCGTGGGAGCCGCTACAGGAGCCCACTCCCA GATG

Multimerization Domains

[0420] In some embodiments, an RNA utilized as described herein encodes a multimerization element (e.g., a heterologous multimerization element). In some embodiments, a heterologous multimerization element comprises a dimerization, trimerization or tetramerization element.

[0421] In some embodiments, a multimerization element is one described in WO2017/081082 (e.g., SEQ ID NOs: 1116-1167, or fragments or variants thereof).

[0422] Exemplary trimerization and tetramerization elements include, but are not limited to, engineered leucine zippers, fibritin foldon domain from enterobacteria phage T4, GCN4pII, GCN4-pII, and p53.

[0423] In some embodiments, a provided encoded polypeptide(s) is able to form a trimeric complex. For example, a utilized encoded polypeptide(s) may comprise a domain allowing formation of a multimeric complex, such as for example particular a trimeric complex of an amino acid sequence comprising an encoded polypeptide(s) as described herein. In some embodiments, a domain allowing formation of a multimeric complex comprises a trimerization domain, for example, a trimerization domain as described herein.

[0424] In some embodiments, an encoded polypeptide(s) can be modified by addition of a T4-fibritin-derived "foldon" trimerization domain, for example, to increase its immunogenicity.

Transmembrane Domains

[0425] In some embodiments, an RNA described herein encodes a membrane association element (e.g., a heterologous membrane association element), such as a transmembrane domain.

[0426] A transmembrane domain can be N-terminal, C-terminal, or internal to an encoded polypeptide. A coding sequence of a transmembrane element is typically placed in frame (i.e., in the same reading frame), 5', 3', or internal to coding sequences of sequences (e.g., sequences encoding polypeptide(s)) with which it is to be linked.

[0427] In some embodiments, a transmembrane domain comprises or is a transmembrane domain of Hemagglutinin (HA) of Influenza virus, Env of HIV-1, equine infectious anaemia virus (EIAV), murine leukaemia virus (MLV), mouse mammary tumor virus, G protein of vesicular stomatitis virus (VSV), Rabies virus, or a seven transmembrane domain receptor.

[0428] In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, or a functional fragment of the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31. In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31.

[0429] In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 54 to 119 of SEQ ID NO: 32, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 54 to 119 of SEQ ID NO: 32, or a fragment of the nucleotide sequence of nucleotides 54 to 119 of SEQ ID NO: 32, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 54 to 119 of SEQ ID NO: 32; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, or a functional fragment of the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31. In one embodiment, RNA encoding a signal sequence (i) comprises the nucleotide sequence of nucleotides 54 to 119 of SEQ ID NO: 32; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31.

[0430] Such signal peptides are preferably used in order to promote secretion of the encoded antigenic peptide or protein. More preferably, a signal peptide as defined herein is fused to an encoded antigenic peptide or protein as defined herein.

[0431] Accordingly, in particularly preferred embodiments, the RNA described herein comprises at least one coding region encoding an antigenic peptide or protein and a signal peptide, said signal peptide preferably being fused to the antigenic peptide or protein, more preferably to the N-terminus of the antigenic peptide or protein as described herein.

[0432] In one embodiment, a vaccine antigen comprises the amino acid sequence of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 7. In one embodiment, a vaccine antigen comprises the amino acid sequence of SEQ ID NO: 1 or 7.

[0433] In one embodiment, RNA encoding a vaccine antigen (i) comprises the nucleotide sequence of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of SEQ ID NO: 2, 8

or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 7. In one embodiment, RNA encoding a vaccine antigen (i) comprises the nucleotide sequence of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 1 or 7.

[0434] In one embodiment, a vaccine antigen comprises the amino acid sequence of SEQ ID NO: 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 7, or an immunogenic fragment of the amino acid sequence of SEQ ID NO: 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 7. In one embodiment, a vaccine antigen comprises the amino acid sequence of SEQ ID NO: 7.

[0435] According to certain embodiments, a trimerization domain is fused, either directly or through a linker, e.g., a glycine/serine linker, to a SARS-CoV-2 S protein, a variant thereof, or a fragment thereof, i.e., the antigenic peptide or protein. Accordingly, in one embodiment, a trimerization domain is fused to the above described amino acid sequences derived from SARS-CoV-2 S protein or immunogenic fragments thereof (antigenic peptides or proteins) comprised by the vaccine antigens described above (which may optionally be fused to a signal peptide as described above).

[0436] Such trimerization domains are preferably located at the C-terminus of the antigenic peptide or protein, without being limited thereto. Trimerization domains as defined herein preferably allow the trimerization of the antigenic peptide or protein as encoded by the RNA. Examples of trimerization domains as defined herein include, without being limited thereto, foldon, the natural trimerization domain of T4 fibritin. The C-terminal domain of T4 fibritin (foldon) is obligatory for the formation of the fibritin trimer structure and can be used as an artificial trimerization domain. In one embodiment, the trimerization domain as defined herein includes, without being limited thereto, a sequence comprising the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10 or a functional variant thereof. In one embodiment, the trimerization domain as defined herein includes, without being limited thereto, a sequence comprising the amino acid sequence of SEQ ID NO: 10 or a functional variant thereof.

[0437] In one embodiment, a trimerization domain comprises the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, or a functional fragment of the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10. In one embodiment, a trimerization domain comprises the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10.

[0438] In one embodiment, RNA encoding a trimerization domain (i) comprises the nucleotide sequence of nucleotides 7 to 87 of SEQ ID NO: 11, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 7 to 87 of SEQ ID NO: 11, or a fragment of the nucleotide sequence of nucleotides 7 to 87 of SEQ ID NO: 11, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 7 to 87 of SEQ ID NO: 11; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, or a functional fragment of the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10, or the amino acid sequence having at least 99%, 98%, 97%,

96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10. In one embodiment, RNA encoding a trimerization domain (i) comprises the nucleotide sequence of nucleotides 7 to 87 of SEQ ID NO: 11; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10.

[0439] In one embodiment, a trimerization domain comprises the amino acid sequence SEQ ID NO: 10, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 10, or a functional fragment of the amino acid sequence of SEQ ID NO: 10, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 10. In one embodiment, a trimerization domain comprises the amino acid sequence of SEQ ID NO: 10.

[0440] In one embodiment, RNA encoding a trimerization domain (i) comprises the nucleotide sequence of SEQ ID NO: 11, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11, or a fragment of the nucleotide sequence of SEQ ID NO: 11, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 10, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 10, or a functional fragment of the amino acid sequence of SEQ ID NO: 10, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 10. In one embodiment, RNA encoding a trimerization domain (i) comprises the nucleotide sequence of SEQ ID NO: 11; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 10.

[0441] Such trimerization domains are preferably used in order to promote trimerization of the encoded antigenic peptide or protein. More preferably, a trimerization domain as defined herein is fused to an antigenic peptide or protein as defined herein.

[0442] Accordingly, in particularly preferred embodiments, the RNA described herein comprises at least one coding region encoding an antigenic peptide or protein and a trimerization domain as defined herein, said trimerization domain preferably being fused to the antigenic peptide or protein, more preferably to the C-terminus of the antigenic peptide or protein.

[0443] According to certain embodiments, a transmembrane domain is fused, either directly or through a linker, e.g., a glycine/serine linker, to a SARS-CoV-2 S protein, a variant thereof, or a fragment thereof, i.e., the antigenic peptide or protein. Accordingly, in one embodiment, a transmembrane domain is fused to the above described amino acid sequences derived from SARS-CoV-2 S protein or immunogenic fragments thereof (antigenic peptides or proteins) comprised by the vaccine antigens described above (which may optionally be fused to a signal peptide and/or trimerization domain as described above).

[0444] Such transmembrane domains are preferably located at the C-terminus of the antigenic peptide or protein, without being limited thereto. Preferably, such transmembrane domains are located at the C-terminus of the trimerization domain, if present, without being limited thereto. In one embodiment, a trimerization domain is present between the SARS-CoV-2 S protein, a variant thereof, or a fragment thereof, i.e., the antigenic peptide or protein, and the transmembrane domain.

[0445] Transmembrane domains as defined herein preferably allow the anchoring into a cellular membrane of the antigenic peptide or protein as encoded by the RNA.

[0446] In one embodiment, the transmembrane domain sequence as defined herein includes, without being limited thereto, the transmembrane domain sequence of SARS-CoV-2 S protein, in particular a sequence comprising the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1 or a functional variant thereof.

[0447] In one embodiment, a transmembrane domain sequence comprises the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1. In one embodiment, a transmembrane domain sequence comprises the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1.

[0448] In one embodiment, RNA encoding a transmembrane domain sequence (i) comprises the nucleotide sequence of nucleotides 3619 to 3762 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 3619 to 3762 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 3619 to 3762 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 3619 to 3762 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1. In one embodiment, RNA encoding a transmembrane domain sequence (i) comprises the nucleotide sequence of nucleotides 3619 to 3762 of SEQ ID NO: 2, 8 or 9; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1.

[0449] In one embodiment, the vaccine antigens described above comprise a contiguous sequence of SARS-CoV-2 coronavirus spike (S) protein that consists of or essentially consists of the above described amino acid sequences derived from SARS-CoV-2 S protein or immunogenic fragments thereof (antigenic peptides or proteins) comprised by the vaccine antigens described above. In one embodiment, the vaccine antigens described above comprise a contiguous sequence of SARS-CoV-2 coronavirus spike (S) protein of no more than 220 amino acids, 215 amino acids, 210 amino acids, or 205 amino acids.

[0450] As used herein, the term "vaccine" refers to a composition that induces an immune response upon inoculation into a subject. In some embodiments, the induced immune response provides protective immunity.

[0451] In one embodiment, the RNA encoding the antigen molecule is expressed in cells of the subject to provide the antigen molecule. In one embodiment, expression of the antigen molecule is at the cell surface or into the extracellular space. In one embodiment, the antigen molecule is presented in the context of MHC. In one embodiment, the RNA encoding the antigen molecule is transiently expressed in cells of the subject. In one embodiment, after administration of the RNA encoding the antigen molecule, in particular after intramuscular administration of the RNA encoding the antigen molecule, expression of the RNA encoding the antigen molecule in muscle occurs. In one embodiment, after administration of the RNA encoding the antigen molecule, expression of the RNA encoding the antigen molecule in spleen occurs. In one embodiment, after administration of the RNA encoding the antigen molecule, expression of the RNA encoding the antigen molecule in antigen presenting cells, preferably professional antigen presenting cells occurs. In one embodiment, the antigen presenting cells are selected from the group consisting of dendritic cells, macrophages and B cells. In one embodiment, after administration of the RNA encoding the antigen molecule, no or essentially no expression of the RNA encoding the antigen molecule in lung and/or liver occurs. In one embodiment, after administration of the RNA encoding the antigen molecule, expression of the RNA encoding the antigen molecule in spleen is at least 5-fold the amount of expression in lung.

[0452] In some embodiments, the methods and agents, e.g., RNA compositions, described herein following administration, in particular following intramuscular administration, to a subject result in delivery of the RNA encoding a vaccine antigen to lymph nodes and/or spleen. In some embodiments, RNA encoding a vaccine antigen is detectable in lymph nodes and/or spleen 6 hours or later following administration and preferably up to 6 days or longer.

[0453] In some embodiments, the methods and agents, e.g., mRNA compositions, described herein following administration, in particular following intramuscular administration, to a subject result in delivery of the RNA encoding a vaccine antigen to B cell follicles, subcapsular sinus, and/or T cell zone, in particular B cell follicles and/or subcapsular sinus of lymph nodes.

[0454] In some embodiments, the methods and agents, e.g., mRNA compositions, described herein following administration, in particular following intramuscular administration, to a subject result in delivery of the RNA encoding a vaccine antigen to B cells (CD19+), subcapsular sinus macrophages (CD169+) and/or dendritic cells (CD11c+) in the T cell zone and intermediary sinus of lymph nodes, in particular to B cells (CD19+) and/or subcapsular sinus macrophages (CD169+) of lymph nodes.

[0455] In some embodiments, the methods and agents, e.g., mRNA compositions, described herein following administration, in particular following intramuscular administration, to a subject result in delivery of the RNA encoding a vaccine antigen to white pulp of spleen.

[0456] In some embodiments, the methods and agents, e.g., mRNA compositions, described herein following administration, in particular following intramuscular administration, to a subject result in delivery of the RNA encoding a vaccine antigen to B cells, DCs (CD11c+), in particular those surrounding the B cells, and/or macrophages of spleen, in particular to B cells and/or DCs (CD11c+).

[0457] In one embodiment, the vaccine antigen is expressed in lymph node and/or spleen, in particular in the cells of lymph node and/or spleen described above.

[0458] The peptide and protein antigens suitable for use according to the present disclosure typically include a peptide or protein comprising an epitope of SARS-CoV-2 S protein or a functional variant thereof for inducing an immune response. The peptide or protein or epitope may be derived from a target antigen, i.e. the antigen against which an immune response is to be elicited. For example, the peptide or protein antigen or the epitope contained within the peptide or protein antigen may be a target antigen or a fragment or variant of a target antigen. The target antigen may be a coronavirus S protein, in particular SARS-CoV-2 S protein.

[0459] The antigen molecule or a procession product thereof, e.g., a fragment thereof, may bind to an antigen receptor such as a BCR or TCR carried by immune effector cells, or to antibodies.

[0460] A peptide and protein antigen which is provided to a subject according to the present disclosure by administering RNA encoding the peptide and protein antigen, i.e., a vaccine antigen, preferably results in the induction of an immune response, e.g., a humoral and/or cellular immune response in the subject being provided the peptide or protein antigen. Said immune response is preferably directed against a target antigen, in particular coronavirus S protein, in particular SARS-CoV-2 S protein. Thus, a vaccine antigen may comprise the target antigen, a variant thereof, or a fragment thereof. In one embodiment, such fragment or variant is immunologically equivalent to the target antigen. In the context of the present disclosure, the term "fragment of an antigen" or "variant of an antigen" means an agent which results in the induction of an immune response which immune response targets the antigen, i.e. a target antigen. Thus, the vaccine antigen may correspond to or may comprise the target antigen, may correspond to or may comprise a fragment of the target antigen or may correspond to or may comprise an antigen which is homologous to the target antigen or a fragment thereof. Thus, according to the present disclosure, a vaccine antigen may comprise an immunogenic fragment of a target antigen or an amino acid sequence being homologous to an immunogenic fragment of a target antigen. An "immunogenic fragment of an antigen" according

to the present disclosure preferably relates to a fragment of an antigen which is capable of inducing an immune response against the target antigen. The vaccine antigen may be a recombinant antigen.

[0461] The term "immunologically equivalent" means that the immunologically equivalent molecule such as the immunologically equivalent amino acid sequence exhibits the same or essentially the same immunological properties and/or exerts the same or essentially the same immunological effects, e.g., with respect to the type of the immunological effect. In the context of the present disclosure, the term "immunologically equivalent" is preferably used with respect to the immunological effects or properties of antigens or antigen variants used for immunization. For example, an amino acid sequence is immunologically equivalent to a reference amino acid sequence if said amino acid sequence when exposed to the immune system of a subject induces an immune reaction having a specificity of reacting with the reference amino acid sequence.

[0462] "Activation" or "stimulation", as used herein, refers to the state of an immune effector cell such as T cell that has been sufficiently stimulated to induce detectable cellular proliferation. Activation can also be associated with initiation of signaling pathways, induced cytokine production, and detectable effector functions. The term "activated immune effector cells" refers to, among other things, immune effector cells that are undergoing cell division.

[0463] The term "priming" refers to a process wherein an immune effector cell such as a T cell has its first contact with its specific antigen and causes differentiation into effector cells such as effector T cells.

[0464] The term "clonal expansion" or "expansion" refers to a process wherein a specific entity is multiplied. In the context of the present disclosure, the term is preferably used in the context of an immunological response in which immune effector cells are stimulated by an antigen, proliferate, and the specific immune effector cell recognizing said antigen is amplified. Preferably, clonal expansion leads to differentiation of the immune effector cells.

[0465] The term "antigen" relates to an agent comprising an epitope against which an immune response can be generated. The term "antigen" includes, in particular, proteins and peptides. In one embodiment, an antigen is presented by cells of the immune system such as antigen presenting cells like dendritic cells or macrophages. An antigen or a procession product thereof such as a T-cell epitope is in one embodiment bound by a T- or B-cell receptor, or by an immunoglobulin molecule such as an antibody. Accordingly, an antigen or a procession product thereof may react specifically with antibodies or T lymphocytes (T cells). In one embodiment, an antigen is a viral antigen, such as a coronavirus S protein, e.g., SARS-CoV-2 S protein, and an epitope is derived from such antigen.

[0466] The term "viral antigen" refers to any viral component having antigenic properties, i.e. being able to provoke an immune response in an individual. The viral antigen may be coronavirus S protein, e.g., SARS-CoV-2 S protein.

[0467] The term "expressed on the cell surface" or "associated with the cell surface" means that a molecule such as an antigen is associated with and located at the plasma membrane of a cell, wherein at least a part of the molecule faces the extracellular space of said cell and is accessible from the outside of said cell, e.g., by antibodies located outside the cell. In this context, a part is preferably at least 4, preferably at least 8, preferably at least 12, more preferably at least 20 amino acids. The association may be direct or indirect. For example, the association may be by one or more transmembrane domains, one or more lipid anchors, or by the interaction with any other protein, lipid, saccharide, or other structure that can be found on the outer leaflet of the plasma membrane of a cell. For example, a molecule associated with the surface of a cell may be a transmembrane protein having an extracellular portion or may be a protein associated with the surface of a cell by interacting with another protein that is a transmembrane protein.

[0468] "Cell surface" or "surface of a cell" is used in accordance with its normal meaning in the art, and thus includes the outside of the cell which is accessible to binding by proteins and other molecules. An antigen is

expressed on the surface of cells if it is located at the surface of said cells and is accessible to binding by e.g. antigen-specific antibodies added to the cells.

[0469] The term "extracellular portion" or "exodomain" in the context of the present disclosure refers to a part of a molecule such as a protein that is facing the extracellular space of a cell and preferably is accessible from the outside of said cell, e.g., by binding molecules such as antibodies located outside the cell. Preferably, the term refers to one or more extracellular loops or domains or a fragment thereof.

[0470] The term "epitope" refers to a part or fragment of a molecule such as an antigen that is recognized by the immune system. For example, the epitope may be recognized by T cells, B cells or antibodies. An epitope of an antigen may include a continuous or discontinuous portion of the antigen and may be between about 5 and about 100, such as between about 5 and about 50, more preferably between about 8 and about 30, most preferably between about 8 and about 25 amino acids in length, for example, the epitope may be preferably 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acids in length. In one embodiment, an epitope is between about 10 and about 25 amino acids in length. The term "epitope" includes T cell epitopes.

[0471] The term "T cell epitope" refers to a part or fragment of a protein that is recognized by a T cell when presented in the context of MHC molecules. The term "major histocompatibility complex" and the abbreviation "MHC" includes MHC class I and MHC class II molecules and relates to a complex of genes which is present in all vertebrates. MHC proteins or molecules are important for signaling between lymphocytes and antigen presenting cells or diseased cells in immune reactions, wherein the MHC proteins or molecules bind peptide epitopes and present them for recognition by T cell receptors on T cells. The proteins encoded by the MHC are expressed on the surface of cells, and display both self-antigens (peptide fragments from the cell itself) and non-self-antigens (e.g., fragments of invading microorganisms) to a T cell. In the case of class I MHC/peptide complexes, the binding peptides are typically about 8 to about 10 amino acids long although longer or shorter peptides may be effective. In the case of class II MHC/peptide complexes, the binding peptides are typically about 10 to about 25 amino acids long and are in particular about 13 to about 18 amino acids long, whereas longer and shorter peptides may be effective.

[0472] The peptide and protein antigen can be 2-100 amino acids, including for example, 5 amino acids, 10 amino acids, 15 amino acids, 20 amino acids, 25 amino acids, 30 amino acids, 35 amino acids, 40 amino acids, 45 amino acids, or 50 amino acids in length. In some embodiments, a peptide can be greater than 50 amino acids. In some embodiments, the peptide can be greater than 100 amino acids.

[0473] The peptide or protein antigen can be any peptide or protein that can induce or increase the ability of the immune system to develop antibodies and T cell responses to the peptide or protein.

[0474] In one embodiment, vaccine antigen is recognized by an immune effector cell. Preferably, the vaccine antigen if recognized by an immune effector cell is able to induce in the presence of appropriate co-stimulatory signals, stimulation, priming and/or expansion of the immune effector cell carrying an antigen receptor recognizing the vaccine antigen. In the context of the embodiments of the present disclosure, the vaccine antigen is preferably presented or present on the surface of a cell, preferably an antigen presenting cell. In one embodiment, an antigen is presented by a diseased cell such as a virus-infected cell. In one embodiment, an antigen receptor is a TCR which binds to an epitope of an antigen presented in the context of MHC. In one embodiment, binding of a TCR when expressed by T cells and/or present on T cells to an antigen presented by cells such as antigen presenting cells results in stimulation, priming and/or expansion of said T cells. In one embodiment, binding of a TCR when expressed by T cells and/or present on T cells to an antigen presented on diseased cells results in cytolysis and/or apoptosis of the diseased cells, wherein said T cells preferably release cytotoxic factors, e.g. perforins and granzymes.

[0475] In one embodiment, an antigen receptor is an antibody or B cell receptor which binds to an epitope in an antigen. In one embodiment, an antibody or B cell receptor binds to native epitopes of an antigen.

Nucleic acids

[0476] The term "polynucleotide" or "nucleic acid", as used herein, is intended to include DNA and RNA such as genomic DNA, cDNA, mRNA, recombinantly produced and chemically synthesized molecules. A nucleic acid may be single-stranded or double-stranded. RNA includes *in vitro* transcribed RNA (IVT RNA) or synthetic RNA. According to the present disclosure, a polynucleotide is preferably isolated.

[0477] Nucleic acids may be comprised in a vector. The term "vector" as used herein includes any vectors known to the skilled person including plasmid vectors, cosmid vectors, phage vectors such as lambda phage, viral vectors such as retroviral, adenoviral or baculoviral vectors, or artificial chromosome vectors such as bacterial artificial chromosomes (BAC), yeast artificial chromosomes (YAC), or P1 artificial chromosomes (PAC). Said vectors include expression as well as cloning vectors. Expression vectors comprise plasmids as well as viral vectors and generally contain a desired coding sequence and appropriate DNA sequences necessary for the expression of the operably linked coding sequence in a particular host organism (e.g., bacteria, yeast, plant, insect, or mammal) or in *in vitro* expression systems. Cloning vectors are generally used to engineer and amplify a certain desired DNA fragment and may lack functional sequences needed for expression of the desired DNA fragments.

[0478] In one embodiment of all aspects of the present disclosure, the RNA encoding the vaccine antigen is expressed in cells such as antigen presenting cells of the subject treated to provide the vaccine antigen.

[0479] The nucleic acids described herein may be recombinant and/or isolated molecules.

[0480] In the present disclosure, the term "RNA" relates to a nucleic acid molecule which includes ribonucleotide residues. In preferred embodiments, the RNA contains all or a majority of ribonucleotide residues. As used herein, "ribonucleotide" refers to a nucleotide with a hydroxyl group at the 2'-position of a β-D-ribofuranosyl group. RNA encompasses without limitation, double stranded RNA, single stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as modified RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations may refer to addition of non-nucleotide material to internal RNA nucleotides or to the end(s) of RNA. It is also contemplated herein that nucleotides in RNA may be non-standard nucleotides, such as chemically synthesized nucleotides or deoxynucleotides. For the present disclosure, these altered RNAs are considered analogs of naturally-occurring RNA.

[0481] In certain embodiments of the present disclosure, the RNA is messenger RNA (mRNA) that relates to a RNA transcript which encodes a peptide or protein. As established in the art, mRNA generally contains a 5' untranslated region (5'-UTR), a peptide coding region and a 3' untranslated region (3'-UTR). In some embodiments, the RNA is produced by *in vitro* transcription or chemical synthesis. In one embodiment, the mRNA is produced by *in vitro* transcription using a DNA template where DNA refers to a nucleic acid that contains deoxyribonucleotides.

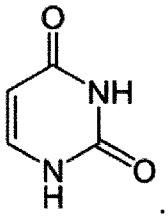
[0482] In one embodiment, RNA is *in vitro* transcribed RNA (IVT-RNA) and may be obtained by *in vitro* transcription of an appropriate DNA template. The promoter for controlling transcription can be any promoter for any RNA polymerase. A DNA template for *in vitro* transcription may be obtained by cloning of a nucleic acid, in particular cDNA, and introducing it into an appropriate vector for *in vitro* transcription. The cDNA may be obtained by reverse transcription of RNA.

[0483] In certain embodiments of the present disclosure, RNA described herein is "replicon RNA" or simply a "replicon", in particular "self-replicating RNA" or "self-amplifying RNA". In one particularly preferred embodiment, the replicon or self-replicating RNA is derived from or comprises elements derived from a ssRNA virus, in particular a positive-stranded ssRNA virus such as an alphavirus. Alphaviruses are typical representatives of positive-stranded

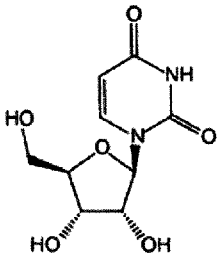
RNA viruses. Alphaviruses replicate in the cytoplasm of infected cells (for review of the alphaviral life cycle see José et al., Future Microbiol., 2009, vol. 4, pp. 837–856). The total genome length of many alphaviruses typically ranges between 11,000 and 12,000 nucleotides, and the genomic RNA typically has a 5'-cap, and a 3' poly(A) tail. The genome of alphaviruses encodes non-structural proteins (involved in transcription, modification and replication of viral RNA and in protein modification) and structural proteins (forming the virus particle). There are typically two open reading frames (ORFs) in the genome. The four non-structural proteins (nsP1–nsP4) are typically encoded together by a first ORF beginning near the 5' terminus of the genome, while alphavirus structural proteins are encoded together by a second ORF which is found downstream of the first ORF and extends near the 3' terminus of the genome. Typically, the first ORF is larger than the second ORF, the ratio being roughly 2:1. In cells infected by an alphavirus, only the nucleic acid sequence encoding non-structural proteins is translated from the genomic RNA, while the genetic information encoding structural proteins is translatable from a subgenomic transcript, which is an RNA molecule that resembles eukaryotic messenger RNA (mRNA; Gould et al., 2010, Antiviral Res., vol. 87 pp. 111–124). Following infection, i.e. at early stages of the viral life cycle, the (+) stranded genomic RNA directly acts like a messenger RNA for the translation of the open reading frame encoding the non-structural poly-protein (nsP1234). Alphavirus-derived vectors have been proposed for delivery of foreign genetic information into target cells or target organisms. In simple approaches, the open reading frame encoding alphaviral structural proteins is replaced by an open reading frame encoding a protein of interest. Alphavirus-based trans-replication systems rely on alphavirus nucleotide sequence elements on two separate nucleic acid molecules: one nucleic acid molecule encodes a viral replicase, and the other nucleic acid molecule is capable of being replicated by said replicase in trans (hence the designation trans-replication system). Trans-replication requires the presence of both these nucleic acid molecules in a given host cell. The nucleic acid molecule capable of being replicated by the replicase in trans must comprise certain alphaviral sequence elements to allow recognition and RNA synthesis by the alphaviral replicase.

[0484] In one embodiment, RNA described herein may have modified nucleosides. In some embodiments, RNA comprises a modified nucleoside in place of at least one (e.g., every) uridine.

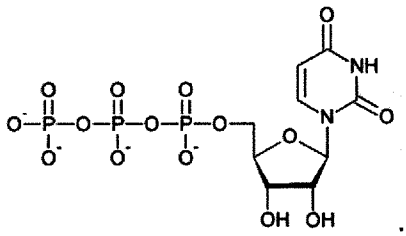
[0485] The term "uracil," as used herein, describes one of the nucleobases that can occur in the nucleic acid of RNA. The structure of uracil is:



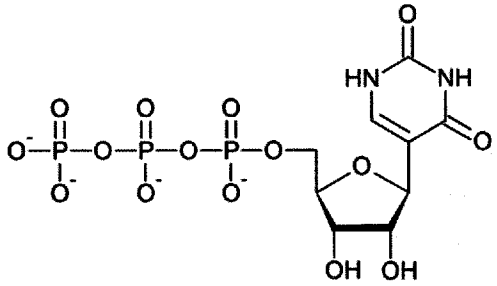
[0486] The term "uridine," as used herein, describes one of the nucleosides that can occur in RNA. The structure of uridine is:



[0487] UTP (uridine 5'-triphosphate) has the following structure:

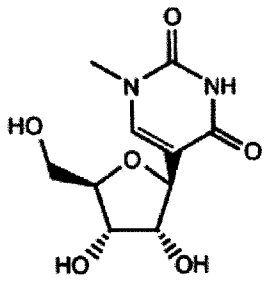


[0488] Pseudo-UTP (pseudouridine 5'-triphosphate) has the following structure:

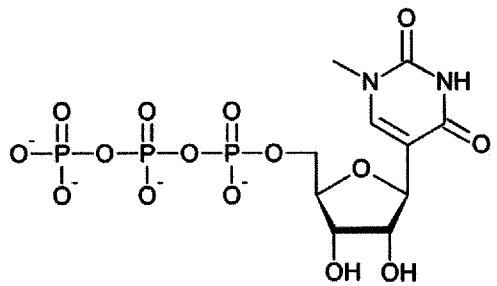


[0489] "Pseudouridine" is one example of a modified nucleoside that is an isomer of uridine, where the uracil is attached to the pentose ring via a carbon-carbon bond instead of a nitrogen-carbon glycosidic bond.

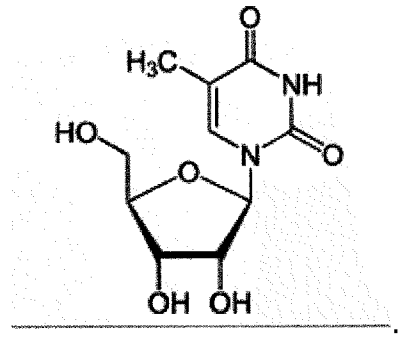
[0490] Another exemplary modified nucleoside is N1-methyl-pseudouridine (m1Ψ), which has the structure:



[0491] N1-methyl-pseudo-UTP has the following structure:



[0492] Another exemplary modified nucleoside is 5-methyl-uridine (m5U), which has the structure:



[0493] In some embodiments, one or more uridine in the RNA described herein is replaced by a modified nucleoside. In some embodiments, the modified nucleoside is a modified uridine.

[0494] In some embodiments, RNA comprises a modified nucleoside in place of at least one uridine. In some embodiments, RNA comprises a modified nucleoside in place of each uridine.

[0495] In some embodiments, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U). In some embodiments, the modified nucleoside comprises pseudouridine (ψ). In some embodiments, the modified nucleoside comprises N1-methyl-pseudouridine (m1ψ). In some embodiments, the modified nucleoside comprises 5-methyl-uridine (m5U). In some embodiments, RNA may comprise more than one type of modified nucleoside, and the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U). In some embodiments, the modified nucleosides comprise pseudouridine (ψ) and N1-methyl-pseudouridine (m1ψ). In some embodiments, the modified nucleosides comprise pseudouridine (ψ) and 5-methyl-uridine (m5U). In some embodiments, the modified nucleosides comprise N1-methyl-pseudouridine (m1ψ) and 5-methyl-uridine (m5U). In some embodiments, the modified nucleosides comprise pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

[0496] In some embodiments, the modified nucleoside replacing one or more, e.g., all, uridine in the RNA may be any one or more of 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), 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), 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), 1-ethyl-pseudouridine, 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(τm5s2U), 1-taurinomethyl-4-thio-pseudouridine), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4ψ$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3ψ$), 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 ($acp^3ψ$), 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), 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, 5-[3-(1-E-propenylamino)uridine, or any other modified uridine known in the art.

[0497] In one embodiment, the RNA comprises other modified nucleosides or comprises further modified nucleosides, e.g., modified cytidine. For example, in one embodiment, in the RNA 5-methylcytidine is substituted partially or completely, preferably completely, for cytidine. In one embodiment, the RNA comprises 5-methylcytidine and one or more selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U). In one embodiment, the RNA comprises 5-methylcytidine and N1-methyl-pseudouridine (m1ψ). In some embodiments, the RNA comprises 5-methylcytidine in place of each cytidine and N1-methyl-pseudouridine (m1ψ) in place of each uridine.

5' Caps

[0498] In some embodiments, an RNA described herein comprises a 5′ cap. Natural eukaryotic mRNA comprises a 7-methylguanosine cap linked to the mRNA via a 5′ to 5′-triphosphate bridge resulting in cap0 structure (m7GpppN). In most eukaryotic mRNA and some viral mRNA, further modifications can occur at the 2'-hydroxy-group (2′-OH) (*e.g.*, the 2'-hydroxyl group may be methylated to form 2'-O-Me) of the first and subsequent nucleotides producing "cap1" and "cap2" five-prime ends, respectively). Diamond, et al., (2014) *Cytokine & growth Factor Reviews*, 25:543–550 reported that cap0-mRNA cannot be translated as efficiently as cap1-mRNA in which the role of 2'-O-Me in the penultimate position at the mRNA 5′ end is determinant. Lack of the 2'-O-met has been shown to trigger innate immunity and activate IFN response. Daffis, et al. (2010) *Nature*, 468:452-456; and Züst et al. (2011) *Nature Immunology*, 12:137-143.

[0499] RNA capping is well researched and is described, e.g., in Decroly E et al. (2012) Nature Reviews 10: 51-65; and in Ramanathan A. et al., (2016) Nucleic Acids Res; 44(16): 7511–7526, the entire contents of each of which is hereby incorporated by reference. For example, in some embodiments, a 5′-cap structure which may be suitable in the context of the present invention is a cap0 (methylation of the first nucleobase, e.g. m7GpppN), cap1 (additional methylation of the ribose of the adjacent nucleotide of m7GpppN), cap2 (additional methylation of the ribose of the 2nd nucleotide downstream of the m7GpppN), cap3 (additional methylation of the ribose of the 3rd nucleotide downstream of the m7GpppN), cap4 (additional methylation of the ribose of the 4th nucleotide downstream of the m7GpppN), ARCA ("anti-reverse cap analogue"), modified ARCA (e.g. phosphothioate modified ARCA), inosine, N1 -methyl-guanosine, 2′-fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

[0500] The term "5'-cap" as used herein refers to a structure found on the 5'-end of an RNA, *e.g.*, mRNA, and generally includes a guanosine nucleotide connected to an RNA, *e.g.*, mRNA, via a 5'- to 5'-triphosphate linkage (also referred to as Gppp or G(5')ppp(5')). In some embodiments, a guanosine nucleoside included in a 5′ cap may be modified, for example, by methylation at one or more positions (*e.g.*, at the 7-position) on a base (guanine), and/or by methylation at one or more positions of a ribose. In some embodiments, a guanosine nucleoside included in a 5′ cap comprises a 3′O methylation at a ribose (3′OMeG). In some embodiments, a guanosine nucleoside included in a 5′ cap comprises methylation at the 7-position of guanine (m7G). In some embodiments, a guanosine nucleoside included in a 5′ cap comprises methylation at the 7-position of guanine and a 3′ O methylation at a ribose (m7(3′OMeG)). It will be understood that the notation used in the above paragraph, *e.g.*, "($m_2^{7,3'-O}$)G" or "m7(3′OMeG)", applies to other structures described herein.

[0501] In some embodiments, providing an RNA with a 5'-cap disclosed herein may be achieved by *in vitro* transcription, in which a 5'-cap is co-transcriptionally expressed into an RNA strand, or may be attached to an RNA post-transcriptionally using capping enzymes. In some embodiments, co-transcriptional capping with a cap disclosed improves the capping efficiency of an RNA compared to co-transcriptional capping with an appropriate reference comparator. In some embodiments, improving capping efficiency can increase a translation efficiency and/or translation rate of an RNA, and/or increase expression of an encoded polypeptide. In some embodiments, alterations to polynucleotides generates a non-hydrolyzable cap structure which can, for example, prevent decapping and increase RNA half-life.

[0502] In some embodiments, T7 RNA polymerase prefers G as the initial site. Accordingly, in some such embodiments, the present disclosure provides caps (e.g., trinucleotide and tetranucleotide caps described herein) wherein the 3'end of the trinucleotide (e.g., N_2) or tetranucleotide cap (e.g.., N_3) is G.

[0503] In some embodiments, it will be appreciated that all compounds or structures (e.g., 5′ caps) provided herein encompass the free base or salt form (e.g., an Na^+ salt) comprising a suitable counterion (e.g., Na^+).

Compounds or structures (e.g., 5′ caps) depicted as a salt also encompass the free base and include suitable counterions (e.g., Na^+).

[0504] In some embodiments, a utilized 5′ caps is a cap0, a cap1, or cap2 structure. *See, e.g.*, Fig. 1 of Ramanathan A et al., and Fig. 1 of Decroly E et al., each of which is incorporated herein by reference in its entirety. *See, e.g.*, Fig. 1 of Ramanathan A et al., and Fig. 1 of Decroly E et al., each of which is incorporated herein by reference in its entirety. In some embodiments, an RNA described herein comprises a cap1 structure. In some embodiments, an RNA described herein comprises a cap2.

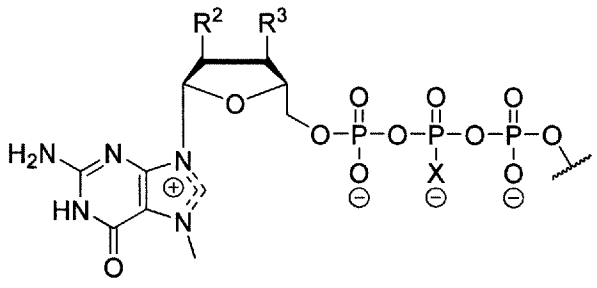
[0505] In some embodiments, an RNA described herein comprises a cap0 structure. In some embodiments, a cap0 structure comprises a guanosine nucleoside methylated at the 7-position of guanine ($(m^7)G$). In some embodiments, such a cap0 structure is connected to an RNA via a 5'- to 5'-triphosphate linkage and is also referred to herein as $(m^7)Gppp$. In some embodiments, a cap0 structure comprises a guanosine nucleoside methylated at the 2′-position of the ribose of guanosine In some embodiments, a cap0 structure comprises a guanosine nucleoside methylated at the 3′-position of the ribose of guanosine. In some embodiments, a guanosine nucleoside included in a 5′ cap comprises methylation at the 7-position of guanine and at the 2′-position of the ribose ($(m_2^{7,2'\text{-O}})G$). In some embodiments, a guanosine nucleoside included in a 5′ cap comprises methylation at the 7-position of guanine and at the 2′-position of the ribose ($(m_2^{7,3'\text{-O}})G$).

[0506] In some embodiments, a cap1 structure comprises a guanosine nucleoside methylated at the 7-position of guanine ($(m^7)G$) and optionally methylated at the 2′ or 3′ position pf the ribose, and a 2′O methylated first nucleotide in an RNA ($(m^{2'\text{-O}})N_1$). In some embodiments, a cap1 structure comprises a guanosine nucleoside methylated at the 7-position of guanine ($(m^7)G$) and the 3′ position of the ribose, and a 2′O methylated first nucleotide in an RNA ($(m^{2'\text{-O}})N_1$). In some embodiments, a cap1 structure is connected to an RNA via a 5'- to 5'-triphosphate linkage and is also referred to herein as, e.g., $((m^7)Gppp(^{2'\text{-O}})N_1)$ or $(m_2^{7,3'\text{-O}})Gppp(^{2'\text{-O}})N_1)$, wherein N_1 is as defined and described herein. In some embodiments, a cap1 structure comprises a second nucleotide, N_2, which is at position 2 and is chosen from A, G, C, or U, e.g., $(m^7)Gppp(^{2'\text{-O}})N_1pN_2$ or $(m_2^{7,3'\text{-O}})Gppp(^{2'\text{-O}})N_1pN_2$, wherein each of N_1 and N_2 is as defined and described herein.

[0507] In some embodiments, a cap2 structure comprises a guanosine nucleoside methylated at the 7-position of guanine ($(m^7)G$) and optionally methylated at the 2′ or 3′ position of the ribose, and a 2′O methylated first and second nucleotides in an RNA ($(m^{2'\text{-O}})N_1p(m^{2'\text{-O}})N_2$). In some embodiments, a cap2 structure comprises a guanosine nucleoside methylated at the 7-position of guanine ($(m^7)G$) and the 3′ position of the ribose, and a 2′O methylated first and second nucleotide in an RNA. In some embodiments, a cap2 structure is connected to an RNA via a 5'- to 5'-triphosphate linkage and is also referred to herein as, e.g., $((m^7)Gppp(^{2'\text{-O}})N_1p(^{2'\text{-O}})N_2)$ or $(m_2^{7,3'\text{-O}})Gppp(^{2'\text{-O}})N_1p(^{2'\text{-O}})N_2)$, wherein each of N_1 and N_2 is as defined and described herein.

[0508] In some embodiments, the 5′ cap is a dinucleotide cap structure. In some embodiments, the 5′ cap is a dinucleotide cap structure comprising N_1, wherein N_1 is as defined and described herein. In some embodiments, the 5′ cap is a dinucleotide cap G^*N_1, wherein N_1 is as defined above and herein, and:

[0509] G* comprises a structure of formula (I):



(I)

or a salt thereof,

wherein

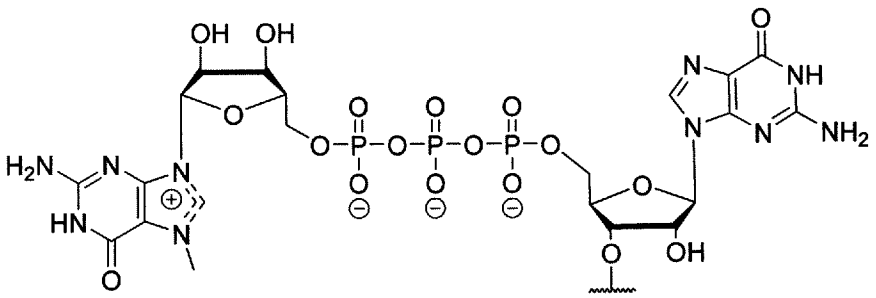
each R^2 and R^3 is -OH or $-OCH_3$; and

X is O or S.

[0510] In some embodiments, R^2 is -OH. In some embodiments, R^2 is $-OCH_3$. In some embodiments, R^3 is -OH. In some embodiments, R^3 is $-OCH_3$. In some embodiments, R^2 is -OH and R^3 is -OH. In some embodiments, R^2 is -OH and R^3 is $-CH_3$. In some embodiments, R^2 is $-CH_3$ and R^3 is -OH. In some embodiments, R^2 is $-CH_3$ and R^3 is $-CH_3$.

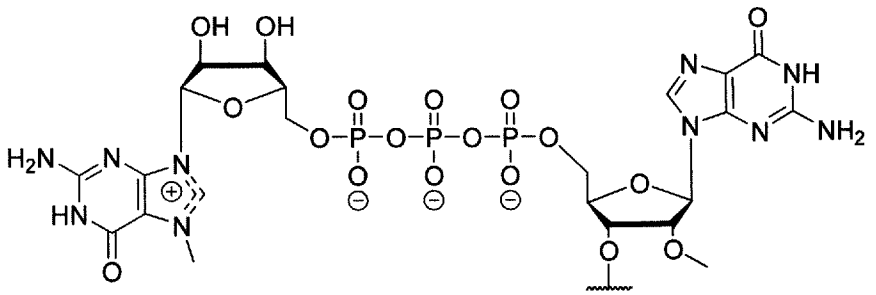
[0511] In some embodiments, X is O. In some embodiments, X is S.

[0512] In some embodiments, the 5′ cap is a dinucleotide cap0 structure (*e.g.*, $(m^7)GpppN_1$, $(m_2^{7,2'-O})GpppN_1$, $(m_2^{7,3'-O})GpppN_1$, $(m^7)GppSpN_1$, $(m_2^{7,2'-O})GppSpN_1$, or $(m_2^{7,3'-O})GppSpN_1$), wherein N_1 is as defined and described herein. In some embodiments, the 5′ cap is a dinucleotide cap0 structure (*e.g.*, $(m^7)GpppN_1$, $(m_2^{7,2'-O})GpppN_1$, $(m_2^{7,3'-O})GpppN_1$, $(m^7)GppSpN_1$, $(m_2^{7,2'-O})GppSpN_1$, or $(m_2^{7,3'-O})GppSpN_1$), wherein N_1 is G. In some embodiments, the 5′ cap is a dinucleotide cap0 structure (*e.g.*, $(m^7)GpppN_1$, $(m_2^{7,2'-O})GpppN_1$, $(m_2^{7,3'-O})GpppN_1$, $(m^7)GppSpN_1$, $(m_2^{7,2'-O})GppSpN_1$, or $(m_2^{7,3'-O})GppSpN_1$), wherein N_1 is A, U, or C. In some embodiments, the 5′ cap is a dinucleotide cap1 structure (*e.g.*, $(m^7)Gppp(m^{2'-O})N_1$, $(m_2^{7,2'-O})Gppp(m^{2'-O})N_1$, $(m_2^{7,3'-O})Gppp(m^{2'-O})N_1$, $(m^7)GppSp(m^{2'-O})N_1$, $(m_2^{7,2'-O})GppSp(m^{2'-O})N_1$, or $(m_2^{7,3'-O})GppSp(m^{2'-O})N_1$), wherein N_1 is as defined and described herein. In some embodiments, the 5′ cap is selected from the group consisting of $(m^7)GpppG$ ("Ecap0"), $(m^7)Gppp(m^{2'-O})G$ ("Ecap1"), $(m_2^{7,3'-O})GpppG$ ("ARCA" or "D1"), and $(m_2^{7,2'-O})GppSpG$ ("beta-S-ARCA"). In some embodiments, the 5′ cap is $(m^7)GpppG$ ("Ecap0"), having a structure:



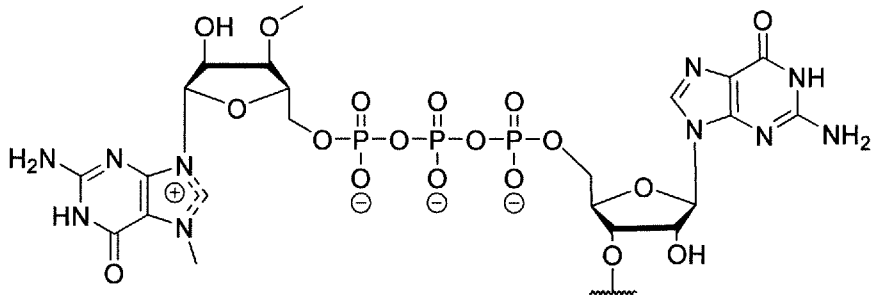
or a salt thereof.

[0513] In some embodiments, the 5′ cap is $(m^7)Gppp(m^{2'-O})G$ ("Ecap1"), having a structure:



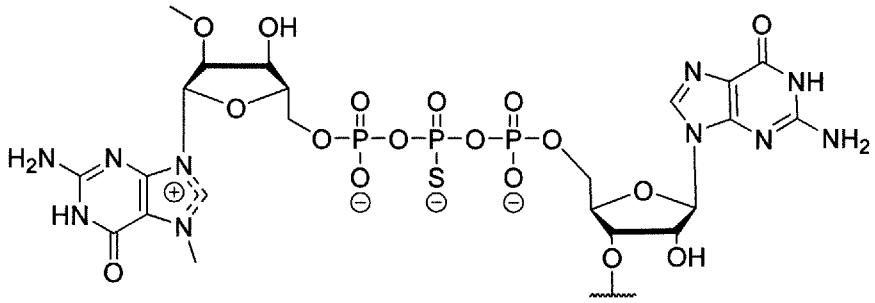
or a salt thereof.

[0514] In some embodiments, the 5′ cap is $(m_2^{7,3'-O})GpppG$ ("ARCA" or "D1"), having a structure:



or a salt thereof.

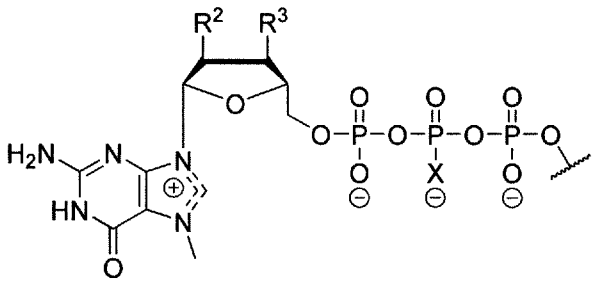
[0515] In some embodiments, the 5′ cap is ($m_2^{7,2'-O}$)GppSpG ("beta-S-ARCA"), having a structure:



or a salt thereof.

[0516] In some embodiments, the 5′ cap is a trinucleotide cap structure. In some embodiments, the 5′ cap is a trinucleotide cap structure comprising N_1pN_2, wherein N_1 and N_2 are as defined and described herein. In some embodiments, the 5′ cap is a trinucleotide cap G*N_1pN_2, wherein N_1 and N_2 are as defined above and herein, and:

[0517] G* comprises a structure of formula (I):

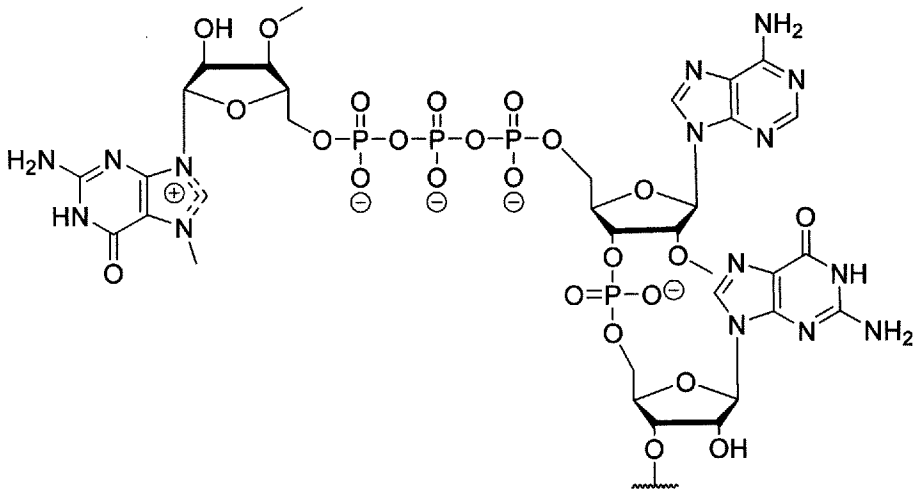


(I)

or a salt thereof, wherein R^2, R^3, and X are as defined and described herein.

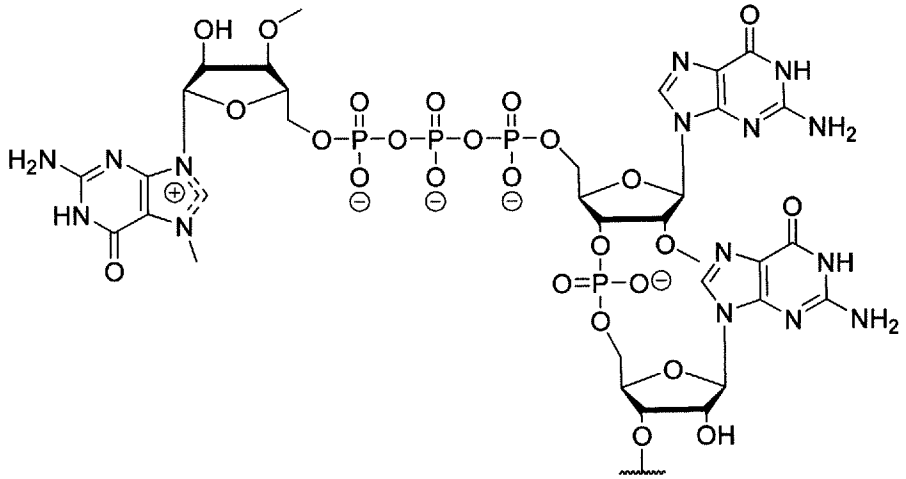
[0518] In some embodiments, the 5′ cap is a trinucleotide cap0 structure (*e.g.* (m^7)GpppN_1pN_2, ($m_2^{7,2'-O}$)GpppN_1pN_2, or ($m_2^{7,3'-O}$)GpppN_1pN_2), wherein N_1 and N_2 are as defined and described herein). In some embodiments, the 5′ cap is a trinucleotide cap1 structure (*e.g.*, (m^7)Gppp($m^{2'-O}$)N_1pN_2, ($m_2^{7,2'-O}$)Gppp($m^{2'-O}$)N_1pN_2, ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)N_1pN_2), wherein N_1 and N_2 are as defined and described herein. In some embodiments, the 5′ cap is a trinucleotide cap2 structure (*e.g.*, (m^7)Gppp($m^{2'-O}$)N_1p($m^{2'-O}$)N_2, ($m_2^{7,2'-O}$)Gppp($m^{2'-O}$)N_1p($m^{2'-O}$)N_2, ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)N_1p($m^{2'-O}$)N_2), wherein N_1 and N_2 are as defined and described herein. In some embodiments, the 5′ cap is selected from the group consisting of ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)ApG ("CleanCap AG 3′ OMe", "CC413"), ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)GpG ("CleanCap GG"), (m^7)Gppp($m^{2'-O}$)ApG, (m^7)Gppp($m^{2'-O}$)GpG, ($m_2^{7,3'-O}$)Gppp($m_2^{6,2'-O}$)ApG, and (m^7)Gppp($m^{2'-O}$)ApU. In some embodiments, the 5′ cap is selected from the group consisting of ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)ApG ("CleanCap AG", "CC413"), ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)GpG ("CleanCap GG"), (m^7)Gppp($m^{2'-O}$)ApG, and ($m_2^{7,3'-O}$)Gppp($m_2^{6,2'-O}$)ApG, (m^7)Gppp($m^{2'-O}$)ApU, and ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)CpG.

[0519] In some embodiments, the 5′ cap is ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)ApG ("CleanCap AG 3′ OMe", "CC413"), having a structure:



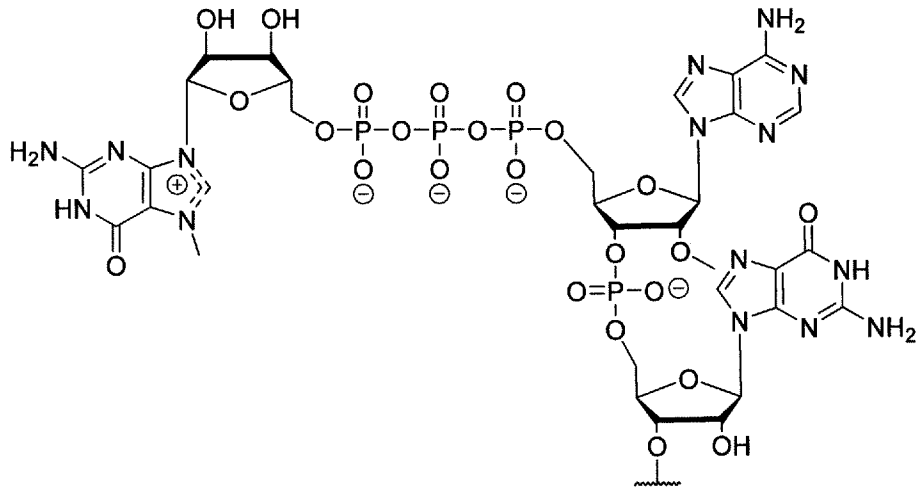
or a salt thereof.

[0520] In some embodiments, the 5′ cap is ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)GpG ("CleanCap GG"), having a structure:



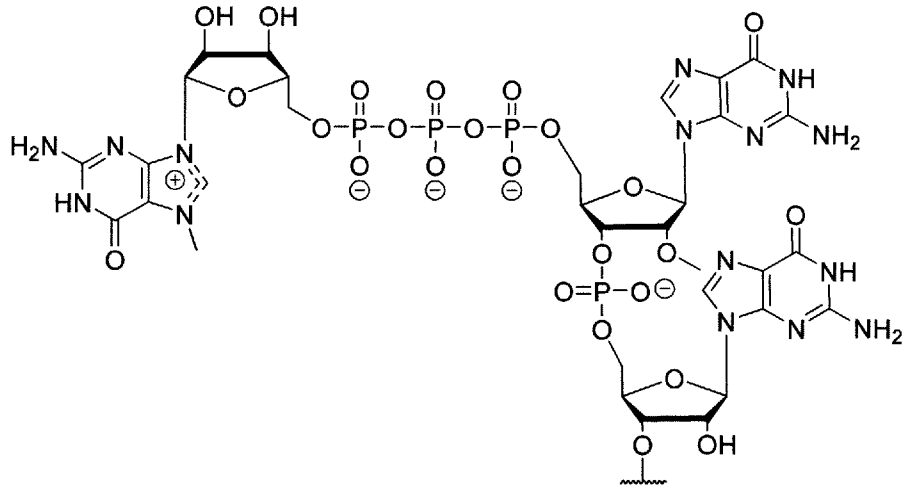
or a salt thereof.

[0521] In some embodiments, the 5′ cap is (m^7)Gppp($m^{2'-O}$)ApG, having a structure:



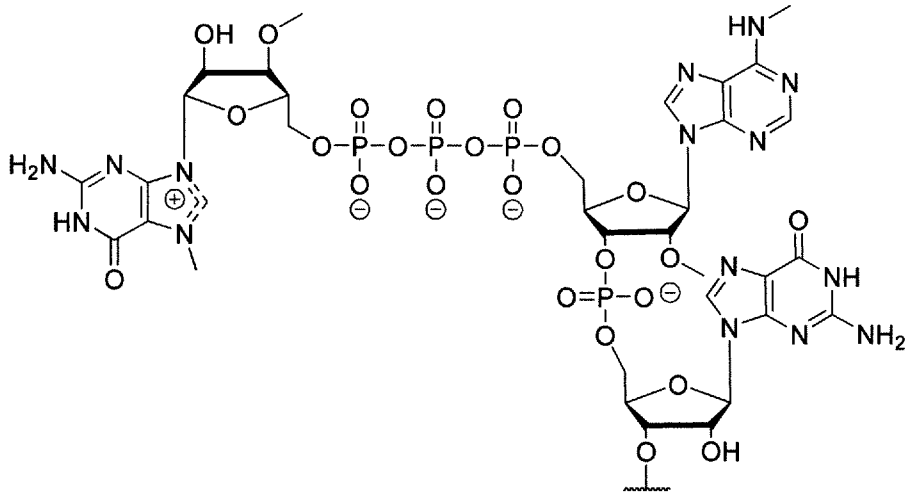
or a salt thereof.

[0522] In some embodiments, the 5′ cap is (m^7)Gppp($m^{2'-O}$)GpG, having a structure:



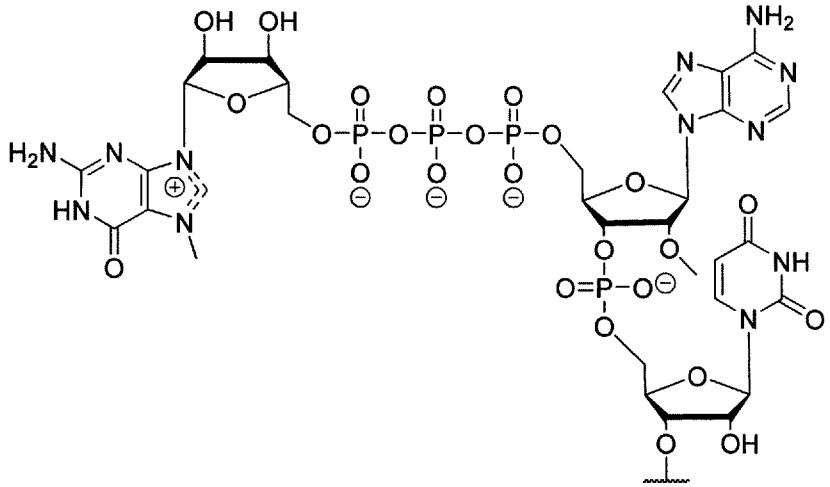
or a salt thereof.

[0523] In some embodiments, the 5′ cap is ($m_2^{7,3'-O}$)Gppp($m_2^{6,2'-O}$)ApG, having a structure:



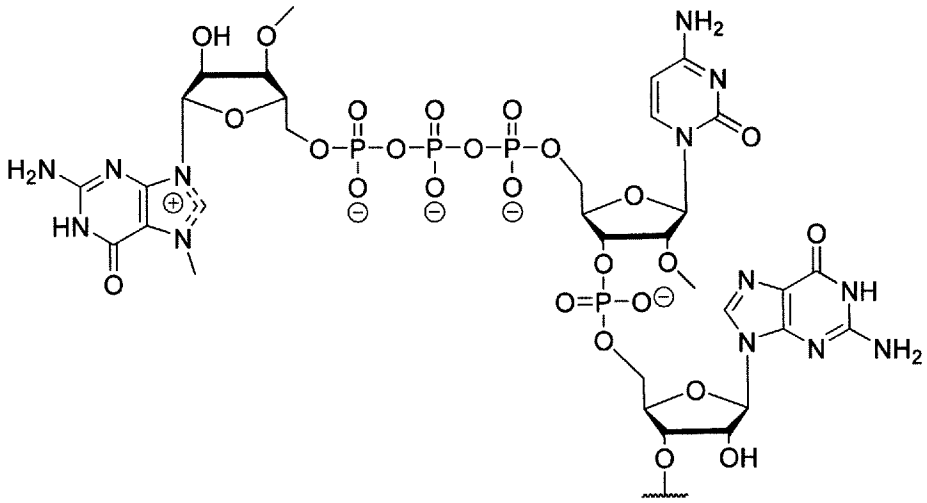
or a salt thereof.

[0524] In some embodiments, the 5′ cap is (m^7)Gppp($m^{2'-O}$)ApU, having a structure:



or a salt thereof.

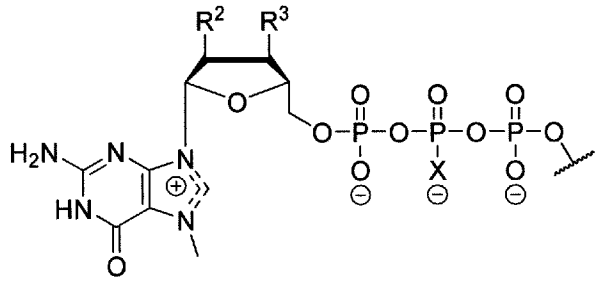
[0525] In some embodiments, the 5′ cap is ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)CpG, having a structure:



or a salt thereof.

[0526] In some embodiments, the 5′ cap is a tetranucleotide cap structure. In some embodiments, the 5′ cap is a tetranucleotide cap structure comprising $N_1pN_2pN_3$, wherein N_1, N_2, and N_3 are as defined and described herein. In some embodiments, the 5′ cap is a tetranucleotide cap $G^*N_1pN_2pN_3$, wherein N_1, N_2, and N_3 are as defined above and herein, and:

[0527] G* comprises a structure of formula (I):

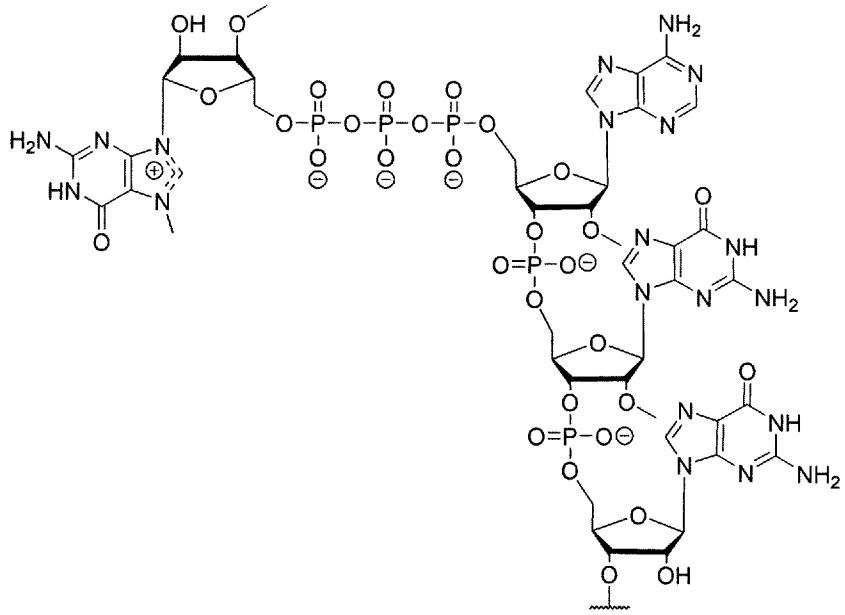


(I)

or a salt thereof, wherein R^2, R^3, and X are as defined and described herein.

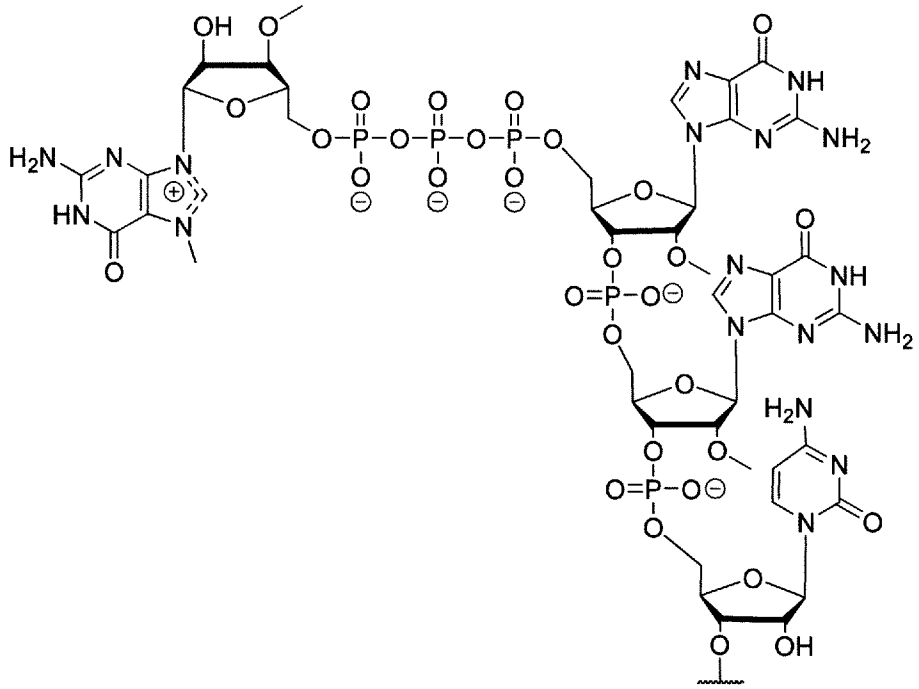
[0528] In some embodiments, the 5′ cap is a tetranucleotide cap0 structure (*e.g.* $(m^7)GpppN_1pN_2pN_3$, $(m_2^{7,2'-O})GpppN_1pN_2pN_3$, or $(m_2^{7,3'-O})GpppN_1N_2pN_3$), wherein N_1, N_2, and N_3 are as defined and described herein). n some embodiments, the 5′ cap is a tetranucleotide Cap1 structure (*e.g.*, $(m^7)Gppp(m^{2'-O})N_1pN_2pN_3$, $(m_2^{7,2'-O})Gppp(m^{2'-O})N_1pN_2pN_3$, $(m_2^{7,3'-O})Gppp(m^{2'-O})N_1pN_2N_3$), wherein N_1, N_2, and N_3 are as defined and described herein. In some embodiments, the 5′ cap is a tetranucleotide Cap2 structure (*e.g.*, $(m^7)Gppp(m^{2'-O})N_1p(m^{2'-O})N_2pN_3$, $(m_2^{7,2'-O})Gppp(m^{2'-O})N_1p(m^{2'-O})N_2pN_3$, $(m_2^{7,3'-O})Gppp(m^{2'-O})N_1p(m^{2'-O})N_2pN_3$), wherein N_1, N_2, and N_3 are as defined and described herein. In some embodiments, the 5′ cap is selected from the group consisting of $(m_2^{7,3'-O})Gppp(m^{2'-O})Ap(m^{2'-O})GpG$, $(m_2^{7,3'-O})Gppp(m^{2'-O})Gp(m^{2'-O})GpC$, $(m^7)Gppp(m^{2'-O})Ap(m^{2'-O})UpA$, and $(m^7)Gppp(m^{2'-O})Ap(m^{2'-O})GpG$.

[0529] In some embodiments, the 5′ cap is $(m_2^{7,3'-O})Gppp(m^{2'-O})Ap(m^{2'-O})GpG$, having a structure:



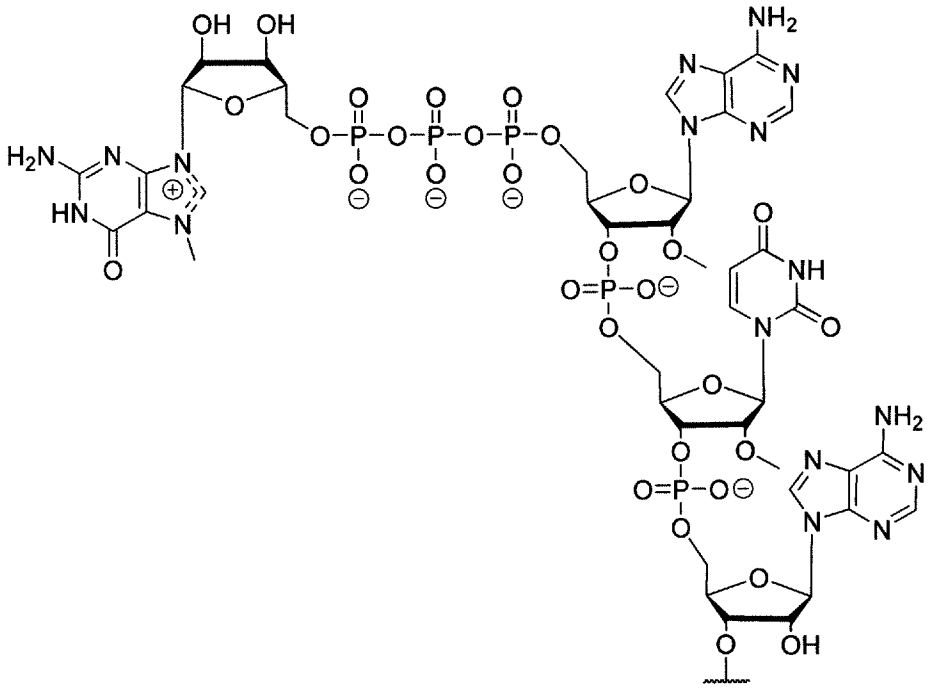
or a salt thereof.

[0530] In some embodiments, the 5′ cap is ($m_2^{7,3'-O}$)Gppp($m^{2'-O}$)Gp($m^{2'-O}$)GpC, having a structure:



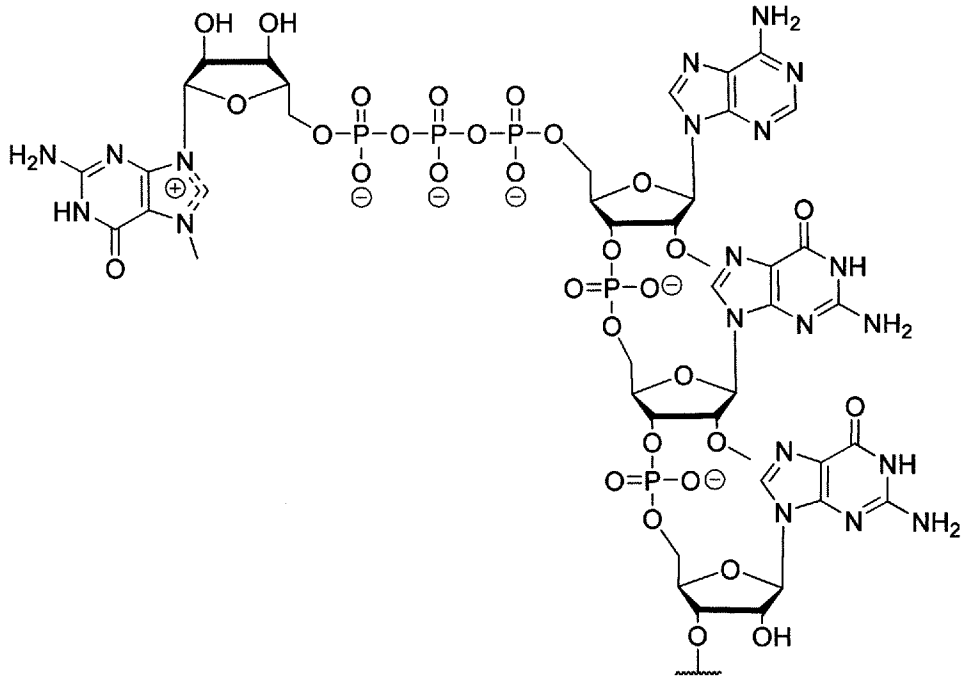
or a salt thereof.

[0531] In some embodiments, the 5′ cap is (m^7)Gppp($m^{2'-O}$)Ap($m^{2'-O}$)UpA, having a structure:



or a salt thereof.

[0532] In some embodiments, the 5′ cap is (m^7)Gppp($m^{2'-O}$)Ap($m^{2'-O}$)GpG, having a structure:



or a salt thereof.

[0533] A particularly preferred cap is beta-S-ARCA(D1) ($m_2^{7,2'-O}$GppSpG) or $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

[0534] In some embodiments, RNA according to the present disclosure comprises a 5'-UTR and/or a 3'-UTR. The term "untranslated region" or "UTR" relates to a region in a DNA molecule which is transcribed but is not translated into an amino acid sequence, or to the corresponding region in an RNA molecule, such as an mRNA molecule. An untranslated region (UTR) can be present 5' (upstream) of an open reading frame (5'-UTR) and/or 3' (downstream) of an open reading frame (3'-UTR). A 5'-UTR, if present, is located at the 5' end, upstream of the start codon of a protein-encoding region. A 5'-UTR is downstream of the 5'-cap (if present), e.g. directly adjacent to the 5'-cap. A 3'-UTR, if present, is located at the 3' end, downstream of the termination codon of a protein-

encoding region, but the term "3'-UTR" does preferably not include the poly(A) sequence. Thus, the 3'-UTR is upstream of the poly(A) sequence (if present), e.g. directly adjacent to the poly(A) sequence.

[0535] In some embodiments, RNA comprises a 5'-UTR comprising the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 12.

[0536] In some embodiments, RNA comprises a 3'-UTR comprising the nucleotide sequence of SEQ ID NO: 13, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 13.

[0537] A particularly preferred 5'-UTR comprises the nucleotide sequence of SEQ ID NO: 12. A particularly preferred 3'-UTR comprises the nucleotide sequence of SEQ ID NO: 13.

[0538] In some embodiments, the RNA according to the present disclosure comprises a 3'-poly(A) sequence.

[0539] As used herein, the term "poly(A) sequence" or "poly-A tail" refers to an uninterrupted or interrupted sequence of adenylate residues which is typically located at the 3'-end of an RNA molecule. Poly(A) sequences are known to those of skill in the art and may follow the 3'-UTR in the RNAs described herein. An uninterrupted poly(A) sequence is characterized by consecutive adenylate residues. In nature, an uninterrupted poly(A) sequence is typical. RNAs disclosed herein can have a poly(A) sequence attached to the free 3'-end of the RNA by a template-independent RNA polymerase after transcription or a poly(A) sequence encoded by DNA and transcribed by a template-dependent RNA polymerase.

[0540] It has been demonstrated that a poly(A) sequence of about 120 A nucleotides has a beneficial influence on the levels of RNA in transfected eukaryotic cells, as well as on the levels of protein that is translated from an open reading frame that is present upstream (5') of the poly(A) sequence (*Holtkamp et al.*, 2006, Blood, vol. 108, pp. 4009-4017).

[0541] The poly(A) sequence may be of any length. In some embodiments, a poly(A) sequence comprises, essentially consists of, or consists of at least 20, at least 30, at least 40, at least 80, or at least 100 and up to 500, up to 400, up to 300, up to 200, or up to 150 A nucleotides, and, in particular, about 120 A nucleotides. In this context, "essentially consists of" means that most nucleotides in the poly(A) sequence, typically at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% by number of nucleotides in the poly(A) sequence are A nucleotides, but permits that remaining nucleotides are nucleotides other than A nucleotides, such as U nucleotides (uridylate), G nucleotides (guanylate), or C nucleotides (cytidylate). In this context, "consists of" means that all nucleotides in the poly(A) sequence, i.e., 100% by number of nucleotides in the poly(A) sequence, are A nucleotides. The term "A nucleotide" or "A" refers to adenylate.

[0542] In some embodiments, a poly(A) sequence is attached during RNA transcription, e.g., during preparation of *in vitro* transcribed RNA, based on a DNA template comprising repeated dT nucleotides (deoxythymidylate) in the strand complementary to the coding strand. The DNA sequence encoding a poly(A) sequence (coding strand) is referred to as poly(A) cassette.

[0543] In some embodiments, the poly(A) cassette present in the coding strand of DNA essentially consists of dA nucleotides, but is interrupted by a random sequence of the four nucleotides (dA, dC, dG, and dT). Such random sequence may be 5 to 50, 10 to 30, or 10 to 20 nucleotides in length. Such a cassette is disclosed in WO 2016/005324 A1, hereby incorporated by reference. Any poly(A) cassette disclosed in WO 2016/005324 A1 may be used in the present disclosure. A poly(A) cassette that essentially consists of dA nucleotides, but is interrupted by a random sequence having an equal distribution of the four nucleotides (dA, dC, dG, dT) and having a length of e.g., 5 to 50 nucleotides shows, on DNA level, constant propagation of plasmid DNA in *E. coli* and is still associated, on RNA level, with the beneficial properties with respect to supporting RNA stability and translational efficiency is encompassed. Consequently, in some embodiments, the poly(A) sequence contained in an RNA molecule described

herein essentially consists of A nucleotides, but is interrupted by a random sequence of the four nucleotides (A, C, G, U). Such random sequence may be 5 to 50, 10 to 30, or 10 to 20 nucleotides in length.

[0544] In some embodiments, no nucleotides other than A nucleotides flank a poly(A) sequence at its 3'-end, i.e., the poly(A) sequence is not masked or followed at its 3'-end by a nucleotide other than A.

[0545] In some embodiments, the poly(A) sequence may comprise at least 20, at least 30, at least 40, at least 80, or at least 100 and up to 500, up to 400, up to 300, up to 200, or up to 150 nucleotides. In some embodiments, the poly(A) sequence may essentially consist of at least 20, at least 30, at least 40, at least 80, or at least 100 and up to 500, up to 400, up to 300, up to 200, or up to 150 nucleotides. In some embodiments, the poly(A) sequence may consist of at least 20, at least 30, at least 40, at least 80, or at least 100 and up to 500, up to 400, up to 300, up to 200, or up to 150 nucleotides. In some embodiments, the poly(A) sequence comprises at least 100 nucleotides. In some embodiments, the poly(A) sequence comprises about 150 nucleotides. In some embodiments, the poly(A) sequence comprises about 120 nucleotides.

[0546] In some embodiments, a poly(A) sequence included in an RNA described herein is a interrupted poly(A) sequence, e.g., as described in WO2016/005324, the entire content of which is incorporated herein by reference for purposes described herein. In some embodiments, a poly(A) sequence comprises a stretch of at least 20 adenosine residues (including, e.g., at least 30, at least 40, at least 50, at least 60, at least 70, or more adenosine residues), followed by a linker sequence (e.g., in some embodiments comprising non-A nucleotides) and another stretch of at least 20 adenosine residues (including, e.g., at least 30, at least 40, at least 50, at least 60, at least 70, or more adenosine residues). In some embodiments, such a linker sequence may be 3-50 nucleotides in length, or 5-25 nucleotides in length, or 10-15 nucleotides in length. In some embodiments, a poly(A) sequence comprises a stretch of about 30 adenosine residues, followed by a linker sequence having a length of about 5-15 nucleoties (e.g., in some embodiments comprising non-A nucleotides) and another stretch of about 70 adenosine residues.

[0547] In some embodiments, RNA comprises a poly(A) sequence comprising the nucleotide sequence of SEQ ID NO: 14, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 14.

[0548] A particularly preferred poly(A) sequence comprises the nucleotide sequence of SEQ ID NO: 14.

[0549] According to the present disclosure, vaccine antigen is preferably administered as single-stranded, 5'-capped RNA (e.g., mRNA) that is translated into the respective protein upon entering cells of a subject being administered the RNA. Preferably, the RNA contains structural elements optimized for maximal efficacy of the RNA with respect to stability and translational efficiency (5'-cap, 5'-UTR, 3'-UTR, poly(A) sequence).

[0550] In one embodiment, beta-S-ARCA(D1) is utilized as specific capping structure at the 5'-end of the RNA. In one embodiment, $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$ is utilized as specific capping structure at the 5'-end of the RNA. In one embodiment, the 5'-UTR sequence is derived from the human alpha-globin mRNA and optionally has an optimized 'Kozak sequence' to increase translational efficiency. In one embodiment, a combination of two sequence elements (FI element) derived from the "amino terminal enhancer of split" (AES) mRNA (called F) and the mitochondrial encoded 12S ribosomal RNA (called I) are placed between the coding sequence and the poly(A) sequence to assure higher maximum protein levels and prolonged persistence of the RNA (e.g., mRNA). In one embodiment, two re-iterated 3'-UTRs derived from the human beta-globin mRNA are placed between the coding sequence and the poly(A) sequence to assure higher maximum protein levels and prolonged persistence of the RNA (e.g., mRNA). In one embodiment, a poly(A) sequence measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a linker sequence (e.g., 10 nucleotide linker sequence) and another 70 adenosine residues is used. This poly(A) sequence was designed to enhance RNA stability and translational efficiency.

[0551] In one embodiment of all aspects of the present disclosure, RNA encoding a vaccine antigen is expressed in cells of the subject treated to provide the vaccine antigen. In one embodiment of all aspects of the present disclosure, the RNA is transiently expressed in cells of the subject. In one embodiment of all aspects of the present disclosure, the RNA is *in vitro* transcribed RNA. In one embodiment of all aspects of the present disclosure, expression of the vaccine antigen is at the cell surface. In one embodiment of all aspects of the present disclosure, the vaccine antigen is expressed and presented in the context of MHC. In one embodiment of all aspects of the present disclosure, expression of the vaccine antigen is into the extracellular space, i.e., the vaccine antigen is secreted.

[0552] In the context of the present disclosure, the term "transcription" relates to a process, wherein the genetic code in a DNA sequence is transcribed into RNA. Subsequently, the RNA may be translated into peptide or protein.

[0553] According to the present disclosure, the term "transcription" comprises "*in vitro* transcription", wherein the term "*in vitro* transcription" relates to a process wherein RNA, in particular mRNA, is *in vitro* synthesized in a cell-free system, preferably using appropriate cell extracts. Preferably, cloning vectors are applied for the generation of transcripts. These cloning vectors are generally designated as transcription vectors and are according to the present disclosure encompassed by the term "vector". According to the present disclosure, the RNA used in the present disclosure preferably is *in vitro* transcribed RNA (IVT-RNA) and may be obtained by *in vitro* transcription of an appropriate DNA template. The promoter for controlling transcription can be any promoter for any RNA polymerase. Particular examples of RNA polymerases are the T7, T3, and SP6 RNA polymerases. Preferably, the *in vitro* transcription according to the disclosure is controlled by a T7 or SP6 promoter. A DNA template for *in vitro* transcription may be obtained by cloning of a nucleic acid, in particular cDNA, and introducing it into an appropriate vector for *in vitro* transcription. The cDNA may be obtained by reverse transcription of RNA.

[0554] With respect to RNA, the term "expression" or "translation" relates to the process in the ribosomes of a cell by which a strand of mRNA directs the assembly of a sequence of amino acids to make a peptide or protein.

[0555] In one embodiment, after administration of the RNA described herein, e.g., formulated as RNA lipid particles, at least a portion of the RNA is delivered to a target cell. In one embodiment, at least a portion of the RNA is delivered to the cytosol of the target cell. In one embodiment, the RNA is translated by the target cell to produce the peptide or protein it encodes. In one embodiment, the target cell is a spleen cell. In one embodiment, the target cell is an antigen presenting cell such as a professional antigen presenting cell in the spleen. In one embodiment, the target cell is a dendritic cell or macrophage. RNA particles such as RNA lipid particles described herein may be used for delivering RNA to such target cell. Accordingly, the present disclosure also relates to a method for delivering RNA to a target cell in a subject comprising the administration of the RNA particles described herein to the subject. In one embodiment, the RNA is delivered to the cytosol of the target cell. In one embodiment, the RNA is translated by the target cell to produce the peptide or protein encoded by the RNA.

[0556] "Encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (i.e., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0557] In one embodiment, the RNA encoding vaccine antigen to be administered according to the present disclosure is non-immunogenic. RNA encoding immunostimulant may be administered according to the present

disclosure to provide an adjuvant effect. The RNA encoding immunostimulant may be standard RNA or non-immunogenic RNA.

[0558] The term "non-immunogenic RNA" as used herein refers to RNA that does not induce a response by the immune system upon administration, e.g., to a mammal, or induces a weaker response than would have been induced by the same RNA that differs only in that it has not been subjected to the modifications and treatments that render the non-immunogenic RNA non-immunogenic, i.e., than would have been induced by standard RNA (stdRNA). In one preferred embodiment, non-immunogenic RNA, which is also termed modified RNA (modRNA) herein, is rendered non-immunogenic by incorporating modified nucleosides suppressing RNA-mediated activation of innate immune receptors into the RNA and removing double-stranded RNA (dsRNA).

[0559] For rendering the non-immunogenic RNA non-immunogenic by the incorporation of modified nucleosides, any modified nucleoside may be used as long as it lowers or suppresses immunogenicity of the RNA. Particularly preferred are modified nucleosides that suppress RNA-mediated activation of innate immune receptors. In one embodiment, the modified nucleosides comprises a replacement of one or more uridines with a nucleoside comprising a modified nucleobase. In one embodiment, the modified nucleobase is a modified uracil. In one embodiment, the nucleoside comprising a modified nucleobase is selected from the group consisting of 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), 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), 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), 1-ethyl-pseudouridine, 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($\tau m5s2U$), 1-taurinomethyl-4-thio-pseudouridine), 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), 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 one particularly preferred embodiment, the nucleoside comprising a modified nucleobase is pseudouridine (ψ), N1-methyl-pseudouridine ($m1\psi$) or 5-methyl-uridine (m5U), in particular N1-methyl-pseudouridine.

[0560] In one embodiment, the replacement of one or more uridines with a nucleoside comprising a modified nucleobase comprises a replacement of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% of the uridines.

[0561] During synthesis of RNA (e.g., mRNA) by *in vitro* transcription (IVT) using T7 RNA polymerase significant amounts of aberrant products, including double-stranded RNA (dsRNA) are produced due to unconventional activity of the enzyme. dsRNA induces inflammatory cytokines and activates effector enzymes leading to protein synthesis inhibition. dsRNA can be removed from RNA such as IVT RNA, for example, by ion-pair reversed phase HPLC using a non-porous or porous C-18 polystyrene-divinylbenzene (PS-DVB) matrix. Alternatively, an enzymatic based method using E. coli RNaseIII that specifically hydrolyzes dsRNA but not ssRNA, thereby eliminating dsRNA contaminants from IVT RNA preparations can be used. Furthermore, dsRNA can be separated from ssRNA by using a cellulose material. In one embodiment, an RNA preparation is contacted with a cellulose material and the ssRNA is separated from the cellulose material under conditions which allow binding of dsRNA to the cellulose material and do not allow binding of ssRNA to the cellulose material.

[0562] As the term is used herein, "remove" or "removal" refers to the characteristic of a population of first substances, such as non-immunogenic RNA, being separated from the proximity of a population of second substances, such as dsRNA, wherein the population of first substances is not necessarily devoid of the second substance, and the population of second substances is not necessarily devoid of the first substance. However, a population of first substances characterized by the removal of a population of second substances has a measurably lower content of second substances as compared to the non-separated mixture of first and second substances.

[0563] In one embodiment, the removal of dsRNA from non-immunogenic RNA comprises a removal of dsRNA such that less than 10%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.3%, or less than 0.1% of the RNA in the non-immunogenic RNA composition is dsRNA. In one embodiment, the non-immunogenic RNA is free or essentially free of dsRNA. In some embodiments, the non-immunogenic RNA composition comprises a purified preparation of single-stranded nucleoside modified RNA. For example, in some embodiments, the purified preparation of single-stranded nucleoside modified RNA is substantially free of double stranded RNA (dsRNA). In some embodiments, the purified preparation is at least 90%, at least 91%, at least 92%, at least 93 %, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 99.9% single stranded nucleoside modified RNA, relative to all other nucleic acid molecules (DNA, dsRNA, etc.).

[0564] In one embodiment, the non-immunogenic RNA is translated in a cell more efficiently than standard RNA with the same sequence. In one embodiment, translation is enhanced by a factor of 2-fold relative to its unmodified counterpart. In one embodiment, translation is enhanced by a 3-fold factor. In one embodiment, translation is enhanced by a 4-fold factor. In one embodiment, translation is enhanced by a 5-fold factor. In one embodiment, translation is enhanced by a 6-fold factor. In one embodiment, translation is enhanced by a 7-fold factor. In one embodiment, translation is enhanced by an 8-fold factor. In one embodiment, translation is enhanced by a 9-fold factor. In one embodiment, translation is enhanced by a 10-fold factor. In one embodiment, translation is enhanced by a 15-fold factor. In one embodiment, translation is enhanced by a 20-fold factor. In one embodiment, translation is enhanced by a 50-fold factor. In one embodiment, translation is enhanced by a 100-fold factor. In one embodiment, translation is enhanced by a 200-fold factor. In one embodiment, translation is enhanced by a 500-fold factor. In one embodiment, translation is enhanced by a 1000-fold factor. In one embodiment, translation is enhanced by a 2000-fold factor. In one embodiment, the factor is 10-1000-fold. In one embodiment, the factor is 10-100-fold. In one embodiment, the factor is 10-200-fold. In one embodiment, the factor is 10-300-fold. In one embodiment, the factor is 10-500-fold. In one embodiment, the factor is 20-1000-fold. In one embodiment, the factor is 30-1000-fold. In one embodiment, the factor is 50-1000-fold. In one embodiment, the factor is 100-1000-fold. In one embodiment, the factor is 200-1000-fold. In one embodiment, translation is enhanced by any other significant amount or range of amounts.

[0565] In one embodiment, the non-immunogenic RNA exhibits significantly less innate immunogenicity than standard RNA with the same sequence. In one embodiment, the non-immunogenic RNA exhibits an innate immune response that is 2-fold less than its unmodified counterpart. In one embodiment, innate immunogenicity is reduced by a 3-fold factor. In one embodiment, innate immunogenicity is reduced by a 4-fold factor. In one embodiment, innate immunogenicity is reduced by a 5-fold factor. In one embodiment, innate immunogenicity is reduced by a 6-fold factor. In one embodiment, innate immunogenicity is reduced by a 7-fold factor. In one embodiment, innate immunogenicity is reduced by a 8-fold factor. In one embodiment, innate immunogenicity is reduced by a 9-fold factor. In one embodiment, innate immunogenicity is reduced by a 10-fold factor. In one embodiment, innate immunogenicity is reduced by a 15-fold factor. In one embodiment, innate immunogenicity is reduced by a 20-fold factor. In one embodiment, innate immunogenicity is reduced by a 50-fold factor. In one embodiment, innate immunogenicity is reduced by a 100-fold factor. In one embodiment, innate immunogenicity is reduced by a 200-fold factor. In one embodiment, innate immunogenicity is reduced by a 500-fold factor. In one embodiment, innate immunogenicity is reduced by a 1000-fold factor. In one embodiment, innate immunogenicity is reduced by a 2000-fold factor.

[0566] The term "exhibits significantly less innate immunogenicity" refers to a detectable decrease in innate immunogenicity. In one embodiment, the term refers to a decrease such that an effective amount of the non-immunogenic RNA can be administered without triggering a detectable innate immune response. In one embodiment, the term refers to a decrease such that the non-immunogenic RNA can be repeatedly administered without eliciting an innate immune response sufficient to detectably reduce production of the protein encoded by the non-immunogenic RNA. In one embodiment, the decrease is such that the non-immunogenic RNA can be repeatedly administered without eliciting an innate immune response sufficient to eliminate detectable production of the protein encoded by the non-immunogenic RNA.

[0567] "Immunogenicity" is the ability of a foreign substance, such as RNA, to provoke an immune response in the body of a human or other animal. The innate immune system is the component of the immune system that is relatively unspecific and immediate. It is one of two main components of the vertebrate immune system, along with the adaptive immune system.

[0568] As used herein "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

[0569] As used herein, the term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

[0570] The term "expression" as used herein is defined as the transcription and/or translation of a particular nucleotide sequence.

[0571] As used herein, the terms "linked," "fused", or "fusion" are used interchangeably. These terms refer to the joining together of two or more elements or components or domains.

Codon-optimization / Increase in G/C content

[0572] In some embodiment, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof described herein is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence. This also includes embodiments, wherein one or more sequence regions of the coding sequence are codon-optimized and/or increased in the G/C content compared to the corresponding sequence regions of the wild type coding sequence. In one embodiment, the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

[0573] The term "codon-optimized" refers to the alteration of codons in the coding region of a nucleic acid molecule to reflect the typical codon usage of a host organism without preferably altering the amino acid sequence encoded by the nucleic acid molecule. Within the context of the present disclosure, coding regions are preferably codon-optimized for optimal expression in a subject to be treated using the RNA molecules described herein. Codon-optimization is based on the finding that the translation efficiency is also determined by a different frequency in the occurrence of tRNAs in cells. Thus, the sequence of RNA may be modified such that codons for which frequently occurring tRNAs are available are inserted in place of "rare codons".

[0574] In some embodiments of the present disclosure, the guanosine/cytosine (G/C) content of the coding region of the RNA described herein is increased compared to the G/C content of the corresponding coding sequence of the wild type RNA, wherein the amino acid sequence encoded by the RNA is preferably not modified compared to the amino acid sequence encoded by the wild type RNA. This modification of the RNA sequence is based on the fact that the sequence of any RNA region to be translated is important for efficient translation of that mRNA. Sequences having an increased G (guanosine)/C (cytosine) content are more stable than sequences having an increased A (adenosine)/U (uracil) content. In respect to the fact that several codons code for one and the same amino acid (so-called degeneration of the genetic code), the most favourable codons for the stability can be determined (so-called alternative codon usage). Depending on the amino acid to be encoded by the RNA, there are various possibilities for modification of the RNA sequence, compared to its wild type sequence. In particular, codons which contain A and/or U nucleotides can be modified by substituting these codons by other codons, which code for the same amino acids but contain no A and/or U or contain a lower content of A and/or U nucleotides.

[0575] In various embodiments, the G/C content of the coding region of the RNA described herein is increased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 55%, or even more compared to the G/C content of the coding region of the wild type RNA. In some embodiments, G/C content of a coding region is increased by about 10% to about 60% (e.g., by about 20% to about 60%, about 30% to about 60%, about 40% to about 60%, about 50% to about 60%, or by about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, or about 60%) compared to the G/C content of the coding region of the wild type RNA.

[0576] In some embodiments, RNA disclosed herein comprises a sequence disclosed herein (e.g., SEQ ID NO: 9), that has been modified to encode one or more mutations characteristic of a SARS-CoV-2 variant (e.g., ones described herein including but not limited to a BA.2 or a BA.4/5 Omicron variant). In some embodiments, RNA can be modified to encode one or more mutations characteristic of a SARS-CoV-2 variant by making as few nucleotide changes as possible. In some embodiments, RNA can be modified to encode one or more mutations that are characteristic of a SARS-CoV-2 variant by introducing mutations that result in high codon-optimization and/or increased G/C content.

[0577] In some embodiments, one or more mutations characteristic of a SARS-CoV-2 variant are introduced onto a full-length S protein (e.g., an S protein comprising SEQ ID NO: 1). In some embodiments one or more mutations characteristic of a SARS-CoV-2 variant are introduced onto a full-length S protein having one or more proline mutations that increase stability of a prefusion confirmation. For example, in some embodiments, proline substitutions are made at positions corresponding to positions 986 and 987 of SEQ ID NO: 1. In some embodiments, at least 4 proline substitutions are made. In some embodiments, at least four of such proline mutations include mutations at positions corresponding to residues 817, 892, 899, and 942 of SEQ ID NO: 1, e.g., as described in WO 2021243122 A2, the entire contents of which are incorporated herein by reference in its entirety. In some embodiments, such a SARS-CoV-2 S protein comprising proline substitutions at positions corresponding to residues 817, 892, 899, and 942 of SEQ ID NO: 1, may further comprise proline substitutions at positions corresponding to

residues 986 and 987 of SEQ ID NO: 1. In some embodiments, one or more mutations characteristic of a SARS-CoV-2 variant are introduced onto an immunogenic fragment of an S protein (e.g., the RBD of SEQ ID NO: 1).

Embodiments of administered RNAs

[0578] In some embodiments, the present disclosure provides an RNA (e.g., mRNA) comprising an open reading frame encoding a polypeptide that comprises at least a portion of a SARS-CoV-2 S protein. The RNA is suitable for intracellular expression of the polypeptide. In some embodiments, such an encoded polypeptide comprises a sequence corresponding to the complete S protein. In some embodiments, such an encoded polypeptide does not comprise a sequence corresponding to the complete S protein. In some embodiments, the encoded polypeptide comprises a sequence that corresponds to the receptor binding domain (RBD). In some embodiments, the encoded polypeptide comprises a sequence that corresponds to the RBD, and further comprises a trimerization domain (e.g., a trimerization domain as disclosed herein, such as a fibritin domain). In some embodiments an RBD comprises a signaling domain (e.g., a signaling domain as disclosed herein). In some embodiments an RBD comprises a transmembrane domain (e.g., a transmembrane domain as disclosed herein). In some embodiments, an RBD comprises a signaling domain and a trimerization domain. In some embodiments, an RBD comprises a signaling domain, a trimerization domain, and transmembrane domain.

[0579] In some embodiments, the encoded polypeptide comprises a sequence that corresponds to two receptor binding domains. In some embodiments, the encoded polypeptide comprises a sequence that corresponds to two receptor binding domains in tandem in an amino acid chain, e.g., as disclosed in Dai, Lianpan, et al. "A universal design of betacoronavirus vaccines against COVID-19, MERS, and SARS," Cell 182.3 (2020): 722-733, the contents of which are incorporated by reference herein in their entirety.

[0580] In some embodiments, a SARS-CoV-2 S protein, or an immunogenic fragment thereof comprises one or more mutations to alter or remove a glycosylation site, e.g., as described in WO2022221835A2, US20220323574A1, or WO2022195351A1.

[0581] In some embodiments, compositions or medical preparations described herein comprise RNA encoding an amino acid sequence comprising SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof. Likewise, methods described herein comprise administration of such RNA.

[0582] The active platform for use herein is based on an antigen-coding RNA vaccine to induce robust neutralising antibodies and accompanying/concomitant T cell response to achieve protective immunization with preferably minimal vaccine doses. The RNA administered is preferably *in-vitro* transcribed RNA.

[0583] Three different RNA platforms are particularly preferred, namely non-modified uridine containing mRNA (uRNA), nucleoside modified mRNA (modRNA) and self-amplifying RNA (saRNA). In one particularly preferred embodiment, the RNA is in vitro transcribed RNA. In some embodiments, uRNA is mRNA. In some embodiments, modRNA is mRNA.

[0584] In the following, embodiments of these three different RNA platforms are described, wherein certain terms used when describing elements thereof have the following meanings:

[0585] **S1S2 protein/S1S2 RBD:** Sequences encoding the respective antigen of SARS-CoV-2.

[0586] **nsP1, nsP2, nsP3, and nsP4:** Wildtype sequences encoding the Venezuelan equine encephalitis virus (VEEV) RNA-dependent RNA polymerase replicase and a subgenomic promotor plus conserved sequence elements supporting replication and translation.

[0587] **virUTR:** Viral untranslated region encoding parts of the subgenomic promotor as well as replication and translation supporting sequence elements.

[0588] **hAg-Kozak:** 5'-UTR sequence of the human alpha-globin mRNA with an optimized 'Kozak sequence' to increase translational efficiency.

[0589] **Sec:** Sec corresponds to a secretory signal peptide (sec), which guides translocation of the nascent polypeptide chain into the endoplasmatic reticulum. In some embodiments, such a secretory signal peptide includes the intrinsic S1S2 secretory signal peptide. In some embodiments, such a secretory signal peptide is a secretory signal peptide from a non-S1S2 protein. For example, an immunoglobulin secretory signal peptide (aa 1-22), an HSV-1 gD signal peptide (MGGAAARLGAVILFVVIVGLHGVRSKY), an HSV-2 gD signal peptide (MGRLTSGVGTAALLVVAVGLRVVCA); a human SPARC signal peptide, a human insulin isoform 1 signal peptide, a human albumin signal peptide, or any other signal peptide described herein.

[0590] **Glycine-serine linker (GS):** Sequences coding for short linker peptides predominantly consisting of the amino acids glycine (G) and serine (S), as commonly used for fusion proteins.

[0591] **Fibritin:** Partial sequence of T4 fibritin (foldon), used as artificial trimerization domain.

[0592] **TM:** TM sequence corresponds to the transmembrane part of a protein. A transmembrane domain can be N-terminal, C-terminal, or internal to an encoded polypeptide. A coding sequence of a transmembrane element is typically placed in frame (i.e., in the same reading frame), 5', 3', or internal to coding sequences of sequences (e.g., sequences encoding polypeptide(s)) with which it is to be linked. In some embodiments, a transmembrane domain comprises or is a transmembrane domain of Hemagglutinin (HA) of Influenza virus, Env of HIV-1, equine infectious anaemia virus (EIAV), murine leukaemia virus (MLV), mouse mammary tumor virus, G protein of vesicular stomatitis virus (VSV), Rabies virus, or a seven transmembrane domain receptor. In some embodiments, the transmembrane part of a protein is from the S1S2 protein.

[0593] **FI element:** The 3'-UTR is a combination of two sequence elements derived from the "amino terminal enhancer of split" (AES) mRNA (called F) and the mitochondrial encoded 12S ribosomal RNA (called I). These were identified by an *ex vivo* selection process for sequences that confer RNA stability and augment total protein expression.

[0594] **A30L70:** A poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence and another 70 adenosine residues designed to enhance RNA stability and translational efficiency in dendritic cells.

[0595] In some embodiments, vaccine RNA described herein may comprise, from 5' to 3', one of the following structures:

Cap-5'-UTR-Vaccine Antigen-Encoding Sequence-3'-UTR-Poly(A), or

Cap- hAg-Kozak-Vaccine Antigen-Encoding Sequence-FI-A30L70.

[0596] In some embodiments, a vaccine antigen described herein may comprise a full-length S protein or an immunogenic fragment thereof (e.g., RBD). In some embodiments where a vaccine antigen comprises a full-length S protein, its secretory signal peptide and/or transmembrane domain may be replaced by a heterologous secretory signal peptide (e.g., as described herein) and/or a heterologous transmembrane domain (e.g., as described herein).

[0597] In some embodiments, a vaccine antigen described herein may comprise, from N-terminus to C-terminus, one of the following structures:

Signal Sequence-RBD-Trimerization Domain, or

Signal Sequence-RBD-Trimerization Domain-Transmembrane Domain.

[0598] RBD and Trimerization Domain may be separated by a linker, in particular a GS linker such as a linker having the amino acid sequence GSPGSGSGS. Trimerization Domain and Transmembrane Domain may be separated by a linker, in particular a GS linker such as a linker having the amino acid sequence GSGSGS.

[0599] Signal Sequence may be a signal sequence as described herein. RBD may be a RBD domain as described herein. Trimerization Domain may be a trimerization domain as described herein. Transmembrane Domain may be a transmembrane domain as described herein.

[0600] In one embodiment, a signal sequence comprises the amino acid sequence of amino acids 1 to 16 or 1 to 19 of SEQ ID NO: 1 or the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to this amino acid sequence,

RBD comprises the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to this amino acid sequence,

Trimerization Domain comprises the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to this amino acid sequence; and

Transmembrane Domain comprises the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to this amino acid sequence.

[0601] In one embodiment,

Signal sequence comprises the amino acid sequence of amino acids 1 to 16 or 1 to 19 of SEQ ID NO: 1 or the amino acid sequence of amino acids 1 to 22 of SEQ ID NO: 31,

RBD comprises the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1,

Trimerization Domain comprises the amino acid sequence of amino acids 3 to 29 of SEQ ID NO: 10 or the amino acid sequence of SEQ ID NO: 10; and

Transmembrane Domain comprises the amino acid sequence of amino acids 1207 to 1254 of SEQ ID NO: 1.

[0602] In some embodiments, an RNA polynucleotide comprising a sequence encoding a vaccine antigen (e.g., a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof) or comprising an open reading frame encoding a vaccine antigen (e.g., a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof) such as the nucleotide sequence of SEQ ID NO: 50 or the nucleotide sequence of SEQ ID NO: 53, a variant or fragment thereof, further comprises a 5′ cap, e.g., a 5′ cap comprising a Cap1 structure, a 5′ UTR sequence, e.g., a 5′ UTR sequence comprising the nucleotide sequence of SEQ ID NO: 12, a 3′ UTR sequence, e.g., a 3′ UTR sequence comprising the nucleotide sequence of SEQ ID NO: 13, and polyA sequence, e.g., a polyA sequence comprising the nucleotide sequence of SEQ ID NO: 14. In some embodiments, RNA is formulated in a composition comprising ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), cholesterol, distearoylphosphatidylcholine, and (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

[0603] RNA described herein or RNA encoding the vaccine antigen described herein may be non-modified uridine containing RNA (uRNA), nucleoside modified RNA (modRNA) or self-amplifying RNA (saRNA). In some embodiments, uRNA is mRNA. In some embodiments, modRNA is mRNA. In one embodiment, RNA described herein or RNA encoding the vaccine antigen described herein is nucleoside modified RNA (modRNA).

Variant Specific Vaccines

[0604] In some embodiments, RNA disclosed herein encodes an S protein comprising one or more mutations that are characteristic of a SARS-CoV-2 variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Alpha variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a Beta variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a Delta variant. In some

embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron variant (e.g., an S protein comprising one or more mutations characteristic of a BA.1, BA.2, BA.4/5 Omicron variant). In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron XBB variant (e.g., an S protein comprising one or more mutations characteristic of an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 variant). In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.1 Omicron variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2 Omicron variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.12.1 Omicron variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.3 Omicron variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BA.4 or BA.5 Omicron variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant. In some embodiments, RNA encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant.

Non-modified uridine RNA (uRNA)

[0605] In some embodiments, a non-modified uridine RNA is a messenger RNA. In some embodiments, the active principle of non-modified messenger RNA drug substance is a single-stranded mRNA that is translated upon entering a cell. In addition to the sequence encoding the coronavirus vaccine antigen (i.e. open reading frame), each uRNA preferably contains common structural elements optimized for maximal efficacy of the RNA with respect to stability and translational efficiency (including, e.g., 5′-cap, 5′-UTR, 3′-UTR, poly(A)-tail as described herein). The preferred 5′ cap structure is beta-S-ARCA(D1) ($m_2^{7,2'\text{-}O}$GppSpG). The preferred 5′-UTR and 3′-UTR comprise the nucleotide sequence of SEQ ID NO: 12 and the nucleotide sequence of SEQ ID NO: 13, respectively. The preferred poly(A)-tail comprises the sequence of SEQ ID NO: 14.

Different embodiments of this platform are as follows:

[0606] **RBL063.1 (SEQ ID NO: 15; SEQ ID NO: 7)**

Structure beta-S-ARCA(D1)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0607] **RBL063.2 (SEQ ID NO: 16; SEQ ID NO: 7)**

Structure beta-S-ARCA(D1)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0608] **BNT162a1; RBL063.3 (SEQ ID NO: 17; SEQ ID NO: 5)**

Structure beta-S-ARCA(D1)-hAg-Kozak-RBD-GS-Fibritin-FI-A30L70

Encoded antigen Viral spike protein (S protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein)

Nucleoside modified RNA (modRNA)

[0609] In some embodiments, nucleoside modified RNA is mRNA. In some embodiments, the active principle of nucleoside modified RNA (modRNA) drug substance is a single-stranded RNA (e.g., mRNA) that can be translated upon entering a cell. In addition to a sequence encoding a coronavirus vaccine antigen (i.e., open reading frame), each modRNA contains common structural elements optimized for maximal efficacy of the RNA as the uRNA (5′-cap, 5′-UTR, 3′-UTR, poly(A)-tail). Compared to uRNA, modRNA comprises at least one nucleotide modification (e.g., as described herein). In some embodiments, modRNA contains 1-methyl-pseudouridine instead of uridine. The preferred 5′ cap structure is $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG. The preferred 5′-UTR and 3′-UTR comprise the nucleotide sequence of SEQ ID NO: 12 and the nucleotide sequence of SEQ ID NO: 13, respectively. The preferred poly(A)-tail comprises the sequence of SEQ ID NO: 14. An additional purification step is applied for modRNA to reduce dsRNA contaminants generated during the in vitro transcription reaction.

[0610] Different embodiment of this platform are as follows:

[0611] **BNT162b2; RBP020.1 (SEQ ID NO: 19; SEQ ID NO: 7)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0612] **BNT162b2; RBP020.2 (SEQ ID NO: 20; SEQ ID NO: 7)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0613] **BNT162b1; RBP020.3 (SEQ ID NO: 21; SEQ ID NO: 5)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-RBD-GS-Fibritin-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein fused to fibritin)

[0614] Figure 2 schematizes the general structure of antigen-encoding RNAs.

[0615] **BNT162b3c (SEQ ID NO: 29; SEQ ID NO: 30)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG-hAg-Kozak-RBD-GS-Fibritin-GS-TM-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein fused to Fibritin fused to Transmembrane Domain (TM) of S1S2 protein); intrinsic S1S2 protein secretory signal peptide (aa 1-19) at the N-terminus of the antigen sequence

[0616] **BNT162b3d (SEQ ID NO: 31; SEQ ID NO: 32)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG-hAg-Kozak-RBD-GS-Fibritin-GS-TM-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein fused to Fibritin fused to Transmembrane Domain (TM) of S1S2 protein); immunoglobulin secretory signal peptide (aa 1-22) at the N-terminus of the antigen sequence.

[0617] **BNT162b2 – Beta variant; RBP020.11 (SEQ ID NO: 57; SEQ ID NO: 55)**

Structure $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant), comprising mutations characteristic of the Beta variant of SARS-CoV-2

[0618] **BNT162b2 – Alpha variant; RBP020.14 (SEQ ID NO: 60; SEQ ID NO: 58)**

Structure $m_2^{7,3'\text{-O}}$Gppp($m_1^{2'\text{-O}}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant), comprising mutations characteristic of the Alpha variant of SARS-CoV-2

BNT162b2 – Delta variant; RBP020.16 (SEQ ID NO: 63a; SEQ ID NO: 61)

Structure $m_2^{7,3'\text{-O}}$Gppp($m_1^{2'\text{-O}}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant), comprising mutations characteristic of the Delta variant of SARS-CoV-2

Table 7: Sequences of RBP020.2 (Wuhan Specific Vaccine)

SEQ ID NO.	Brief Description	Sequence
7	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from a Wuhan strain	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNG TKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYHKNNK SWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEP LVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKC TLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTF KCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLHAPATVC GPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITP GTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIGAGICASY QTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECS NLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKV TLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQ MAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISS VLNDILSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLM SFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSG NCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL QELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
9	RNA sequence encoding a SARS-CoV-2 S protein from an Wuhan strain	Auguucguguuccuggugcugcuguccuggugucccagcuguguguggaaccugaccaccagaacacagcugcccuccagccuaca ccaacagcuuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuuccugcc uuucuucagcaacgugaccugguuccacgccauccacgugucccggcaccaauggcaccagagaguucgacaaccccgugcugcccu ucaacgacgggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagac ccagagccugcugaucgugaacaacgccaccaacguggucaucaaaguguucgagguuccaguucugcaacgaccccuucuggggc gucuacuaccacaagaacacaagagcuggauggaaagcgaguuccggguguacagcagcgccaacaacugcaccuucgaguacg ugucccagccuuuccugauggaccuggaaggcaagcagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacg gcuacuucaagaucuacagcaagcacacccccuaucaaccucgugcgggaucugccucagggcuucucugcucuggaaccccuggu ggaucugcccaucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacaccuggcgauagcagca gcggauggacagcuggugccgccgcuuacuauguggggcuaccugcagccuagaaccuuccugcugaaguacaacgagaacggcac caucaccgacgccguggauugugcucuggauccucugagcgagacaaagugcacccugaaguccuucaccguggaaaagggcauc uaccagaccagcaacuucgggugcagcccaccgaauccaucgugcggucccccaauaucaccaacugugcccccuucggcgaggu guucaaugccacagauucgccucuguguacgccuggaaccggaagcggaucagcaauugcguggccgacuacuccgugcuguac aacuccgccagcuucagcaccuucaagugcuacggcgugucccccuaccaagcugaacgaccugugcuucacaaacguguacgcca

		cagcuucgugauccgggggagaugaagugcggcagauugccccuggacagacaggcaagaucgccgacuacaacuacaagcugccc
		gacgacuucaccggcugugugauugccuggaacagcaacaaccuggacuccaaagucggcggcaacuacaauuaccuguaccggc
		uguuccggaaguccaaucugaagccccuucgagcgggacaucuccaccgagaucuaucaggccggcagcacccccuuguaacggcgu
		ggaaggcuucaacugcuacuucccacugcaguccuacggcuuucagcccacaaauggcgugggcuaucagcccuacagaguggug
		gugcugagcuucgaacugcugcaugcccccugccacaguguggcggcccuaagaaaagcaccaaucucgugaagaacaaaugcguga
		acuucaacuucaacggccugaccggcacggcgugcugacagagagcaacaagaaguuccugccauuccagcaguuuggccggga
		uaucgccgauaccacagacgccguuagaggauccccagacacuggaaauccuggacacucacccccuugcagcuucggcggaguucu
		gugaucacccccuggcaccaacaccagcaaucagguggcagugcuguaccaggacgugaacuguaccgaagugucccguggccauuc
		acgccgaucagcugacaccuacauggcggguguacuccaccggcagcaauguguuucagaccagagccggcugucugaucggagc
		cgagcacgugaacaauagcuacgagugcgacaucccccaucggcgcuggaaucugcgccagcuaccagacacagacaaacagcccuc
		ggagagccagaaagcguggccagccagaggcaucauugccuacacaaugucucugggcgccgagaacagcguggccuacuccaacaa
		cucuaucgcuaucccccaccaacuucaccaucagcgugaccacagagauccugccuguguccaugaccaagaccagcguggacugca
		ccauguacaucugcggcgauuccaccgagugcuccaaccugcugcugcaguacggcagcuucugcacccagcugaauagagcccu
		gacagggaucgccguggaacaggacaagaacacccaagagguguucgcccaagugaagcagaucuacaagaccccuccuaucaag
		gacuucggcggcuucaauuucagccagauucugcccgauccuagcaagcccagcaagcggagcuucaucgaggaccugcuguuca
		acaaagugacacuggccgacgccggcuucaucaagcaguauggcgauugucugggcgacauugccgccagggaucugauuugcg
		cccagaaguuuaacggacugacagugcugccuccucugcugaccgaugagaugaucgcccaguacacaucugcccugcuggccgg
		cacaaucacaagcggcuggacauuuggagcaggcgccgcucugcagauccccuuugcuaugcagauggccuaccgguucaacggc
		aucggagugacccagaaugugcugcuacgagaaccagaagcugaucgccaaccaguucaacagcgccaucggcaagauccaggaca
		gccugagcagcacagcaagcgcccugggaaagcugcaggacguggucaaccagaaugcccaggcacugaacaccccuggucaagca
		gcuguccucaacuucggcgccaucagcucugugcugaacgauauccugagcagacuggaccccuccugaggccgaggugcagauc
		gacagacugaucacaggcagacugcagagccucccagacauacgugacccagcagcugaucagagccgccgagauuagagccucug
		ccaaucuggccgccaccaagaugucugagugugcuggccagaggagaguggacuuuugcggcaagggcuaccaccuga
		ugagcuucccucagucugccccucacggcguggguguuucugcacgugacauaugugcccgcucagagaagaauuucaccaccgc
		uccagccaucugccacgacggcaaagcccacuuuccuagagaaggcguguucgugucccaacggcacccauuggguucgugacacag
		cggaacuucuacgagcccagaucaucaccaccgacaacaccuucguucuggcaacugcgacgucgugaucggcauuguugaaca
		auaccguguacgacccucugcagccgagcuggacacuucaaagaggaacuggacaaguacuuuaagaaccacacaagccccga

		cguggaccuggcgauaucagcggaaucaaugccagcgucgugaacauccagaaagagaucgaccggcugaacgaggugccaa gaaucugaacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggcccugguacaucuggcuggg cuuuaucgccggacugauugccaucgugaugucacaaucaugcugcuguugcaugaccagcugcuguagccugaaggcug uuguagcugugcagcugcugcaagguucgacgaggacgauucugagcccgugcugaaggcgugaaacugcacuacaca
20	Full length RNA construct sequence of RBP020.2	agaauaaaacuagauauucuucuggucccccagacucagagagaacccgccaccauguucguguucccuggugcugccucugg uguccagccaguguugugaaccugaccaccagaacacagcugccuccagccuacaccaacagcuuuaccagaggcguguacuacccc gacaagguguucagaauccagcgugcugcacucuacccaggaccuguuccugccuuucuucagcaacgugaccuggguuccacgcca uccacguguccggcaccaauggcaccagagauucgacaccccgugcugcccuucaacgacgggguguacuuugccagcaccga gaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcugaucgugaacaacgccacc aacgugucaucaaaguguugcgaguuccaguucugcaacgacgcccuucccuggcgcucuacuaccacaagaacaacaagagcugga uggaaagcgaguucccggguguacagcagcgccaacaacugcaccuucgaguacgugucccagccuuuccugauggaccuggaag gcaagcagggcaacuucaagaaccugcgcgaguucgugguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccc uaucaaccucgugcgggaucugccucagggcuucucugcucuggaacccccuggugggaucugcccaucggcaucaacaucacccgg uuucagacacugcuggcccugcacagaagcuaccugacaccuggcgauagcagcagcggauggacagcuggugccgccgcuuacu auggggcuaccugcagccuagaacuuccugcugaaguacaacgagaacggcaccaucaccgacgccguggauuugugcucugga uccucugagcgagacaaagugcacccugaaguccuucaccguggaaaagggcaucuaccagaccagcaacuucccgggugcagccc accgaauccaucgugcgguucccaauaucaccaaucugugcccccuucggcgagguguucaaugccaccagauucgccucugugu acgccuggaaccggaagcggaucagcaauugcguggccgacuacuccgugcuguacaacucccgccagcuucagcaccuucaagug cuacggcguguccccuaccagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugauccgggggaggaugaagug cggcagauugccccuggacagacaggcaagaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccu ggaacagcaacaaccuggacuccaaagucgcggcgcaacuacaauuaccuguacggcuguuccggaaguccaaucugaagcccuu cgagcgggacaucuccaccgagaucuauucaggccggcagcacccccuuguaacggcguggaaggcuucaacugcuacuucccacug caguccuacggcuuucagcccacaaauggcguggguaucagcccuacagaguggugugcugagcuucgaacugcugcaugccc cugccacagugugcggcccuaagaaaagcaccaaucucgugaagaacaaaugcgugaacuucaacuucaacggccugaccggcac cggcgugcugacagagagcaacaagaaguuccugccauuccagcaguuuggccgggauaucgccgauaccacagacgccguuaga gaucccagacacuggaaauccuggacaucacccuugcagcuucgcggagugucugaucagcugccgaucagcaccuacauggcgg ucaggugcagugcuguaccaggacgugaacuguaccgaagugcccguggccauucacgccgaucagcugacaccuacauggcgg

		guguacuccaccggcagcaauguguuucagaccagagccggcugucugaucggagccgagcacgugaacaauagcuacgagugc
		gacauccccaucggcgcuggaaucugcgccagcuaccagacacagacaaacagcccucggagagccagaagcguggccagccagag
		caucauugccuacacaauguucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuacuccccaccaacuucacca
		ucagcgugaccacagagauccugccuguguccaugaccaagaccagcguggacugcaccauguacaucugcggcgauuccaccga
		gugcuccaaccugcugcugcaguacggcagcuucugcacccagcugaauagagcccugacagggaucgccguggaacaggacaag
		aacacccaagagguguucgcccaagugaagcagaucuacaagacccccuccuaucaaggacuucggcggcuucaauuucagccaga
		uucugcccgauccuagcaagcccagcaagcgggagcuucaucgaggaccugcuguucaacaaagugacacuggccgacgccggcuu
		caucaagcaguauggcgauugucugggcgacauugccgccagggaucugauuugcgcccagaaguuuaacggacugacagugcu
		gccucccucgugaccgaugagaugaucgcccaguacacaucugcccugcuggccggcacaaucacaagcggcuggacauuugga
		gcaggcgccgcucugcagauccccuuugcuaugcagauggccuaccgguucaacggcaucgagugacccagaaaugugcuguacg
		agaaccagaagcugaugaucgccaaccaguucaacagcgccaucggcaagauccaggacagccugagcacagcaagcgccccuggga
		aagcugcaggacguggucaaccagaaaugcccaggcacugaacacccuggucaagcagcuguccuccaacuucgggccgccaucagcuc
		ugugcugaacgauauccugagcagacuggacacccuccugaggccgaggugcagaucgacagaucugaucacaggcagacugcagag
		ccuccagacauacgugacccagcagcugaucagagccgccgagauuagagccucugccaaucuggccgccaccaagaugucugag
		ugugugcugggccagagcaagagagugggacuuuugcggcaagggcuaccaccugaugagcuucccucagucugccccucacggc
		guggguguucugcacgugacauaugugcccgcucaagagaagaauuucaccaccgcucccagccaucugccacgacggcaaagccc
		acuuuccuagagaaggcguguucgugucccaacggcacccauuggguucgugacacagcggaacuucuacgagccccagaucaucac
		caccgacaacaccuucgugucuggcaacugcgacgcugaucggcauugugaacaauaccgugucgacccucugcagcccgag
		cuggacagcuucaaagaggaacuggacaaguacuuuaagaacccacacaagccccgacguggaccuggggcgauaucagcggaauca
		augccagcgucgugaacauccagaaagagaucgaccggcugaacgagguggccaagaaucugaacgagccgaucgaccugc
		aagaacuggggaaguacgagcaguacaucaaguggccccugguacaucuggcuggguuuauucgccggacugauuugccaucguga
		uggucacaaucaugcuguguugcaugaccagcugcuguagcugccugaagggcuguuguagcuguggcagcugcugcaaguuc
		gacgaggacgauucugagcccgugcugaagggcgugaaacugcacuacacaugaugacucgagcugguacugcaugcacgcaau
		gcuagcugcccuuucccguccuggguaccccgagucucccccgaccuggguccccagguaugcucccaccuccaccugccccacuc
		accaccucugcuaguuccagacaccucccaagcacgcagcaaugcagcucaaaacgcuuagccuagccacacccccagggaaacag
		cagugauuaaccuuuagcaauaaacgaaaguuuaacuaagcuauacuaacccccagggguuggucaauuucgugccagccacaccc

		uggagcuagcaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaagcauaugacuaaaaaaaaaaaaaaaaaaa

Table 8: Sequences of RBP020.22 (Omicron BA.4/BA.5-specific RNA vaccine)

SEQ ID NO.	Brief Description	Sequence
69	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron BA.4/BA.5 variant (with PRO mutations at positions corresponding to positions K986P and V987P of SEQ ID NO: 7, i.e., at residues 981 and 982 of SEQ ID NO: 69)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAISGTNGTKRFD NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYYHKNNKSWME SEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLGRDLPQGFSALEPLVDLP IGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSF TVEKGIYQTSNFRVQPTESIVRFPNITNLCPFDEVFNATRFASVYAWNRKRISNCVADYSVLYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVGGNYNYRYRL FRKSNLKPFERDISTEIYQAGNKPCNGVAGVNCYFPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT**
70	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.4/BA.5 variant	AUGUUCGUGUUCCUGGUGCUGCUGCCUCUGGUGUCCAGCCAGUGUGUGAACCUGAUCACCAGAACACAG UCAUACACCAACAGCUUUACCAGAGGCGUGUACUACCCCGACAAGGUGUUCAGAUCCAGCGUGCUGCACU CUACCCAGGACCUGUUCCUGCCUUUCUUCAGCAACGUGACCUGGUUCCACGCCAUCUCCGGCACCAAUGG CACCAAGAGAUUCGACAACCCCGUGCUGCCCUUCAACGACGGGGUGUACUUUGCCAGCACCGAGAAGUCC AACAUCAUCAGAGGCUGGAUCUUCGGCACCACACUGGACAGCAAGACCCAGAGCCUGCUGAUCGUGAACA ACGCCACCAACGUGGUCAUCAAAGUGUGCGAGUUCCAGUUCUGCAACGACCCCUUCCUGGACGUCUACUA CCACAAGAACAACAAGAGCUGGAUGGAAAGCGAGUUCCGGGUGUACAGCAGCGCCAACAACUGCACCUUC GAGUACGUGUCCCAGCCUUUCCUGAUGGACCUGGAAGGCAAGCAGGGCAACUUCAAGAACCUGCGCGAGU

		UCGUGUUUAAGAACAUCGACGGCUACUUCAAGAUCUACAGCAAGCACACCCCUAUCAACCUCGGCCGGGA
		UCUGCCUCAGGGCUUCUCUGCUCUGGAACCCCUGGUGGAUCUGCCCAUCGGCAUCAACAUCACCCGGUUU
		CAGACACUGCUGGCCCUGCACAGAAGCUACCUGACACCUGGCGAUAGCAGCGGAUGGACAGCUGGUG
		CCGCCGCUUACUAUGUGGGCUACCUGCAGCCUAGAACCUUCCUGCUGAAGUACAACGAGAACGGCACCAU
		CACCGACGCCGUGGAUUGUGCUCUGGAUCCUCUGAGCGAGACAAAGUGCACCCUGAAGUCCUUCACCGUG
		GAAAAGGGCAUCUACCAGACCAGCAACUUCCGGGUGCAGCCCACCGAAUCCAUCGUGCGGUUCCCCAAUA
		UCACCAAUCUGUGCCCCUUCGACGAGGUGUUCAAUGCCACCAGAUUCGCCUCUGUGUACGCCUGGAACCG
		GAAGCGGAUCAGCAAUUGCGUGGCCGACUACUCCGUGCUGUACAACUUCGCCCCCUUCUUCGCAUUCAAG
		UGCUACGGCGUGUCCCCUACCAAGCUGAACGACCUGUGCUUCACAAACGUGUACGCCGACAGCUUCGUGA
		UCCGGGGAAACGAAGUGCGGCAGAUUGCCCCUGGACAGACAGGCAACAUCGCCGACUACAACUACAAGCU
		GCCCGACGACUUCACCGGCUGUGUGAUUGCCUGGAACAGCAACAAGCUGGACUCCAAAGUCGGCGGCAAC
		UACAAUUACAGGUACCGGCUGUUCCGGAAGUCCAAUCUGAAGCCCUUCGAGCGGGACAUCUCCACCGAGA
		UCUAUCAGGCCGGCAACAAGCCUUGUAACGGCGUGGCAGGCGUGAACUGCUACUUCCCACUGCAGUCCUA
		CGGCUUUAGGCCCACAUACGGCGUGGGCCACCAGCCCUACAGAGUGGUGGUGCUGAGCUUCGAACUGCU
		GCAUGCCCCUGCCACAGUGUGCGGCCCUAAGAAAAGCACCAAUCUCGUGAAGAACAAAUGGCGUGAACUUC
		AACUUCAACGGCCUGACCGGCACCGGCGUGCUGACAGAGAGCAACAAGAAGUUCCUGCCCAUUCCAGCAGU
		UUGGCCGGGAUAUCGCCGAUACCACAGACGCCGUUAGAGAUCCCCAGACACUGGAAAUCCUGGACAUCAC
		CCCUUGCAGCUUCGGCGGAGUGUCUGUGAUCACCCCUGGCACCAACACCAGCAAUCAGGUGGCAGUGCUG
		UACCAGGGCGUGAACUGUACCGAAGUGCCCGUGGCCAUUCACGCCGAUCAGCUGACACCUACAUGGCGGG
		UGUACUCCACCGGCAGCAAUGUGUUUCAGACCAGAGCCGGCUGUCUGAUCGGAGCCGAGUACGUGAACAA
		UAGCUACGAGUGCGACAUCCCCAUCGGCGCUGGAAUCUGCGCCAGCUACCAGACACAGACAAAGAGCCACC
		GGAGAGCCAGAAGCGUGGCCAGCCAGAGCAUCAUUGCCUACACAAUGUCUCUGGGCGCCGAGAACAGCGU
		GGCCUACUCCAACAACUCUAUCGCUAUCCCCACCAACUUCACCAUCAGCGUGACCACAGAGAUCCUGCCUG
		UGUCCAUGACCAAGACCAGCGUGGACUGCACCAUGUACAUCUGCGGCGAUUCCACCGAGUGCUCCAACCU
		GCUGCUGCAGUACGGCAGCUUCUGCACCCAGCUGAAAAGAGCCCUGACAGGGAUCGCCGUGGAACAGGAC
		AAGAACACCCAAGAGGUGUUCGCCCAAGUGAAGCAGAUCUACAAGACCCCUCCUAUCAAGUACUUCGGCG
		GCUUCAAUUUCAGCCAGAUUCUGCCCGAUCCUAGCAAGCCCAGCAAGCGGAGCUUCAUCGAGGACCUGCU

		GUUCAACAAAGUGACACUGGCCGACGCCGGCUUCAUCAAGCAGUAUGGCGAUUGUCUGGGCGACAUUGCC
		GCCAGGGAUCUGAUUUGCGCCCAGAAGUUUAACGGACUGACAGUGCUGCCUCCUCUGCUGACCGAUGAGA
		UGAUCGCCCAGUACACAUCUGCCCUGCUGGCCGGCACAAUCACAAGCGGCUGGACAUUUGGAGCAGGCGC
		CGCUCUGCAGAUCCCCUUUGCUAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGAGUGACCCAGAAUGUG
		CUGUACGAGAACCAGAAGCUGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGACAGCCUGA
		GCAGCACAGCAAGCGCCCUGGGAAAGCUGCAGGACGUGGUCAACCACAAUGCCCAGGCACUGAACACCCU
		GGUCAAGCAGCUGUCCUCCAAGUUCGGCGCCAUCAGCUCUGUGCUGAACGAUAUCCUGAGCAGACUGGAC
		CCUCCUGAGGCCGAGGUGCAGAUCGACAGACUGAUCACAGGCAGACUGCAGAGCCUCCAGACAUACGUGA
		CCCAGCAGCUGAUCAGAGCCGCCGAGAUUAGAGCCUCUGCCAAUCUGGCCGCCACCAAGAUGUCUGAGUG
		UGUGCUGGGCCAGAGCAAGAGAGUGGACUUUUUGCGGCAAGGGCUACCACCUGAUGAGCUUCCCCUCAGUC
		UGCCCCUCACGGCGUGGUGUUUCUGCACGUGACAUAUGUGCCCGCUCAAGAGAAGAAUUUCACCACCGCU
		CCAGCCAUCUGCCACGACGGCAAAGCCCACUUUCCUAGAGAAGGCGUGUUCGUGUCCAACGGCACCCAUU
		GGUUCGUGACACAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCGACAACACCUUCGUGUCUGGCAA
		CUGCGACGUCGUGAUCGGCAUUGUGAACAAUACCGUGUACGACCCUCUGCAGCCCGAGCUGGACAGCUUC
		AAAGAGGAACUGGACAAGUACUUUAAGAACCACACAAGCCCCGACGUGGACCUGGGCGAUAUCAGCGGAA
		UCAAUGCCAGCGUCGUGAACAUCCAGAAAGAGAUCGACCGGCUGAACGAGGUGGCCAAGAAUCUGAACGA
		GAGCCUGAUCGACCUGCAAGAACUGGGGAAGUACGAGCAGUACAUCAAGUGGCCCUGGUACAUCUGGCUG
		GGCUUUAUCGCCGGACUGAUUGCCAUCGUGAUGGUCACAAUCAUGCUGUGUUGCAUGACCAGCUGCUGU
		AGCUGCCUGAAGGGCUGUUGUAGCUGUGGCAGCUGCUGCAAGUUCGACGAGGACGAUUCUGAGCCCGUG
		CUGAAGGGCGUGAAACUGCACUACACAUGAUGA
71	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.4/BA.5 variant	ATGTTCGTGTTCCTGGTGCTGCTGCCTCTGGTGTCCAGCCAGTGTGTGAACCTGATCACCAGAACACAGTCA
		TACACCAACAGCTTTACCAGAGGCGTGTACTACCCCGACAAGGTGTTCAGATCCAGCGTGCTGCACTCTACC
		CAGGACCTGTTCCTGCCTTTCTTCAGCAACGTGACCTGGTTCCACGCCATCTCCGGCACCAATGGCACCAAG
		AGATTCGACAACCCCGTGCTGCCCTTCAACGACGGGGTGTACTTTGCCAGCACCGAGAAGTCCAACATCATC
		AGAGGCTGGATCTTCGGCACCACACTGGACAGCAAGACCCAGAGCCTGCTGATCGTGAACAACGCCACCAAC
		GTGGTCATCAAAGTGTGCGAGTTCCAGTTCTGCAACGACCCCTTCCTGGACGTCTACTACCACAAGAACAAC
		AAGAGCTGGATGGAAAGCGAGTTCCGGGTGTACAGCAGCGCCAACAACTGCACCTTCGAGTACGTGTCCCA

GCCTTTCCTGATGGACCTGGAAGGCAAGCAGGGCAACTTCAAGAACCTGCGCGAGTTCGTGTTTAAGAACAT	
CGACGGCTACTTCAAGATCTACAGCAAGCACACCCCTATCAACCTCGGCCGGGATCTGCCTCAGGGCTTCTC	
TGCTCTGGAACCCCTGGTGGATCTGCCCATCGGCATCAACATCACCCGGTTTCAGACACTGCTGGCCCTGCA	
CAGAAGCTACCTGACACCTGGCGATAGCAGCAGCGGATGGACAGCTGGTGCCGCCGCTTACTATGTGGGCT	
ACCTGCAGCCTAGAACCTTCCTGCTGAAGTACAACGAGAACGGCACCATCACCGACGCCGTGGATTGTGCTC	
TGGATCCTCTGAGCGAGACAAAGTGCACCCTGAAGTCCTTCACCGTGGAAAAGGGCATCTACCAGACCAGCA	
ACTTCCGGGTGCAGCCCACCGAATCCATCGTGCGGTTCCCCAATATCACCAATCTGTGCCCCTTCGACGAGG	
TGTTCAATGCCACCAGATTCGCCTCTGTGTACGCCTGGAACCGGAAGCGGATCAGCAATTGCGTGGCCGACT	
ACTCCGTGCTGTACAACTTCGCCCCCTTCTTCGCATTCAAGTGCTACGGCGTGTCCCCTACCAAGCTGAACG	
ACCTGTGCTTCACAAACGTGTACGCCGACAGCTTCGTGATCCGGGGAAACGAAGTGCGGCAGATTGCCCCT	
GGACAGACAGGCAACATCGCCGACTACAACTACAAGCTGCCCGACGACTTCACCGGCTGTGTGATTGCCTGG	
AACAGCAACAAGCTGGACTCCAAAGTCGGCGGCAACTACAATTACAGGTACCGGCTGTTCCGGAAGTCCAAT	
CTGAAGCCCTTCGAGCGGGACATCTCCACCGAGATCTATCAGGCCGGCAACAAGCCTTGTAACGGCGTGGC	
AGGCGTGAACTGCTACTTCCCACTGCAGTCCTACGGCTTTAGGCCCACATACGGCGTGGGCCACCAGCCCTA	
CAGAGTGGTGGTGCTGAGCTTCGAACTGCTGCATGCCCCTGCCACAGTGTGCGGCCCTAAGAAAAGCACCA	
ATCTCGTGAAGAACAAATGCGTGAACTTCAACTTCAACGGCCTGACCGGCACCGGCGTGCTGACAGAGAGCA	
ACAAGAAGTTCCTGCCATTCCAGCAGTTTGGCCGGGATATCGCCGATACCACAGACGCCGTTAGAGATCCCC	
AGACACTGGAAATCCTGGACATCACCCCTTGCAGCTTCGGCGGAGTGTCTGTGATCACCCCTGGCACCAACA	
CCAGCAATCAGGTGGCAGTGCTGTACCAGGGCGTGAACTGTACCGAAGTGCCCGTGGCCATTCACGCCGAT	
CAGCTGACACCTACATGGCGGGTGTACTCCACCGGCAGCAATGTGTTTCAGACCAGAGCCGGCTGTCTGAT	
CGGAGCCGAGTACGTGAACAATAGCTACGAGTGCGACATCCCCATCGGCGCTGGAATCTGCGCCAGCTACC	
AGACACAGACAAAGAGCCACCGGAGAGCCAGAAGCGTGGCCAGCCAGAGCATCATTGCCTACACAATGTCTC	
TGGGCGCCGAGAACAGCGTGGCCTACTCCAACAACTCTATCGCTATCCCCACCAACTTCACCATCAGCGTGA	
CCACAGAGATCCTGCCTGTGTCCATGACCAAGACCAGCGTGGACTGCACCATGTACATCTGCGGCGATTCCA	
CCGAGTGCTCCAACCTGCTGCAGTACGGCAGCTTCTGCACCCAGCTGAAAAGAGCCCTGACAGGGATC	
GCCGTGGAACAGGACAAGAACACCCAAGAGGTGTTCGCCCAAGTGAAGCAGATCTACAAGACCCCTCCTATC	
AAGTACTTCGGCGGCTTCAATTTCAGCCAGATTCTGCCCGATCCTAGCAAGCCCAGCAAGCGGAGCTTCATC	

		GAGGACCTGCTGTTCAACAAAGTGACACTGGCCGACGCCGGCTTCATCAAGCAGTATGGCGATTGTCTGGG
		CGACATTGCCGCCCAGGGATCTGATTTGCGCCCCAGAAGTTTAACGGACTGACAGTGCTGCCTCCTCTGCTGAC
		CGATGAGATGATCGCCCAGTACACATCTGCCCTGCTGGCCGGCACAATCACAAGCGGCTGGACATTTGGAG
		CAGGCGCCGCTCTGCAGATCCCCTTTGCTATGCAGATGGCCTACCGGTTCAACGGCATCGGAGTGACCCAG
		AATGTGCTGTACGAGAACCAGAAGCTGATCGCCAACCAGTTCAACAGCGCCATCGGCAAGATCCAGGACAGC
		CTGAGCAGCACAGCAAGCGCCCTGGGAAAGCTGCAGGACGTGGTCAACCACAATGCCCAGGCACTGAACAC
		CCTGGTCAAGCAGCTGTCCTCCAAGTTCGGCGCCATCAGCTCTGTGCTGAACGATATCCTGAGCAGACTGGA
		CCCTCCTGAGGCCGAGGTGCAGATCGACAGACTGATCACAGGCAGACTGCAGAGCCTCCAGACATACGTGA
		CCCAGCAGCTGATCAGAGCCGCCGAGATTAGAGCCTCTGCCAATCTGGCCGCCACCAAGATGTCTGAGTGT
		GTGCTGGGCCAGAGCAAGAGAGTGGACTTTTGCGGCAAGGGCTACCACCTGATGAGCTTCCCTCAGTCTGC
		CCCTCACGGCGTGGTGTTTCTGCACGTGACATATGTGCCCGCTCAAGAGAAGAATTTCACCACCGCTCCAGC
		CATCTGCCACGACGGCAAAGCCCACTTTCCTAGAGAAGGCGTGTTCGTGTCCAACGGCACCCATTGGTTCGT
		GACACAGCGGAACTTCTACGAGCCCCAGATCATCACCACCGACAACACCTTCGTGTCTGGCAACTGCGACGT
		CGTGATCGGCATTGTGAACAATACCGTGTACGACCCTCTGCAGCCCGAGCTGGACAGCTTCAAAGAGGAACT
		GGACAAGTACTTTAAGAACCACACAAGCCCCGACGTGGACCTGGGCGATATCAGCGGAATCAATGCCAGCG
		TCGTGAACATCCAGAAAGAGATCGACCGGCTGAACGAGGTGGCCAAGAATCTGAACGAGAGCCTGATCGAC
		CTGCAAGAACTGGGGAAGTACGAGCAGTACATCAAGTGGCCCTGGTACATCTGGCTGGGCTTTATCGCCGG
		ACTGATTGCCATCGTGATGGTCACAATCATGCTGTGTTGCATGACCAGCTGCTGTAGCTGCCTGAAGGGCT
		GTTGTAGCTGTGGCAGCTGCTGCAAGTTCGACGAGGACGATTCTGAGCCCGTGCTGAAGGGCGTGAAACTG
		CACTACACATGATGA
72	Full length RNA construct sequence of RBP020.22	AGAAUAAACUAGUAUUCUUCUGGUCCCCACAGACUCAGAGAGAACCCGCCACCAUGUUCGUGUUCCUGGU
		GCUGCUGCCUCUGGUGUCCAGCCAGUGUGUGAACCUGAUCACCAGAACACAGUCAUACACCAACAGCUUU
		ACCAGAGGCGUGUACUACCCCGACAAGGUGUUCAGAUCCAGCGUGCUGCACUCUACCCAGGACCUGUUCC
		UGCCUUUCUUCAGCAACGUGACCUGGUUCCACGCCAUCUCCGGCACCAAUGGCACCAAGAGAUUCGACAA
		CCCCGUGCUGCCCUUCAACGACGGGGUGUACUUUGCCAGCACCGAGAAGUCCAACAUCAUCAGAGGCUGG
		AUCUUCGGCACCACACUGGACAGCAAGACCCAGAGCCUGCUGAUCGUGAACAACGCCACCAACGUGGUCAU
		CAAAGUGUGCGAGUUCCAGUUCUGCAACGACCCCUUCCUGGACGUCUACUACCACAAGAACAACAAGAGC

		UGGAUGGAAAGCGAGUUCCGGGUGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGUCCCAGCCUU
		UCCUGAUGGACCUGGAAGGCAAGCAGGGCAACUUCAAGAACCUGCGCGAGUUCGUGUUUAAGAACAUCGA
		CGGCUACUUCAAGAUCUACAGCAAGCACACCCCUAUCAACCUCGGCCGGGAUCUGCCUCAGGGCUUCUCU
		GCUCUGGAACCCCUGGUGGAUCUGCCCAUCGGCAUCAACAUCACCCGGUUUUCAGACACUGCUGGCCCUGC
		ACAGAAGCUACCUGACACCUGGCGAUAGCAGCAGCGGAUGGACAGCUGGUGCCGCCGCUUACUACUAUGUGGG
		CUACCUGCAGCCUAGAACCUUCCUGCUGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGGAUUGU
		GCUCUGGAUCCCUCUGAGCGAGACAAAGUGCACCCUGAAGUCCUUCACCGUGGAAAAGGGCAUCUACCAGA
		CCAGCAACUUCCGGGUGCAGCCCACCGAAUCCAUCGUGCGGUUCCCCAAUAUCACCAAUCUGUGCCCCUU
		CGACGAGGUGUUCAAUGCCACCAGAUUCGCCUCUGUGUACGCCUGGAACCGGAAGCGGAUCAGCAAUUGC
		GUGGCCGACUACUCCGUGCUGUACAACUUCGCCCCCUUCUUCGCAUUCAAGUGCUACGGCGUGUCCCCUA
		CCAAGCUGAACGACCUGUGCUUCACAAACGUGUACGCCGACAGCUUCGUGAUCCGGGGAAACGAAGUGCG
		GCAGAUUGCCCCUGGACAGACAGGCAACAUCGCCGACUACAACUACAAGCUGCCCGACGACUUCACCGGCU
		GUGUGAUUGCCUGGAACAGCAACAAGCUGGACUCCAAAGUCGGCGGCAACUACAAUUACAGGUACCGGCU
		GUUCCGGAAGUCCAAUCUGAAGCCCUUCGAGCGGGACAUCUCCACCGAGAUCUAUCAGGCCGGCAACAAG
		CCUUGUAACGGCGUGGCAGGCGUGAACUGCUACUUCCCACUGCAGUCCUACGGCUUUUAGGCCCACAUACG
		GCGUGGGCCACCAGCCCUACAGAGUGGUGGUGCUGAGCUUCGAACUGCUGCAUGCCCCUGCCACAGUGU
		GCGGCCCUAAGAAAAGCACCAAUCUCGUGAAGAACAAAUGCGUGAACUUCAACUUCAACGGCCUGACCGGC
		ACCGGCGUGCUGACAGAGAGCAACAAGAAGUUCCUGCCAUUCCAGCAGUUUGGCCGGGAUAUCGCCGAUA
		CCACAGACGCCGUUAGAGAUCCCCAGACACUGGAAAUCCUGGACAUCACCCCUUGCAGCUUCGGCGGAGU
		GUCUGUGAUCACCCCUGGCACCAACACCAGCAAUCAGGUGGCAGUGCUGUACCAGGGCGUGAACUGUACC
		GAAGUGCCCGUGGCCAUUCACGCCGAUCAGCUGACACCUACAUGGCGGGUGUACUCCACCGGCAGCAAUG
		UGUUUCAGACCAGAGCCGGCUGUCUGAUCGGAGCCGAGUACGUGAACAAUAGCUACGAGUGCGACAUCCC
		CAUCGGCGCUGGAAUCUGCGCCAGCUACCAGACACAGACAAAGAGCCACCGGAGAGCCAGAAGCGUGGCC
		AGCCAGAGCAUCAUUGCCUACACAAUGUCUCUGGGCGCCGAGAACAGCGUGGCCUACUCCAACACAACUCUA
		UCGCUAUCCCCACCAACUUCACCAUCAGCGUGACCACAGAGAUCCUGCCUGUGUCCAUGACCAAGACCAGC
		GUGGACUGCACCAUGUACAUCUGCGGCGAUUCCACCGAGUGCUCCAACCUGCUGCUGCAGUACGGCAGCU
		UCUGCACCCAGCUGAAAAGAGCCCUGACAGGGAUCGCCGUGGAACAGGACAAGAACACCCAAGAGGUGUU

		CGCCCAAGUGAAGCAGAUCUACAAGACCCCUCCUAUCAAGUACUUCGGCGGCUUCAAUUUCAGCCAGAUU
		CUGCCCGAUCCUAGCAAGCCCAGCAAGCGGAGCUUCAUCGAGGACCUGCUGUUCAACAAAGUGACACUGG
		CCGACGCCGGCUUCAUCAAGCAGUAUGGCGAUUGUCUGGGCGACAUUGCCGCCAGGGAUCUGAUUUGCG
		CCCAGAAGUUUAACGGACUGACAGUGCUGCCUCCUCUGCUGACCGAUGAGAUGAUCGCCCAGUACACAUC
		UGCCCUGCUGGCCGGCACAAUCACAAGCGGCUGGAGACAUUUGGAGCAGGCGCCGCUCUGCAGAUCCCCUUU
		GCUAUGCAGAUGGCCUACCGUUCAACGGCAUCGGAGUGACCCAGAAUGUGCUGUACGAGAACCAGAAGC
		UGAUCGCCAACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGACAGCCUGAGCAGCACAGCAAGCGCCCUG
		GGAAAGCUGCAGGACGUGGUCAACCACAAUGCCCAGGCACUGAACACCCUGGUCAAGCAGCUGUCCUCCA
		AGUUCGGCGCCAUCAGCUCUGUGCUGAACGAUAUCCUGAGCAGACUGGACCCUCCUGAGGCCGAGGUGCA
		GAUCGACAGACUGAUCACAGGCAGAGCCUCCAGACAUACGUGACCCAGCAGCUGAUCAGAGCC
		GCCGAGAUUAGAGCCUCUGCCAAUCUGGCCGCCACCAAGAUGUCUGAGUGUGUGGGCCAGAGCAAGA
		GAGUGGACUUUUGCGGCAAGGGCUACCACCUGAUGAGCUUCCCUCAGUCUGCCCCUCACGGCGUGGUGU
		UUCUGCACGUGACAUAUGUGCCCGCUCAAGAGAAGAAUUUCACCACCGCUCCAGCCAUCUGCCACGACGG
		CAAAGCCCACUUUCCUAGAGAAGGCGUGUUCGUGUCCAACGGCACCCAUUGGUUCGUGACACAGCGGAAC
		UUCUACGAGCCCCAGAUCAUCACCACCGACAACACCUUCGUGUCUGGCAACUGCGACGUCGUGAUCGGCA
		UUGUGAACAAUACCGUGUACGACCCUCUGCAGCCCGAGCUGGACAGCUUCAAAGAGGAACUGGACAAGUA
		CUUUAAGAACCACACAAGCCCCGACGUGGACCUGGGCGAUAUCAGCGGAAUCAAUGCCAGCGUCGUGAAC
		AUCCAGAAAGAGAUCGACCGGCUGAACGAGGUGGCCAAGAAUCUGAACGAGAGCCUGAUCGACCUGCAAG
		AACUGGGGAAGUACGAGCAGUACAUCAAGUGGCCCUGGUACAUCUGGCUGGGGCUUUAUCGCCGGACUGA
		UUGCCAUCGUGAUGGUCACAAUCAUGCUGUGUUGCAUGACCAGCUGCUGUAGCUGCCUGAAGGGCUGUU
		GUAGCUGUGGGCAGCUGCUGCAAGUUCGACGAGGACGAUUCUGAGCCCGUGCUGAAGGGCGUGAAACUGC
		ACUACACAUGAUGACUCGAGCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUUCCCGUCCUGGGUAC
		CCCGAGUCUCCCCCGACCUCGGGUCCCAGGUAUGCUCCCCACCUCCACCCUGCCCCACUCACCACCUCUGCUA
		GUUCCAGACACCUCCCCAAGCACGCAGCAAUGCAGCUCAAAACGCUUAGCCUAGCCACACCCCCACGGGAAA
		CAGCAGUGAUUAACCUUUAGCAAUAAACGAAAGUUUAACUAAGCUAUACUAACCCCCAGGGUUGGUCAAUU
		UCGUGCCAGCCACACCCUGGAGCUAGCAAA

73	Full length DNA construct sequence of RBP020.22	AGAATAAACTAGTATTCTTCTGGTCCCCACAGACTCAGAGAGAACCCGCCACCATGTTCGTGTTCCTGGTGC
		TGCTGCCTCTGGTGTCCAGCCAGTGTGTGAACCTGATCACCAGAACACAGTCATACACCAACAGCTTTACCA
		GAGGCGTGTACTACCCCGACAAGGTGTTCAGATCCAGCGTGCTGCACTCTACCCAGGACCTGTTCCTGCCTT
		TCTTCAGCAACGTGACCTGGTTCCACGCCATCTCCGGCACCAATGGCACCAAGAGATTCGACAACCCCGTGC
		TGCCCTTCAACGACGGGGTGTACTTTGCCAGCACCGAGAAGTCCAACATCATCAGAGGCTGGATCTTCGGCA
		CCACACTGGACAGCAAGACCCAGAGCCTGCTGATCGTGAACAACGCCACCAACGTGGTCATCAAAGTGTGCG
		AGTTCCAGTTCTGCAACGACCCCTTCCTGGACGTCTACTACCACAAGAACAACAAGAGCTGGATGGAAAGCG
		AGTTCCGGGTGTACAGCAGCGCCAACAACTGCACCTTCGAGTACGTGTCCCAGCCTTTCCTGATGGACCTGG
		AAGGCAAGCAGGGCAACTTCAAGAACCTGCGCGAGTTCGTGTTTAAGAACATCGACGGCTACTTCAAGATCT
		ACAGCAAGCACACCCCTATCAACCTCGGCCGGGATCTGCCTCAGGGCTTCTCTGCTCTGGAACCCCTGGTGG
		ATCTGCCCATCGGCATCAACATCACCCGGTTTCAGACACTGCTGGCCCTGCACAGAAGCTACCTGACACCTG
		GCGATAGCAGCAGCGGATGGACAGCTGGTGCCGCCGCTTACTATGTGGGCTACCTGCAGCCTAGAACCTTC
		CTGCTGAAGTACAACGAGAACGGCACCATCACCGACGCCGTGGATTGTGCTCTGGATCCTCTGAGCGAGAC
		AAAGTGCACCCTGAAGTCCTTCACCGTGGAAAAGGGCATCTACCAGACCAGCAACTTCCGGGTGCAGCCCAC
		CGAATCCATCGTGCGGTTCCCCAATATCACCAATCTGTGCCCCTTCGACGAGGTGTTCAATGCCACCAGATT
		CGCCTCTGTGTACGCCTGGAACCGGAAGCGGATCAGCAATTGCGTGGCCGACTACTCCGTGCTGTACAACT
		TCGCCCCCTTCTTCGCATTCAAGTGCTACGGCGTGTCCCCTACCAAGCTGAACGACCTGTGCTTCACAAACG
		TGTACGCCGACAGCTTCGTGATCCGGGGAAACGAAGTGCGGCAGATTGCCCCCTGGACAGACAGGCAACATC
		GCCGACTACAACTACAAGCTGCCCGACGACTTCACCGGCTGTGTGATTGCCTGGAACAGCAACAACAAGCTGGAC
		TCCAAAGTCGGCGGCAACTACAATTACAGGTACCGGCTGTTCCGGAAGTCCAATCTGAAGCCCTTCGAGCGG
		GACATCTCCACCGAGATCTATCAGGCCGGCAACAAGCCTTGTAACGGCGTGGCAGGCGTGAACTGCTACTTC
		CCACTGCAGTCCTACGGCTTTAGGCCCACATACGGCGTGGGCCACCAGCCCTACAGAGTGGTGGTGCTGAG
		CTTCGAACTGCTGCATGCCCCTGCCACAGTGTGCGGCCCTAAGAAAAGCACCAATCTCGTGAAGAACAAATG
		CGTGAACTTCAACTTCAACGGCCTGACCGGCACCGGCGTGCTGACAGAGAGCAACAAGAAGTTCCTGCCATT
		CCAGCAGTTTGGCCGGGATATCGCCGATACCACAGACGCCGTTAGAGATCCCCAGACACTGGAAATCCTGGA
		CATCACCCCTTGCAGCTTCGGCGGAGTGTCTGTGATCACCCCTGGCACCAACACCAGCAATCAGGTGGCAGT
		GCTGTACCAGGGGCGTGAACTGTACCGAAGTGCCCGTGGCCATTCACGCCGATCAGCTGACACCTACATGGC

		GGGTGTACTCCACCGGCAGCAATGTGTTTCAGACCAGAGCCGGCTGTCTGATCGGAGCCGAGTACGTGAAC
		AATAGCTACGAGTGCGACATCCCCATCGGCGCTGGAATCTGCGCCAGCTACCAGACACAGACAAAGAGCCAC
		CGGAGAGCCAGAAGCGTGGCCAGCCAGAGCATCATTGCCTACACAATGTCTCTGGGCGCCGAGAACAGCGT
		GGCCTACTCCAACAACTCTATCGCTATCCCCACCAACTTCACCATCAGCGTGACCACAGAGATCCTGCCTGT
		GTCCATGACCAAGACCAGCGTGGACTGCACCATGTACATCTGCGGCGATTCCACCGAGTGCTCCAACCTGCT
		GCTGCAGTACGGCAGCTTCTGCACCCAGCTGAAAAGAGCCCTGACAGGGATCGCCGTGGAACAGGACAAGA
		ACACCCAAGAGGTGTTCGCCCAAGTGAAGCAGATCTACAAGACCCCTCCTATCAAGTACTTCGGCGGCTTCA
		ATTTCAGCCAGATTCTGCCCGATCCTAGCAAGCCCAGCAAGCGGAGCTTCATCGAGGACCTGCTGTTCAACA
		AAGTGACACTGGCCGACGCCGGCTTCATCAAGCAGTATGGCGATTGTCTGGGCGACATTGCCGCCAGGGAT
		CTGATTTGCGCCCAGAAGTTTAACGGACTGACAGTGCTGCCTCCTCTGCTGACCGATGAGATGATCGCCCAG
		TACACATCTGCCCTGCTGGCCGGCACAATCACAAGCGGCTGGACATTTGGAGCAGGCGCCGCTCTGCAGAT
		CCCCTTTGCTATGCAGATGGCCTACCGGTTCAACGGCATCGGAGTGACCCAGAATGTGCTGTACGAGAACCA
		GAAGCTGATCGCCAACCAGTTCAACAGCGCCATCGGCAAGATCCAGGACAGCCTGAGCAGCACAGCAAGCG
		CCCTGGGAAAGCTGCAGGACGTGGTCAACCACAATGCCCAGGCACTGAACACCCTGGTCAAGCAGCTGTCC
		TCCAAGTTCGGCGCCATCAGCTCTGTGCTGAACGATATCCTGAGCAGACTGGACCCTCCTGAGGCCGAGGT
		GCAGATCGACAGACTGATCACAGGCAGACTGCAGAGCCTCCAGACATACGTGACCCAGCAGCTGATCAGAG
		CCGCCGAGATTAGAGCCTCTGCCAATCTGGCCGCCACCAAGATGTCTGAGTGTGCTGGGCCAGAGCAAG
		AGAGTGGACTTTTGCGGCAAGGGCTACCACCTGATGAGCTTCCCTCAGTCTGCCCCTCACGGCGTGGTGTT
		TCTGCACGTGACATATGTGCCCGCTCAAGAGAAGAATTTCACCACCGCTCCAGCCATCTGCCACGACGGCAA
		AGCCCACTTTCCTAGAGAAGGCGTGTTCGTGTCCAACGGCACCCATTGGTTCGTGACACAGCGGAACTTCTA
		CGAGCCCCAGATCATCACCACCGACAACACCTTCGTGTCTGGCAACTGCGACGTCGTGATCGGCATTGTGAA
		CAATACCGTGTACGACCCTCTGCAGCCCGAGCTGGACACAGCTTCAAAGAGGAACTGGACAAGTACTTTAAGAA
		CCACACAAGCCCCGACGTGGACCTGGGCGATATCAGCGGAATCAATGCCAGCGTCGTGAACATCCAGAAAG
		AGATCGACCGGCTGAACGAGGTGGCCAAGAATCTGAACGAGAGCCTGATCGACCTGCAAGAACTGGGGAAG
		TACGAGCAGTACATCAAGTGGCCCTGGTACATCTGGCTGGGCTTTATCGCCGGACTGATTGCCATCGTGAT
		GGTCACAATCATGCTGTGTTGCATGACCAGCTGCTGTAGCTGCCTGAAGGGCTGTTGTAGCTGTGGCAGCT
		GCTGCAAGTTCGACGAGGACGATTCTGAGCCCGTGCTGAAGGGCGTGAAACTGCACTACACATGATGACTC

	GAGCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCT
	CGGGTCCCAGGTATGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGC
	ACGCAGCAATGCAGCTCAAAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGC
	AATAAACGAAAGTTTAACTAAGCTATACTAACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTGGAGC
	TAGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Table 9: Description of RBP020.22 (Omicron BA.4/BA.5-specific RNA vaccine) as shown in Table 8 above (positioning of amino acid mutations shown relative to SEQ ID NO: 1)

Construct	**Omicron BA.4/BA.5 P2**	
Antigen	P2-mutated full spike protein	
Changes	Amino Acid[a]	mRNA Nucleotides (location)
Furin site	RRAR	CGGAGAGCCAGA (2082-2093)
Proline	K986P	CCU (3000-3002)
	V987P	CCU (3003-3005)
Lineage	T19I	AUC (108-110)
	L24del	/
	P25del	/
	P26del	/
	A27S	UCA (123-125)
	H69del	/
	V70del	/
	G142D	GAC (462-464)
	V213G	GGC (675-677)
	G339D	GAC (1053-1055)
	S371F	UUC (1149-1151)
	S373P	CCC (1155-1157)
	S375F	UUC (1161-1163)
	T376A	GCA (1164-1166)
	D405N	AAC (1251-1253)
	K417N	AAC (1287-1289)
	N440K	AAG (1356-1358)
	L452R	AGG (1392-1394)

	S477N	AAC (1467-1469)
	T478K	AAG (1470-1472)
	E484A	GCA (1488-1490)
	F486V	GUG (1494-1496)
	Q498R	AGG (1530-1532)
	N501Y	UAC (1539-1541)
	Y505H	CAC (1551-1553)
	D614G	GGC (1878-1880)
	H655Y	UAC (2001-2003)
	N679K	AAG (2073-2075)
	P681H	CAC (2079-2081)
	N764K	AAA (2328-2330)
	D796Y	UAC (2424-2426)
	Q954H	CAC (2898-2900)
	N969K	AAG (2943-2945)

Table 12. Sequence of one embodiment of an exemplary Omicron BA.2.75-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
80	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron BA.2.75 variant (with PRO mutations at positions corresponding to positions K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 983 and 984 of SEQ ID NO: 80)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYYHENNKSRM ESELRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPVNLGRDLPQGFSALEPLVD LPIGINITRFQTLLALHRSYLTPGDSSSSWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLK SFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATRFASVYAWNRKRISNCVADYSVLYNFAPFFAFKCY GVSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVSGNYNYLYR LFRKSKLKPFERDISTEIYQAGNKPCNGVAGFNCYFPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKK STNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNT SNQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQT KSHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLL QYGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLAD AGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYR FNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDI LSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQS APHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELG KYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
81	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.2.75 variant	auguucguguuccuggugcugcugccucugguguccagccagugugugaaccugaucaccagaacacagucauacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccugguuccacgccauccacguguccggcaccaauggcaccaagagauucgacaaccccgugcugcccuucaacgac gggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacguggucaucaaagugugcgaguuccaguucugcaacgaccccuuccuggacgucuacua ccacgagaacaacaagagcaggauggaaagcgagcuccggguguacagcagcgccaacaacugcaccuucgaguacgugucccag ccuuuccugauggaccuggaaggcaagcagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuuc

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		ucaccggcuguguugauugccuggaacagcaacaagcuggacuccaaagucagcggcaacuacaauuaccuguaccggcuguuccg
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		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggccccugguacaucuggcugggcuuuauc
		gccggacugauuugccaucgugauggucacaaucaugcugugcugaccagcugcuguagccugccugaagggcguuguuguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggcgugaaaacugcacuacacaugauga
82	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.2.75 variant	atgttcgtgttcctggtgctgctcctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactaccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgc
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		accagctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgt
		gaaactgcactacacatgatga

83	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron BA.2.75 variant	agaauaaacuaguauucuucugguccccacagacucagagagaaacccgccaccauguucguguuccuggugcugccucugg uguccagccaguguguggugaaccugaucaccagaacacagucauacaccaacagcuuuaccagaggcguguacuaccccgacaaaggu guucagauccagcgugcugcacucuacccaggaccuguuccugccuuucucagcaacgugaccuggguuccagccgccaucccacgug uccggcaccaauggcaccaagagauucgacaacccccgugcugcccuucaacgacgggguguacuuugccagcaccgagaaagucca acaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcugaucgugaacaacgccaccaacguggu caucaaagugugcgaguuccaguucugcaacgaccccuucuccuggacgucuacuaccacagagaacacaagagcaggauggaaagc gagcuccggguguacagcagccgccaacaacugcaccuucgaguacgugucccagccuuuccugauggaccuggaaggcaagcagg gcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccugugaaccu cggccgggaucugccucagggcuucucugcucuggguggaucugccaucggcaucaacaucacccgguuucagaca cugcuggcccugcacagaagcuaccugacaccuggcgauagcagcagcuggacagcugguggccgccgccuuacuauguggggcu accugcagccuagaaccuuccugcugaaguacaacgagaacggcaccaucaccgacgccguggauuugugcucuggaauccucugag cgagacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagaccagcaacuuccgggugcagcccaccgaaucca ucgugcgguucccaauaucaccaaucugugcccuuccacgagguguucaaugccaccagauucgccucugugauacgccuggaa ccggaagcggaucagcaauugcgugggccgacuacucccgugcugcuacaacuucgccccccuucucgcauucaagugcuacggcgug uccccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugaucccgggggaaacgaagugucacagauug cccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccuggaacagcaac aagcuggacuccaaagucagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggaca ucuccaccgagaucuaucaggccggcaacaagccuuguaaacggcguggcaggcuucaacugcuaccuucccacugcagucccuacgg cuuuaggcccacauacggcguggggccaccagcccuacagaguggugugcugagcuucgaacugcugcaugccccugccacagug ugcggcccuaagaaaagcaccaaucucguguggaagaacaaaugcgugaacuucaacuucaacggccugaccggcacccggcgugcuga cagagagcaacaagaaguuccugccauuccagcaguuuggcccgggauaucgccgauaccacagacgccguuagagaauccccagac acuggaaauccuggacaucacccccuugcagcuucggcggaguucugugaucaccccuggcaccaacaccagcaaucaggugga gugcuguaccagggcgugaacuguaccgaaguugcccguuucacgccgaucagcugacaccuacaauggcgggguguacucca ccggcagcaauguguuucagaccagagccggcugucugaucgggagccgaguacgugaacaauagcuacgagugcgacaucccccau cggcgcuggaaucugccgccagcuaccagacacagacaaagagccaccgggagagccgugggccagccagagcaucauugcc uacacaaugucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuaucccccaccaacuucaccaucagcgugac cacagagauccugccuguguccaugaccaagaccagcguggacugcaccauguacaucugcggcgauuccacccgagugcuccaac

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ctgtaccggctgttccggaagtccaagctgaagccttcgagcgggacatctccaccgagatctatcaggccggcaacaagccttgtaacgg		
cgtggcaggcttcaactgctacttcccactgcagtcctacggctttaggcccacatacggcgtgggccaccagccctacagagtggtggtgct		
gagcttcgaactgctgcatgcccctgccacagtgtgcggccctaagaaaagcaccaatctcgtgaagaacaaatgcgtgaacttcaacttcaa		
cggcctgaccggcaccggcgtgctgacagagagcaacaagaagttcctgccattccagcagtttggccgggatatcgccgataccacagac		
gccgttagagatcccccagacactggaaatcctggacatcaccccttgcagcttcggcggagtgtctgtgatcaccctggcaccaacaccagc		
aatcaggtggcagtgctgtaccagggcgtgaactgtaccgaagtgcccgtggccattcacgccgatcagctgacacctacatggcgggtgta		
ctccaccggcagcaatgtgtttcagaccagagccggctgtctgatcggagccgagtacgtgaacaatagctacgagtgcgacatccccatcg		
gcgctggaatctgcgccagctaccagacacagacaaagagcccaccggagagccagaagcgtggccagccagagcatcattgcctacaca		
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ctgtgtccatgaccaagaccagcgtggactgcaccatgtacatcatctgcggcgattccaccgagtgctccaacctgctgctgcagtacggcagctt		
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ctgctgttcaacaaagtgacactggccgacgccggcttcatcaagcagtatggcgattgtctgggcgacattgccgccagggatctgatttgc		
gcccagaagtttaacggactgacagtgctgcctcctctgctgaccgatgagatgatcgcccagtacacatctgccctgctggccggcacaatc		
acaagcggctggacatttggagcaggcgccgctctgcagatcccctttgctatgcagatggcctaccggttcaacggcatcggagtgaccca		

	gaatgtgctgtacgagaaccagaagctgatcgccaaccagttcaacagcgccatcggcaagatccaggacagcctgagcagcacagcaag
	cgccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaacaccctggtcaagcagctgtcctccaagttcggcgccatca
	gctctgtgctgaacgatatcctgagcagactggacccttcctgaggccgaggtgcagatcgacagactgatcacaggcagactgcagagcctc
	cagacatacgtgacccagcagctgatcagagccgccgagattagagcctctgccaatctggccgccaccaagatgtctgagtgtgctgctggg
	ccagagcaagagagtggactttttgcggcaagggctaccacctgatgagcttccctcagtctgccctcacggcgtggtgtttctgcacgtgac
	atatgtgcccgctcaagagaagaatttcaccaccgctccagccatctgccacgacggcaaagcccacttcctagagaaggcgtgttcgtgtc
	caacggcacccattggttcgtgacacagcggaacttctacgagccccagatcatcaccaccgacaacaccttcgtgtctggcaactgcgacgt
	cgtgatcggcattgtgaacaataccgtgtacgaccctctgcagcccgagctggacagcttcaaagaggaactggacaagtactttaagaacc
	acacaagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgtcgtgaacatccagaaaagagatcgaccggctgaacgag
	gtggccaagaatctgaacgagagcctgatcgacctgcaagaactgggggaagtacgagcagtacatcaagtggccctggtacatctggctgg
	gctttatcgccggactgattgccatcgtgatggtcacaatcatgctgttgttgcatgaccagctgctgtagctgcctgaagggctgttgtagctgtg
	gcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgtgaaactgcactacacatgatgactcgagctggtactgcat
	gcacgcaatgctagctgccctttcccgtcctgggtacccgagtctccccgacctcgggtcccaggtatgctcccacctcacctgccccact
	caccacctctgctagttccagacacctcccaagcacgcagcaatgcagcttagcctagccacaccccacgggaaacagcagt
	gattaacctttagcaataaacgaaagtttaactaagctatactaaccccagggttggtcaatttcgtgccagccacaccctggagctagcaaaa
	aaaaaaaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
	aaaaaaaaaaaaaaaaaaaa

Table 13. Sequence of one embodiment of an exemplary Omicron BA.2.75.2-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
85	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron BA.2.75.2 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 983 and 984 of SEQ ID NO: 85)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYYHENNKSRM ESELRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPVNLGRDLPQGFSALEPLVD LPIGINITRFQTLLALHRSYLTPGDSSSSWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLK SFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVLYNFAPFFAFKCY GVSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVSGNYNYLYR LFRKSKLKPFERDISTEIYQAGNKPCNGVAGSNCYFPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKK STNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNT SNQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQT KSHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLL QYGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLAD AGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYR FNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDI LSRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQS APHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDV VIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLINLQELG KYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
86	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.2.75.2 variant	auguucguguuccuggugcugccucuggguccagccaguguggugaaccugaucaccagaacacagucaucacaccaacagc uuuaccagaggcguguacuacccgacaaggguguucagauccagcgugcugcacucuaccaggaccuguuccugccuuucuca gcaacgugaccuggguuccacgccauccacgugucccggcaccaauggcaccaagagauucgacaacccccgugcugcccuucaacgac gggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacgugguucaucaaagugugcgaguuccaguucugcaacgacccccuuccuggacgucuacua ccacgagaacaacaagagcaggaugguaaagcgaagcuccggguguacagcagcgccaacaacugcaccuucgaguacguguccag ccuuuccugauggaccuggaaggcaagcagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuuc

		aagaucuacagcaagcacacccccuguugaaccucggccgggaucugccucagggcuucucugcucuggaaccccugguggaucugc
		ccaucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacaccuggcgauagcagcagcagcugg
		acagcuggugccgccgcuuacuauguggggcuaccugcagccuagaaaccuuccugcugaaguacaacgagaacggcaccaucaccg
		acgccguggaauugugcucuggaauccucugagcgagacaaagugcacccugaaguccuucaccguggaaaagggcaucuaccagac
		cagcaacuuccgggugcagcccaccgaauccaucgugcgguuucccaauaucaccaaucugugcccccuuccacgagguguucaaug
		ccaccaccuucgccucuguguacgccuggaaccggaagcggaucagcaauugcguggccgacuacuccgugcuguacaacuucgc
		ccccuucuucgcauucaagugcuacggcgcuguccccuaccaagcugaacgaccugugcuucacaaacguguacgcccgacagcuuc
		gugauccggggaaacgaagugucacagauugccccuggacagaggcaacaucgccgacuacaacuacaagcugcccgacgacu
		ucaccggcuguguugauugccuggaacagcaacaagcuggacuccaaagucagcggcaacuacaauuaccuguaccggcuguuccg
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		agcaacugcuacuucccacugcaguccuacggcuuuaaggcccacauacggcguggccaccagcccuacagagugguggugcuga
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		cuucaacggccugaccggcaccggcgugcugacagagaagcaacaagaaguuccugccauucccagcaguuuggccgggauaucgcc
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		ccccuggcaccaacaccagcaaucagguggcagugcuguaccagggcgugaacuguaccgaagugcccguggccauucacgccga
		ucagcugacacccuacauggcggguguacuccaccggcagcaauguguuucagaccagagccggcugucugaucggagccgaguac
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		acaucugcggcgauuccaccgagugcuccaaccugcugcuucgcaguacggcagcuucugcacccagcugaaaagagcccugacagg
		gaucgccguggaacaggacaagaacacccaagaggugucgcccaagugaagcagaucuacaagaccccuccuaucaaguacuuc
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		ugacacuggccgacgccggcuucaucaagcaguauggcgauugucugggcgacauugccgccagggaucugauuugcgcccaga
		aguuuaacggacugacagugcugccucccucugcugaccgaugagaugaucgcccaguacacaucugccccugcuggccggcacaau
		cacaagcggcuggacauuuggagcaggcgccgcucugcagauccccuuugcuaugcagauggccuaccgguucaacggcaucgga
		gugacccagaaugugcuguacgagaaccagaagcugaucgccaaccaguucaacagcgccaucggcaagauccaggacagccuga
		gcagcacagcaagcgcccuggaaagcugcaggacguggucaaccacaaugcccaggcacugaacacccuggucaagcagcugucc

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		ugaucacaggcagacugcagagccucccagacauacgugacccagcagcugaucagagccgccgaggauuagagccucugccaaucu
		ggccgccaccaagaugucugagugugugcuggggccagagcaagaggaguggacuuuugcggcaaggguaccaccugaugagcuu
		cccucagucugccccucacggcgugguguuucugcacgugacauaugugcccgcucaagagaagaaguuucaccaccgcuccagcc
		aucugccacgacggcaaagcccacacuuuccuagagaaaggcguguucguguccaacggcacccauuggguucgugacacagcggaacu
		ucuacgagcccagaucaucaccaccgacaacaccuucgugucuggcaacugcgacgucgugaucggcauugugaacaauaccgu
		guacgacccucugcagcccgagcuggacagcuucaaagaggaacuggacaaguacuuuaagaaccacacaagcccgacguggac
		cugggcgauaucagcggaaucaaugccagcgucgugaacaucagaaagagaucgaccggcugaacgagguggccaagaaucug
		aacgagagccugaucaaccugcaagaacugggaaguacgagcagcaguacaucaaguggcccugguacaucuggcugggcuuuauc
		gccggacugauugccaucgugaugucacaaucaugcugugcaugaccagcugcuguagccugcaaggcuguuguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaaagggcgugaaacugcacuacacaugauga
87	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.2.75.2 variant	atgttcgtgttcctggtgctgctgcctctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactacccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgc
		catccacgtgtccggcaccaatggcaccaagagattcgacaaccccgtgctgccctttcaacgacgggtgtactttgccagcaccgagaagt
		ccaacatcatcagaggctggatcttcggcaccacactggacagcaagacccagagcctgctgatcgtgaacaacgccaccaacgtggtcatc
		aaagtgtgcgagttccagttctgcaacgaccccttcctggacgtctactaccacgagaacaagagcaggatggaaagcgagctccggg
		tgtacagcagcgccaacaactgcaccttcgagtacgtgtcccagccttttctgatggacctggaaggcaagcagggcaacttcaagaacctg
		cgcgagttcgtgtttaagaacatcgacggctacttcaagatctacagcaagcacaccccgtgaacctcggccgggatctgcctcagggcttct
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		cgatagcagcagctggacagctggtgccgccgcttactatgtgggctacctgcagcctagaaccttcctgctgaagtacaacgagaacg
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		attccagcagtttggccgggatatcgccgataccacagacgccgttagagatcccccagacactggaaatcctggacatcacccctgcagctt
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		tccaccgagtgctccaacctgctgctgcagtacggcagcttctgcacccagctgaaaagagccctgacagggatcgccgtggaacaggaca
		agaacacccaagaggtgttcgcccaagtgaagcagatctacaagaccctcctatcaagtacttcggcggcttcaatttcagccagattctgcc
		cgatcctagcaagcccagcaagcggagcttcatcgaggacctgctgttcaacaaagtgacactggccgacgccggcttcatcaagcagtatg
		gcgattgtctgggcgacattgccgccagggatctgatttgcgcccagaagtttaacggactgacagtgctgcctcctctgctgaccgatgagat
		gatcgcccagtacacatctgccctgctggccggcacaatcacaagcggctggacatttggagcaggcgccgctctgcagatccccttgctat
		gcagatggcctaccggttcaacggcatcggagtgacccagaatgtgctgtacgagaaccagaagctgatcgccaaccagttcaacagcgcc
		atcggcaagatccaggacagcctgagcagcacagcaagcgccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaa
		caccctggtcaagcagctgtcctccaagttcggcgccatcagctctgtgctgaacgatatcctgagcagactggaccctcctgaggccgaggt
		gcagatcgacagactgatcacaggcagactgcagaggcctccagacatacgtgacccagcagctgatcagagccgccgagattagaggcctct
		gccaatctggccgccaccaagatgtctgagtgtgtgctgggccagagcaagagagtggactttgcggcaagggctaccacctgatgagctt
		ccctcagtctgcccctcacggcgtggtgtttctgcacgtgacatatgtgcccgctcaagagaagaaatttcaccaccgctccagccatctgccacg
		acggcaaagcccacctttctagagaaaggcgtgttcgtgtccaacggcacccattggttcgtgacacagcggaacttctacgagccccagatca
		tcaccaccgacaacacctttcgtgtctggcaactgcgacgtcgtgatcggcattgtgaacaataccgtgtacgacctctgcagcccgagctgg
		acagcttcaaagaggaactggacaagtactttaagaaccacacaagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgt
		cgtgaacatccagaaaagagatcgaccggctgaacgaggtggccaagaatctgaacgagagcctgatcaacctgcaagaactgggggaagt
		acgagcagtacatcaagtggccctggtacatctggctgggctttatcgccggactgattgccatcgtgatggtcacaatcatgctgtgttgcatg
		accagctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgt
		gaaactgcactacacatgatga

88	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron BA.2.75.2 variant	agaauaaacuaguauucuucuggucccccagacucagagagaaacccgccaccauguucguguuccuggugcugccuccugg
		uguccagccaguguguggugaaccugaucaccagaacacagucauacacccaacagcuuuaccagaggcguguacuaccccgacaaaggu
		guucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuucagcaacgugaccugguuccacgccaucccacgug
		uccggcaccaauggcaccaagagauucgacaacccccgugcugcccuucaacgacgggguguacuuugccagcaccgagaaagucca
		acaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcugaucgugaacaacgccaccaacguggu
		caucaaaguguugcgaguuccaguucugcaacgaccccuucccuggacgucuacuaccacgagaacaacaagagcaggauggaaagc
		gagcuccggguguacagcagcgccaacaacugcaccuucgaguacguguccagccuuuccugauggaccuggaaggcaagcagg
		gcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccugugaaccu
		cggccgggaucugccucagggcuucucugcucuggaacccccuggugguggaucugcccaucggcaucaacaucacccgguuucagaca
		cugcuggcccugcacagaagcuaccugacaccuggcgauagcagcagcagcuggacagcuggugccgccgcuuacuauguggcu
		accugcagccuagaaccuuccugcugaaguacaacgagaaacggcaccaucaccgacgccguggauugugcucuggaauccucugag
		cgagacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagaccaacuuccgggugcagcccaccgaaucca
		ucgugcgguucccaauaucaccaauugugccccuuccacgagguguucaaugccaccaccuucgccucuguguacgccuggaa
		ccggaagcggaucagcaauugcguggccgacuacuccgugcuguacaacuccgccccuucucgcauucaagugcuacggcgug
		uccccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugauccgggggaaacgaagugucacagauug
		ccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccuggaacagcaac
		aagcuggacuccaaagucagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggaca
		ucuccaccgagaucuaucaggccggcaacaagccuuguaacggcgugggcaggcagcaacugcuacuucccacugcaguccuacgg
		cuuuaggcccacauacggcguggggccaccagcccuacagagugguggugcugagcuucgaacugcugcaugccccugccacagug
		ugcggcccuaagaaaagcaccaaucucgugugaagaacaaaugcgugaacuucaacuucaacggccugaccggcaccggcgugcuga
		cagagagcaacaagaaguuccugccauuccagcaguuuuggccgggauaucgccgauaccacagacgccguuagagauccccagac
		acuggaaauccuggacaucacccccuugcagcuucggcggaguucugugaucacccccuggcaccaacaccagcaaucagguggca
		gugcuguaccagggcgugaacuguaccgaaguugcccguggccauucacgccgaucagcugacaccuacaauggcgggguguacucca
		ccggcagcaauguguuucagaccagagccggcuucugaucgggagccgaguacgugaacaauagcuacgagugcgacaucccccau
		cggcgcuggaaucugccagcuaccagacacagacaaagagccaccgggagccagaagcgguggccagccagagcaucauuugcc
		uacacaaugucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuauccccacaacuucaccaacagcgugac
		cacagagauccugccuguguccaugaccaagaccagcguggacugcaccauguacaucugcggcgauuccaccgagugcuccaac

		cugcugcugcaguacggcagcuucugcacccagcugaaaagagcccugacagggaucgccguggaacaggacaagaacacccaag
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		uccuagcaagcccagcaagcggagcuucaucgaggaccugcuguucacaaagugacacuggccgacgccggcuucaucaagcag
		uauggcgauuguucuggggcgacauugccgccagggaucugauuuugcgcccagaaguuuaacggacugacagugcugccucccucug
		cugaccgaugagaaugaucgcccaguacacaucugcccugcuggccggcacaaucacaagcggcuggacauuuggagcaggcgccg
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	aaaaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
	aaaaaaaaaaaaaaaaa

5

Table 14. Sequence of one embodiment of an exemplary Omicron BA.4.6/BF.7-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
90	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron BA.4.6/BF.7 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 981 and 982 of SEQ ID NO: 90)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAISGTNGTKRFD NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYYHKNNKSWME SEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLGRDLPQGFSALEPLVDLP IGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSF TVEKGIYQTSNFRVQPTESIVRFPNITNLCPFDEVFNATTFASVYAWNRKRISNCVADYSVLYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVGGNYNYRYRL FRKSNLKPFERDISTEIYQAGNKPCNGVAGVNCYFPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
91	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.4.6/BF.7 variant	auguucguguuccuggugcugcugccucugguguccagccagugugugaaccugaucaccagaacacagucauacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccuggcuuccacgccaucuccggcaccaauggcaccaagagauucgacaaccccgugcugcccuucaacgacggggug uacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcuga ucgugaacaacgccaccaacguggucaucaaagugugcgaguuccaguucugcaacgaccccuuccuggacgucuacuaccacaa gaacaacaagagcuggauggaaagcgaguuccggguguacagcagcgccaacaacugcaccuucgaguacgugucccagccuuuc cugauggaccuggaaggcaagcagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagauc

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		caucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugaccuggcgauagcagcagcggauggacagcu
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		uggauugugcucuggaucccucugagcgagacaaagugcacccugaaguccuucaccgugaaaagggcaucuaccagaccagca
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		ggacugauuggccaucgugauggucacaaucaugcuguguuugcaugaccagcugcuguagcugccugaagggcguguuguagcug
		uggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggccgugaaacugcacuacacaugauga
92	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron BA.4.6/BF.7 variant	atgttcgtgttcctggtgctgctgcctctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactacccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgcctttcttcagcaacgtgacctggttccacgc
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		ctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgtgaaact
		gcactacacatgatga

93	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron BA.4.6/BF.7 variant	agaauaaacuaguauucuucuggucccccacagacucagagagaacccgccaccauguucgugucugcugcuccucugg uguccagccaguguggugaaccugaucaccagaacacagucauacacaacagcuuuaccagaggcguguacuaccccgacaaggu guucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuucagcaacgugaccuggguuccacgccaucuccggc accaauggcaccaagagauucgacaacccccgugcugcccuucaacgacgggguguacuuugccagcaccgagaaguccaacauca ucagaggcuggauucuucggcaccacacuggacagcaagacccagagccugcugaucgugaacaacgccaccaacguggucaucaa aguguucgaguuccaguucugcaacgaccccuucuccuggacgucuacuaccacaagaacacaacgagcuggauggaaagcgaguuc cggguguacagcagcgccaacaacugcaccuucgaguacguguccccagccuuucuccugauggaccuggaaggcaagcagggcaacu ucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccuaucaaccucggccg ggaucugccccagggcuucucugcucuggaaccccuggugguggaucugcccaucggcaucaacaucacccgguuucagacacugcug gcccugcacagaagcuaccugacaccuggcgauagcagcggauggacagcuggugccgccgcuuuacuauguggguccaccugc agccuagaaccuucccugcugaaguacaacgagaacggcaccaucaccgacgccguggauuguucuggaucccucugagcgagac aaagugcacccugaaguccuucaccguggaaaagggcaucuaccagaccagcaacuucgggugcagcccaccgaauccaucgug cgguucccccaauaucacccaaucugugcccccuucgacgagguguucaaugccacccaccuucgccucuguguacgccuggaaccgga agcggaucagcaauugcguggccgacuacuccgugcuguacaacuucgccccccuucuucgcauucaagugcuacggcguguucccc uaccaagcugaacgaccugcuucacaaacguguacgccgacagcuucgugauccgggggaaacgaagugcggcagauugccccu ggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugcuguggaauugccuggaacagcaacaagc uggacuccaaagucgggcggcaacuacaauuacagguaccggcuguuccggaaguccaaucugaaagcccuucgagcgggacaucuc caccgagaucuaucaggccggcaacaagccuuguaacggcguggcaggcguguaacugcuacuucccacugcaguccuacggcuuu aggcccacauacgggcguggccaccagcccuacagaguggugguggucugagcuucgaacugcugcaugccccugccacaguugugcg gcccuaagaaaagcaccaauucucgugaagaacaaaugcgugaacuucaacuucaacggccugaccggcacccggcgugcugacaga gagcaacaagaaguuccugccaauccagcaguuuggccgggauaucgccgauaccacagacgccguuagagauccccagacacug gaaauccuggacaucacccccuugcagcuucggcggagugucugugaucaccccuggcaccaacacccagcaaucaggugguggcagugc uguaccagggcguugaacuguaccgaagugcccguggccaauucacgccgaucagcugacaccuacaugggcgggguguacuccaccgg cagcaauguguuucagaccagagccggcugucugaucggagccgaguacgugaacaauagcuacgagugcgacaucccccaucggc gcuggaaucugcgccagcuaccagacacagacaaagagccaccggagagccgaagcguggccagccagagcaucauugccuacac aaugucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuaucccccaccaacuucaccaucagcgugaccacag agauccugccuguguccaugaccagacgguggacugcaccauguacaucugcggcgauucccaccgagugcuccaaccugcu

		gcugcaguacggcagcuucugcacccagcugaaaagagcccugacagggaucgccguggaacaggacaagaacacccaagaggug
		uucgcccaagugaagcagaucuacaagacccccuccuaucaaguacuucggcggcuucaauuucagccagauucugccgauccua
		gcaagcccagcaagcggagcuucaucgaggaccugcuguucaacaaagugacacuggccgacgccggcuucaucaagcaguaugg
		cgauugucuggggcgacauugccgccaggaucugauuugcgcccagaaguuuaacggacugacagugcugccucccucugcugac
		cgaugagaugaucgcccaguacacaucugcccugcuggccggcacaaucacaagcggcuggacauuuggagcaggcgccgcucug
		cagauccccuuugcuaugcagauggccuaccggcaucggagugacccagaaaugugcuguacgagaaccagaagcug
		aucgccaaccaguucaacagcgccaucggcaagauccaggacagccugagcagcacagcaagcgccccugggaaagcugcaggacg
		uggucaaccacaaugcccaggcacugaacacccuggucaagcagcugucccaaguucggcgccaucagcucugugcugaacga
		uauccugagcagacuggacccucccugaggccgaggugcagaucgacacagaucacaggcagacugcagaccuccagacauac
		gugacccagcagcugaucagagccgccgagauuagagccucugccaaucuggccgccaccaagaugucugaguguugugcugggcc
		agagcaagagaguggacuuuugcggcaagggcuaccaccugaugagcuucccucagucugccccucacggcguggugguuucugc
		acgugacauaugugcccgcucaagagaagaauuucaccaccgcuccagccaucugccacgacggcaaagccccacuuuccuagagaa
		ggcguguucguguccaacggcacccauuggguucgugacacagcggaacuucuacgagcccagaucaucaccaccgacaacaccu
		ucgugucuggcaacugcgacgucgugaucggcauugugaacaauaccguguacgacccucugcagcccgagcuggacagcuucaa
		agaggaacuggacaaguacuuuaagaaccacacaagccccgacguggaccuggggcgauaucagcggaaucaaugccagcgucgu
		gaacauccagaaagagaucgaccggcugaacgagguggccaagaaucugaacgagagccugaucgaccugcaagaacuggggaa
		guacgagcaguacaucaagugggcccuggguacaucuggcuuuaaucgccggacugauuggccaucaugguucacaaucau
		gcuguguugcaugaccagcugcuguagccugaagggcuguuguagcuggcagcugcugcaaguucgacgaggacgauu
		cugagcccgugcugaagggcgugaaacugcacuacacaugaugacucgagcugguacugcaugcaugcuagcugcccuu
		ucccguccuggguaccccgaguucucccccgaccucgggucccagguaugcucccaccuccacccacccacccucugcuag
		uuccagacaccucccaagcacgcagcaaugcagcucuaaaacgcuuagccuagccacaccccacgggaaacagcagugauuaaccu
		uuagcaauaaacgaaaguuuaacuaagcuauacuaaccccagggguuggucaauuucgugccagccacaccuggagcuagcaaa
		aaaa

		cgtgctgcccttcaacgacgggggtgtactttgccagcaccgagaagtccaacatcatcagaggctggatcttcggcaccactggacagca
		agacccagagcctgctgatcgtgaacaacgccaccaacgtggtcatcaaagtgtgcgagttccagttctgcaacgacccctcctggacgtct
		actaccacaagaacaacaagagctggatggaaagcgagttccgggtgtacagcagcgccaacaactgcaccttcgagtacgtgtcccagcc
		ttcctgatggacctggaaggcaagcagggcaacttcaagaacctgcgcgagttcgtgtttaagaacatcgacggctacttcaagatctacag
		caagcacaccctatcaacctcggccgggatctgcctcagggcttctctgctctggaaccctggtggatctgcccatcggcatcaacatcacc
		cggtttcagacactgctggccctgcacagaagctacctgacacctggcgatagcagcggatggacagctggtgccgccgcttactatgt
		gggctacctgcagcctagaacctcctgctgaagtacaacgagaacggcaccatcaccgacgccgtggattgtgctctggatcctctgagcga
		gacaaagtgcacctgaagtccttcaccgtggaaaagggcatctaccagaccagcaacttcgggtgcagcccaccgaatccatcgtgcggt
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		ttgcgtggccgactactccgtgctgtacaacttcgccccttcttcgcattcaagtgctacggcgtgtccctaccaagctgaacgacctgtgctt
		cacaaacgtgtacgccgacagcttcgtgatccgggggaaacgaagtgcggcagattgcccctggacagacaggcaacatcgccgactacaa
		ctacaagctgcccgacgacttcaccggctgtgtgattgcctggaacagcaacaagctggactccaaagtcggcggcaactacaattacaggt
		accggctgttccggaagtccaatctgaagcccttcgagcgggacatctccaccgagatctatcaggccggcaacaagccttgtaacggcgtg
		gcaggcgtgaactgctacttcccactgcagtcctacggctttaggcccacatacggcgtgggccaccagccctacagagtggtggtgctgagc
		ttcgaactgctgcatgcccctgccacagtgtgcggccctaagaaaagcaccaatcttcgtgaagaacaaatgcgtgaacttcaacttcaacggc
		ctgaccggcaccggcgtgctgacagaggagcaacaagaagttcctgccattccagcagtttggccgggatatcgccgataccacagacgccg
		ttagagatcccccagacactggaaatcctggacatcacccttgcagcttcggcgggagtgtctgtgatcaccctggcaccaacaccagcaatc
		aggtggcagtgctgtaccagggcgtgaactgtaccgaagtgcccgtggccattcacgccgatcagctgacacctacatggcgggtgtactcc
		accggcagcaatgtgtttcagaccagagccggctgtctgatcggagccgagtacgtgaacaatagctacgagtgcgacatcccccatcggcgc
		tggaatctgcgccagctaccagacacagacaaagagccaccggagagccagaagcgtggccagccagagcatcattgcctacacaatgtc
		tctgggcgccgagaacagcgtggcctactccaacaactctatcgctatcccccaccaacttcaccatcagcgtgaccacagagatcctgcctgtg
		tccatgaccaagaccagcgtggactgcaccatgtacatctgcggcgattccaccgagtgctccaacctgctgctgcagtacggcagcttctgc
		acccagctgaaaagagccctgacagggatcgccgtggaacaggacaagaacacccaagaggttgttcgcccaagtgaagcagatctacaa
		gacccctcctatcaagtacttcggcggcttcaatttcagccagattctgcccgatcctagcaagcccagcaagcggagcttcatcgaggacctg
		ctgttcaacaaagtgacactggccgacgccggcttcatcaagcagtatggcgattgtctgggcgacattgccgccagggatctgatttgcgcc
		cagaagtttaacggactgacagtgctgcctcctctgctgaccgatgagatgatcgcccagtacacatctgccctgctggccggcacaatcaca
		agcggctggacatttggagcaggcgccgctctgcagatccccttttgctatgcagatggcctaccggttcaacggcatcggagtgacccagaat

	gtgctgtacgagaaccagaagctgatcgccaaccagttcaacagcgccatcggcaagatccaggacagcctgagcagcacagcaagcgcc
	ctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaacaccctggtcaagcagctgtcctccaagttcggcgccatcagctc
	tgtgctgaacgatatcctgagcagactggacccttcctgaggccgaggtgcagatcgacagactgatcacaggcagactgcagagcctccag
	acatacgtgacccagcagctgatcagagccgccgagattagagcctctggccgccaccaagatgtctgagtgtgctgtgctgggcca
	gagcaagagagtggactttgcggcaagggctaccacctgatgagcttccctcagtctgcccctcacggcgtggtgtttctgcacgtgacatat
	gtgcccgctcaagagaagaatttcaccaccgctccagccatctgccacgacggcaaagcccacttcctagagaaggcgtgttcgtgtccaac
	ggcacccattggttcgtgacacagcggaacttctacgagccccagatcatcaccaccgacaacacctttcgtgtctggcaactgcgacgtcgtg
	atcggcattgtgaacaataccgtgtacgaccctctgcagcccgagctggacagcttcaaagaggaactggacaagtactttaagaaccacac
	aagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgtcgtgaacatccagaaagagatcgaccggctgaacgaggtggc
	caagaatctgaacgagagcctgatcgacctgcaagaactgggggaagtacgagcagtacatcaagtggccctggtacatctggctgggcttta
	tcgccggactgattgccatcgtgatggtcacaatcatgctgtgttgcatgaccagctgctgtagctgcctgaagggctgttgtagctggcagc
	tgctgcaagttcgacgaggacgatttctgagcccgtgctgaagggcgtgaaactgcactacacatgatgactcgagctggtactgcatgcacg
	caatgctagctgccccttcccgtcctgggtaccccgagtctccccccgacctcgggtcccaggtatgctcccacctccacctgccccactcaccac
	ctctgctagttccagacacctcccaagcacgcagcaatgcagctcaaaacgcttagcctagccacaccccacgggaaacagcagtgattaa
	cctttagcaataaacgaaagtttaactaagctatactaaccccagggttggtcaatttcgtgccagccacaccctggagctagcaaaaaaaaa
	aaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
	aaaaaaaaaaaaaaa

Table 15. Sequence of one embodiment of an exemplary Omicron XBB-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
95	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron XBB variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 981 and 982 of SEQ ID NO: 95)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPALPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYQKNNKSWM ESEFRVYSSANNCTFEYVSQPFLMDLEGKEGNFKNLREFVFKNIDGYFKIYSKHTPINLERDLPQGFSALEPLVDL PIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS FTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVIYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKPSGNYNYLYRL FRKSKLKPFERDISTEIYQAGNKPCNGVAGSNCYSPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
96	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB variant	auguucguguuccuggugcugcugccucuggugucccagccaguguggugaaccugaucaccagaacacagUCAuacaccaacagc uuuaccagaggcguguacuacccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccuggguuccacgccaucccacguguccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgac gggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacgugguucaucaaagugugcgaguuccaguucugcaacgacccccuuccuggacgucuacca gaagaacacaagagcuggaauggaaagcgaguuccggguguacagcagccgccaacacugcaccuucgaguacguguucccagccu

		uuccugauggaccuggaaggcaaggagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaag
		aucuacagcaagcacacccccuaucaaccucgagcgggaucugccucagggcuucucugcucugcuggaaccccugguggaucugccca
		ucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacacccuggcgauaagcagcaggcggauggac
		agcuggugccgccgcuuacuauguggggcuaccugcagccuagaaccuuccugcugaaguacaacgagaacggcaccaucaccgac
		gccguggauuugugcucuggaucccucugagcgagacaaagugcacccugaaguccuucaccguggaaaagggcaucuaccagacca
		gcaacuuccgggugcagcccaccgaauccaucgugcgguucccaauaucaccaaucugugccccuuccacgagguguucaaugcc
		accaccuucgccucuguguacgccuggaaccggaagcggaucagcaauugcguggccgacuacuccgugaucuacaacuucgccc
		ccuucuucgcauucaagugcuacggcgugucccuaccaagcugaacgaccuugugcuucacaaacguguacgccgacagcuucgu
		gauccgggaaacgaagugucacagauugccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuuc
		accggcugugugauugccuggaacagcaacaagcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccgga
		aguccaagcugaagcccuucgagcgggacaucuccaccgagaucuacaggccggcaacaagccuugucaacggcgugguggcaggcag
		caacugcuacagcccacugcaguccuacggcuuuaggcccacauacggcgugggccaccagcccuacagaguggugguggcugagc
		uucgaacugcugcaugcccccugccacaguguggcggcccuaagaaaaagcaccaaucucgugaagaacaaaugcgugaacuucaacu
		ucaacggccugaccggcaccggcgugcugacagagagcaacaagaaguuccugccauuccagcaguuuggcccgggauaucgccga
		uaccacagacgccguuagagaucccagacacuggaaauccuggacaucacccccuugcagcuucggcggagugucugugaucacc
		ccuggcaccaacaccagcaaucaggugggcagugcuguaccagggcgugaacugcuaccgaagugcccgugggccauucacgcccgauc
		agcugacaccuacaugggcgggguguacuccaccggcagcaauguguuucagaccagaggccggcugucugaucgggagccgaguacg
		ugaacaauagcuacgagugugcgacauccccaucggcgcuggaaucugcgccagcuaccagacacagacaaagagccaccggagagc
		cagaagcguggccagccagagcaucauuugccuacacaauguucucugggcgccgagaacagcgcuggccuacuccaacaacucuauc
		gcuauccccaccaacuucaccaucagcgugaccacagaggauccugccugugucaccaagaccagcgcuggacugcaccaugua
		caucugcggcgauuccaccgagugcuccaaccugcugcugcagcuucugcacccagcugaaaagagcccugacaggg
		aucgccguggaacaggacaagaacacccaagagguguucgcccaagugaagcagaucuacaagaccccuccuaucaaguacuucg
		gcggcuucaauuucagccagauuucugcccgauccuaccuagcaagcccagcaagcggaggccuucgaggaccugcugcugcuguuca
		gacacuggccgacgccggcuucaucaagcaguauggcgauugucuggggcgacauugccgccagggaucugauuugcgccccagaa
		guuuaacggacugacagugcugccuccucugcugaccgaugagaugaucgcccaguacacacaucugccccugcuggccggcacaauc
		acaagcggcuggacauuuggagcaggcgccgcucugcagauccccuuugcuaugcagauggccuaccgguucaacggcaucgga
		gugacccagaaugugcuguacgagaaccagaagcugaucgccaaccaguucaacagcgccaucggcaagauccaggacagccuga

		gcagcacagcaagcgcccugggaaagcugcaggacgugggucaaccacaaugcccaggcacugaacacccuggucaagcagcugucc
		uccaaguucggcgccaucagcucugugcugaacgauauccugagcagacgguggaccccuccugaggccgaggugcagaucgacagac
		ugaucacaggcagacugcagaggccuccagacauacgugacccagcagcugaucagaagccgccggagauuagagccucugccaaucu
		ggccgccaccaagaugucugaguguguggcugcugggccagagcaagagaguggacuuuugcggcaagggcuaccaccugaugagcuu
		cccucagucugccccucacggcgugguguuucugcacgugacauauguggcccgcucaagagaagaauuucaccaccgcuccagcc
		aucugccacgacggcaaagcccaccacuuuccuagagaaggcguguucgugucccaacggcacccauuggguucgugacacagcggaacu
		ucuacgagccccagaucaucaccaccgacaacaccuucgugucuggcaacugcgacgucgugaucggcauugugaacaauaccgu
		guacgacccucugcagcccgagcuggacagcuucaaagaggaacuggacaaguacuuuaagaaccacacaagccccgacguggac
		cugggcgauaucagcggaaucaaugccagcgucgugaacauccagaaagagaucgaccggcugaacgaggugggccaagaaucug
		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggcccugguacaucuggcugggcuuuauc
		gccggacugauugccaucgugaugucacaaucaugcugugguugcaugaccagcugcuguagccugaagggcuguugguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggcgugaaacugcacuacacaugauga
97	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB variant	atgttcgtgttcctggtgctgctgccucuggugucuccagccagugugaaccugaucaccagaacacagTCAtacaccaacagctttaccagag
		gcgugtactaccccgacaaggugttcagaucccagcgugcugcacucuaccaggacgugaccuuuuucaucgacgugaccgugguuccac
		gccaucgacgugucccggcaccaaugguaccaagagauucgcaacccccgccugccuucaacgacgggguguacuucgccagcaccgagaa
		gucuaacaucaucagaggcugaucuucgccgccacacccuggacgcagcacccagagcucugcugaucgugcagaacgccaccaacgugguc
		aucaaagugugcgaguuccaguucaucgacaugcaggagcugggcaaccccgacgccccaucaacgagcagaccgccgugaagaucaag
		gucacagcaguucaugagcuucgccgugaacaagcccgagggcgugcaggccgccaccgugggcgagagcaagaucuucgugaccgcc
		gcgagcucgugcugcagggcgccgacgugaacgccgccaagaccaagccccgcgaggagcagcugcugggcaccaccgccgccgaccc
		ugcaccgacaugaccuucgagcaggaggccgccgugaagaacaccccuuucgugaccgaccgcccugccgaucgaggugaugggcagc
		gagaucgaccagcugaacgagagcgacgaggaggaccaggccgacaagagcgugaagcagcacaagaagcugcgcggcuacgagcac
		cagaacgaccccuucaagggcccccagaagcacggcgagcugggcgacgugcaccccaacagcaugaagaaggacgaccccgacaag
		gagaagagccaccaccaccaccaccaccacuaagaaggccggcggcaacaagcugagccugccccgcgagaaguccgugcagugg
		gccgugaccaagggcaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaagaag
		aagaagaagaagaag

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gaaactgcactacacatgatga	

98	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB variant	agaauaaacuagauauucuucuggucccacagacucagagagaacccgccaccauguucguguuccuggugcugccucugg uguccagccaguguguugaaccugaucaccagaacacagUCAuacaccaacagcuuuaccagaggcguguacuaccccgacaaagg uguucagauccagcgugcugcacucuacccaggaccuguuccugccuuuucuucagcaacgugaccuggguuccacgccauccacgu guccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgacggggguguacuuugccagcaccgagaagucca acaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcccugcugaucgugaacaacgccaccaacguggu caucaaaguguugcgaguuccaguucugcaacgaccccuucuccuggacgucuaccagaagaacaacaagagcuggauggaaagcga guucccggguguacagcagccgccaacaacugcaccuucgaguacguguucccagccuuuccugauggaccuggaaggcaaggagggc aacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccuaucaaccucg agcgggaucugccucagggcuucucugcucuggugguggaucugccccaucggcaucaacaucacccgguuucagacacu gcuggcccugcacagaagcuaccugacaccuggcgauagcagcagcggauggacagcuggugccgccgccguuacuauguggguuac cugcagccuagaaccuucccugcugaaguacaacgagaaacggcaccaucaccgacgccguggaauugugcucuggaucccugagcg agacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagaccaacuuccgggugcagcccaccgaauccauc gugcgguucccaauaucaccaaucugugcccccuuccacgagguguucaaugccaccaccuucgccucuguguacgccuggaaccg gaagcggaucagcaauugcguggccgacuaucuccgugaucuacaacuucgcccccuucuucgcauucaagugcuacgcggcgugucc ccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugauccgggggaaacgaagugucacagauugccc cuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccuggaacagcaacaa gcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagccccuucgagcgggacauc uccaccgagaucuaucaggccggcaacaagccuuguaacggcguggcaggcagcaacugcuacagcccacugcaguccuacggcu uuaggcccacauacggcguggggccaccagcccuacagagugguggugcugagcuucgaacugcugcaugccccugccacagugug cggcccuaagaaaagcaccaaucucguguggaagaacaaaugcgugaacuucaacuucaacggccugaccggcacggcgugcugaca gagagcaacaagaaguuccugccaauuccagcaguuuggccgggauaucgccgauaccacagacgccguuagagaauccccagacac uggaaauccuggacaucacccccuugcagcuucggcggaguucugugaucaccccuggcaccaacaccagcaaucagguggcagu gcuguaccagggcgugaacuguaccgaagugcccgugggccaauucacgccgaucagcugacaccuacaauggcgggguguacuccacc ggcagcaauguguuucagaccagagccggcugucugaucgguggagccgaguacgugaacaauagcuacgagugcgacaucccccauc ggcgcuggaaucugcgccagcuaccagacacagacaaagagccaccgggagccgaagcguggccagccagaucauuugccu acacaaugucucugggcgccgagaacagcguggccuacucccaacaacucuaucgcuaucccccaccaacuucaccaucagcgugacc acagagauccugccuguguccaugaccaagacccagcguggacugcaccauguacaucugcggcgauuccaccgagugcuccaacc

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		aaaa

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		gcctgaccggcaccggcgtgctgacagagagcaacaagaagttcctgccattccagcagtttggccgggatatcgccgataccacagacgc
		cgttagagatcccagacactggaaatcctggacatcacccttgcagcttcggcggagtgtctgtgatcacccctggcaccaacaccagcaa
		tcaggtggcagtgctgtaccagggcgtgaactgtaccgaagtgcccgtggccattcacgccgatcagctgacacctacatggcgggtgtactc
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		ctctgggcgccgagaacagcgtggcctactccaacaactctatcgctatcccccaccaacttcaccatcagcgtgaccacagagatcctgcctgt
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		cacccagctgaaaagagcctgacagggatcgccgtggaacaggacaagaacacccaagaggttgttcgcccaagtgaagcagatctaca
		agacccctcctatcaagtacttcggcggcttcaatttcagccagattctgcccgatcctagcaagcccagcaagcgggagcttcatcgaggacct
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		ccagaagtttaacggactgacagtgctgcctcctctgctgaccgatgagatgatcgcccagtacacatctgccctgctggccggcacaatcac
		aagcggctggacatttggagcaggcgccgctctgcagatccccttgctatgcagatggcctaccggttcaacggcatcggagtgacccaga

		atgtgctgtacgagaaccagaagctgatcgccaaccagttcaacagcgccatcggcaagatccaggacagcctgagcagcacagcaagcg
		ccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaacaccctggtcaagcagctgtcctccaagttcggcgccatcagc
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		caagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgtcgtgaacatccagaaagagatcgaccgctgaacgaggtgg
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		acctctgctagttccagacacctcccaagcacgcagcaatgcagctcaaaacgcttagcctagccacaccccacgggaaacagcagtgatt
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		aaaaaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
		aaaaaaaaaaaaaaaaa

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Table 16. Sequence of one embodiment of an exemplary Omicron BQ.1.1-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
100	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron BQ.1.1 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 981 and 982 of SEQ ID NO: 100)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAISGTNGTKRFD NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYYHKNNKSWME SEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLGRDLPQGFSALEPLVDLP IGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSF TVEKGIYQTSNFRVQPTESIVRFPNITNLCPFDEVFNATTFASVYAWNRKRISNCVADYSVLYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSTVGGNYNYRYRL FRKSKLKPFERDISTEIYQAGNKPCNGVAGVNCYFPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
101	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron BQ.1.1 variant	AUGUUCGUGUUCCUGGUGCUGCUGCCUCUGGUGUCCAGCCAGUGUGUGAACCUGAUCACCAGAACACAG UCAUACACCAACAGCUUUACCAGAGGCGUGUACUACCCCGACAAGGUGUUCAGAUCCAGCGUGCUGCACU CUACCCAGGACCUGUUCCUGCCUUUCUUCAGCAACGUGACCUGGUUCCACGCCAUCUCCGGCACCAAUGG CACCAAGAGAUUCGACAACCCCGUGCUGCCCUUCAACGACGGGGUGUACUUUGCCAGCACCGAGAAGUCC AACAUCAUCAGAGGCUGGAUCUUCGGCACCACACUGGACAGCAAGACCCAGAGCCUGCUGAUCGUGAACA ACGCCACCAACGUGGUCAUCAAAGUGUGCGAGUUCCAGUUCUGCAACGACCCCUUCCUGGACGUCUACUA CCACAAGAACAACAAGAGCUGGAUGGAAAGCGAGUUCCGGGUGUACAGCAGCGCCAACAACUGCACCUUC

		GAGUACGUGUCCCAGCCUUUCCUGAUGGACCUGGAAGGCAAGCAGGGCAACUUCAAGAACCUGCGCGAGU
		UCGUGUUUAAGAACAUCGACGGCUACUUCAAGAUCUACAGCAAGCACACCCCUAUCAACCUCGGCCGGGA
		UCUGCCUCAGGGCUUCUCUGCUCUGGAACCCCUGGUGGAUCUGCCCAUCGGCAUCAACAUCACCCGGUUU
		CAGACACUGCUGGCCCUGCACAGAAGCUACCUGACACCUGGCGAUAGCAGCGGGAUGGACAGCUGGUG
		CCGCCGCUUACUAUGUGGGGCUACCUGCAGCCUAGAACCUUCCUGCUGAAGUACAACGAGAACGGCACCAU
		CACCGACGCCGUGGAUUGUGCUCUGGAUCCUCUGAGCGAGACAAAGUGCACCCUGAAGUCCUUCACCGUG
		GAAAAGGGCAUCUACCAGACCAGCAACUUCCGGGUGCAGCCCACCGAAUCCAUCGUGCGGUUCCCCAAUA
		UCACCAAUCUGUGCCCCUUCGACGAGGUGUUCAAUGCCACCACCUUCGCCUCUGUGUACGCCUGGAACCG
		GAAGCGGAUCAGCAAUUGCGUGGCCGACUACUCCGUGCUGUACAACUUCGCCCCCUUCUUCGCAUUCAAG
		UGCUACGGCGUGUCCCCUACCAAGCUGAACGACCUGUGCUUCACAAACGUGUACGCCGACAGCUUCGUGA
		UCCGGGGAAACGAAGUGUCACAGAUUGCCCCUGGACAGACAGGCAACAUCGCCGACUACAACUACAAGCU
		GCCCGACGACUUCACCGGCUGUGUGAUUGCCUGGAACAGCAACAAGCUGGACUCCACCGUCGGCGGCAAC
		UACAAUUACAGGUACCGGCUGUUCCGGAAGUCCAAGCUGAAGCCCUUCGAGCGGGACAUCUCCACCGAGA
		UCUAUCAGGCCGGCAACAAGCCUUGUAACGGCGUGGCAGGCGUGAACUGCUACUUCCCACUGCAGUCCUA
		CGGCUUUAGGCCCACAUACGGCGUGGGCCACCAGCCCUACAGAGUGGUGGUGCUGAGCUUCGAACUGCU
		GCAUGCCCCUGCCACAGUGUGCGGCCCUAAGAAAAGCACCAAUCUCGUGAAGAACAAAUGCGUGAACUUC
		AACUUCAACGGCCUGACCGGCACCGGCGUGCUGACAGAGAGCAACAAGAAGUUCCUGCCAUUCCAGCAGU
		UUGGCCGGGAUAUCGCCGAUACCACAGACGCCGUUAGAGAUCCCCAGACACUGGAAAUCCUGGACAUCAC
		CCCUUGCAGCUUCGGCGGAGUGUCUGUGAUCACCCCUGGCACCAACACCAGCAAUCAGGUGGCAGUGCUG
		UACCAGGGCGUGAACUGUACCGAAGUGCCCGUGGCCAUUCACGCCGAUCAGCUGACACCUACAUGGCGGG
		UGUACUCCACCGGCAGCAAUGUGUUUCAGACCAGAGCCGGCUGUCUGAUCGGAGCCGAGUACGUGAACAA
		UAGCUACGAGUGCGACAUCCCCAUCGGCGCUGGAAUCUGCGCCAGCUACCAGACACAGACAAAGAGCCACC
		GGAGAGCCAGAAGCGUGGCCAGCCAGAGCAUCAUUGCCUACACAAUGUCUCUGGGCGCCGAGAACAGCGU
		GGCCUACUCCAACAACUCUAUCGCUAUCCCCACCAACUUCACCAUCAGCGUGACCACACAGAGAUCCUGCCUG
		UGUCCAUGACCAAGACCAGCGUGGACUGCACCAUGUACACUCUGCGGCGAUUCCACCGAGUGCUCCAACCU
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		AAGAACACCCAAGAGGUGUUCGCCCAAGUGAAGCAGAUCUACAAGACCCCUCCUAUCAAGUACUUCGGCG

		GCUUCAAUUUCAGCCAGAUUCUGCCCGAUCCUAGCAAGCCCAGCAAGCGGAGCUUCAUCGAGGACCUGCU
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		GCCAGGGAUCUGAUUUGCGCCCAGAAGUUUAACGGACUGACAGUGCUGCCUCCUCUGCUGACCGAUGAGA
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		CGCUCUGCAGAUCCCCCUUUGCUAUGCAGAUGGCCUACCGGUUCAACGGCAUCGGAGUGACCCAGAAUGUG
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		GCAGCACAGCAAGCGCCCCUGGGAAAGCUGCAGGACGUGGUCAACCACAAUGCCCAGGCACUGAACACCCU
		GGUCAAGCAGCUGUCCUCCAAGUUCGGCGCCAUCAGCUCUGUGCUGAACGAUAUCCUGAGCAGACUGGAC
		CCUCCUGAGGCCGAGGUGCAGAUCGACAGACUGAUCACAGGCAGACUGCAGAGCCUCCAGACAUACGUGA
		CCCAGCAGCUGAUCAGAGCCGCCGAGAUUAGAGCCUCUGCCAAUCUGGCCGCCACCAAGAUGUCUGAGUG
		UGUGCUGGGCCAGAGCAAGAGAGUGGACUUUUGCGGCAAGGGCUACCACCUGAUGAGCUUCCCUCAGUC
		UGCCCCUCACGGCGUGGUGUUUCUGCACGUGACAUAUGUGCCCGCUCAAGAGAAGAAUUUCACCACCGCU
		CCAGCCAUCUGCCACGACGGCAAAGCCCACUUUCCUAGAGAAGGCGUGUUCGUGUCCAACGGCACCCAUU
		GGUUCGUGACACAGCGGAACUUCUACGAGCCCCAGAUCAUCACCACCACACCUUCGUGUCUGGCAA
		CUGCGACGUCGUGAUCGGCAUUGUGAACAAUACCGUGUACGACCCUCUGCAGCCCGAGCUGGACAGCUUC
		AAAGAGGAACUGGACAAGUACUUUAAGAACCACACAAGCCCCGACGUGGACCUGGGCGAUAUCAGCGGAA
		UCAAUGCCAGCGUCGUGAACAUCCAGAAAGAGAUCGACCGGCUGAACGAGGUGGCCAAGAAUCUGAACGA
		GAGCCUGAUCGACCUGCAAGAACUGGGGAAGUACGAGCAGUACAUCAAGUGGCCCUGGUACAUCUGGCUG
		GGCUUUAUCGCCGGACUGAUUGCCAUCGUGAUGGUCACAAUCAUGCUGUGUUGCAUGACCAGCUGCUGU
		AGCUGCCUGAAGGGCUGUUGUAGCUGUGGCAGCUGCUGCAAGUUCGACGAGGACGAUUCUGAGCCCGUG
		CUGAAGGGCGUGAAACUGCACUACACAUGAUGA
102	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron BQ.1.1 variant	ATGTTCGTGTTCCTGGTGCTGCCTCTGGTGTCCAGCCAGTGTGTGAACCTGATCACCAGAACACAGTCA
		TACACCAACAGCTTTACCAGAGGCGTGTACTACCCCGACAAGGTGTTCAGATCCAGCGTGCTGCACTCTACC
		CAGGACCTGTTCCTGCCTTTCTTCAGCAACGTGACCTGGTTCCACGCCATCTCCGGCACCAATGGCACCAAG
		AGATTCGACAACCCCGTGCTGCCCTTCAACGACGGGGTGTACTTTGCCAGCACCGAGAAGTCCAACATCATC
		AGAGGCTGGATCTTCGGCACCACACTGGACAGCAAGACCCAGAGCCTGCTGATCGTGAACAACGCCACCAAC
		GTGGTCATCAAAGTGTGCGAGTTCCAGTTCTGCAACGACCCCTTCCTGGACGTCTACTACCACAAGAACAAC

	AAGAGCTGGATGGAAAGCGAGTTCCGGGTGTACAGCAGCGCCAACAACTGCACCTTCGAGTACGTGTCCCA
	GCCTTTCCTGATGGACCTGGAAGGCAAGCAGGGCAACTTCAAGAACCTGCGCGAGTTCGTGTTTAAGAACAT
	CGACGGCTACTTCAAGATCTACAGCAAGCACACCCCTATCAACCTCGGCCGGGATCTGCCTCAGGGCTTCTC
	TGCTCTGGAACCCCTGGTGGATCTGCCCATCGGCATCAACATCACCCGGTTTCAGACACTGCTGGCCCTGCA
	CAGAAGCTACCTGACACCTGGCGATAGCAGCAGCGGATGGACAGCTGGTGCCGCCGCTTACTATGTGGGCT
	ACCTGCAGCCTAGAACCTTCCTGCTGAAGTACAACGAGAACGGCACCATCACCGACGCCGTGGATTGTGCTC
	TGGATCCTCTGAGCGAGACAAAGTGCACCCTGAAGTCCTTCACCGTGGAAAAGGGCATCTACCAGACCAGCA
	ACTTCCGGGTGCAGCCCACCGAATCCATCGTGCGGTTCCCCAATATCACCAATCTGTGCCCCTTCGACGAGG
	TGTTCAATGCCACCACCTTCGCCTCTGTGTACGCCTGGAACCGGAAGCGGATCAGCAATTGCGTGGCCGACT
	ACTCCGTGCTGTACAACTTCGCCCCCTTCTTCGCATTCAAGTGCTACGGCGTGTCCCCTACCAAGCTGAACG
	ACCTGTGCTTCACAAACGTGTACGCCGACAGCTTCGTGATCCGGGGAAACGAAGTGTCACAGATTGCCCCTG
	GACAGACAGGCAACATCGCCGACTACAACTACAAGCTGCCCGACGACTTCACCGGCTGTGTGATTGCCTGGA
	ACAGCAACAAGCTGGACTCCACCGTCGGCGGCAACTACAATTACAGGTACCGGCTGTTCCGGAAGTCCAAGC
	TGAAGCCCTTCGAGCGGGACATCTCCACCGAGATCTATCAGGCCGGCAACAAGCCTTGTAACGGCGTGGCA
	GGCGTGAACTGCTACTTCCCACTGCAGTCCTACGGCTTTAGGCCCACATACGGCGTGGGCCACCAGCCCTAC
	AGAGTGGTGGTGCTGAGCTTCGAACTGCTGCATGCCCCTGCCACAGTGTGCGGCCCTAAGAAAAGCACCAA
	TCTCGTGAAGAACAAATGCGTGAACTTCAACTTCAACGGCCTGACCGGCACCGGCGTGCTGACAGAGAGCAA
	CAAGAAGTTCCTGCCATTCCAGCAGTTTGGCCGGGATATCGCCGATACCACAGACGCCGTTAGAGATCCCCA
	GACACTGGAAATCCTGGACATCACCCCTTGCAGCTTCGGCGGAGTGTCTGTGATCACCCCTGGCACCAACAC
	CAGCAATCAGGTGGCAGTGCTGTACCAGGGCGTGAACTGTACCGAAGTGCCCGTGGCCATTCACGCCGATC
	AGCTGACACCTACATGGCGGGTGTACTCCACCGGCAGCAATGTGTTTCAGACCAGAGCCGGCTGTCTGATC
	GGAGCCGAGTACGTGAACAATAGCTACGAGTGCGACATCCCCATCGGCGCTGGAATCTGCGCCAGCTACCA
	GACACAGACAAAGAGCCACCGGAGAGCCAGAAGCGTGGCCAGCCAGAGCATCATTGCCTACACAATGTCTCT
	GGGCGCCGAGAACAGCGTGGCCTACTCCAACAACTCTATCGCTATCCCCACCAACTTCACCATCAGCGTGAC
	CACAGAGATCCTGCCTGTGTCCATGACCAAGACCAGCGTGGACTGCACCATGTACATCTGCGGCGATTCCAC
	CGAGTGCTCCAACCTGCTGCAGTACGGCAGCTTCTGCACCCAGCTGAAAAGAGCCCTGACAGGGATCG
	CCGTGGAACAGGACAAGAACACCCAAGAGGTGTTCGCCCAAGTGAAGCAGATCTACAAGACCCCTCCTATCA

		AGTACTTCGGCGGCTTCAATTTCAGCCAGATTCTGCCCGATCCTAGCAAGCCCAGCAAGCGGAGCTTCATCG AGGACCTGCTGTTCAACAAAGTGACACTGGCCGACGCCGGCTTCATCAAGCAGTATGGCGATTGTCTGGGC GACATTGCCGCCAGGGATCTGATTTGCGCCCAGAAGTTTAACGGACTGACAGTGCTGCCTCCTCTGCTGACC GATGAGATGATCGCCCAGTACACATCTGCCCTGCTGGCCGGCACAATCACAAGCGGCTGGACATTTGGAGC AGGCGCCGCTCTGCAGATCCCCCTTTGCTATGCAGATGGCCTACCGGTTCAACGGCATCGGAGTGACCCAGA ATGTGCTGTACGAGAACCAGAAGCTGATCGCCAACCAGTTCAACAGCGCCATCGGCAAGATCCAGGACAGCC TGAGCAGCACAGCAAGCGCCCTGGGAAAGCTGCAGGACGTGGTCAACCACAATGCCCAGGCACTGAACACC CTGGTCAAGCAGCTGTCCTCCAACTTCGGCGCCATCAGCTCTGTGCTGAACGATATCCTGAGCAGACTGGAC CCTCCTGAGGCCGAGGTGCAGATCGACAGACTGATCACAGGCAGACTGCAGAGCCTCCAGACATACGTGAC CCAGCAGCTGATCAGAGCCGCCGAGATTAGAGCCTCTGCCAATCTGGCCGCCACCAAGATGTCTGAGTGTG TGCTGGGCCAGAGCAAGAGAGTGGACTTTTGCGGCAAGGGCTACCACCTGATGAGCTTCCCTCAGTCTGCC CCTCACGGCGTGGTGTTTCTGCACGTGACATATGTGCCCGCTCAAGAGAAGAATTTCACCACCGCTCCAGCC ATCTGCCACGACGGCAAAGCCCACTTTCCTAGAGAAGGCGTGTTCGTGTCCAACGGCACCCATTGGTTCGTG ACACAGCGGAACTTCTACGAGCCCCAGATCATCACCACCGACAACACCTTCGTGTCTGGCAACTGCGACGTC GTGATCGGCATTGTGAACAATACCGTGTACGACCCTCTGCAGCCCGAGCTGGACAGCTTCAAAGAGGAACT GGACAAGTACTTTAAGAACCACACAAGCCCCGACGTGGACCTGGGCGATATCAGCGGAATCAATGCCAGCG TCGTGAACATCCAGAAAGAGATCGACCGGCTGAACGAGGTGGCCAAGAATCTGAACGAGAGCCTGATCGAC CTGCAAGAACTGGGGAAGTACGAGCAGTACATCAAGTGGCCCTGGTACATCTGGCTGGGCTTTATCGCCGG ACTGATTGCCATCGTGATGGTCACAATCATGCTGTGTTGCATGACCAGCTGCTGTAGCTGCCTGAAGGGCT GTTGTAGCTGTGGCAGCTGCTGCAAGTTCGACGAGGACGATTCTGAGCCCGTGCTGAAGGGCGTGAAACTG CACTACACATGATGA
103	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron BQ.1.1 variant	AgaauaaacuaguauucuucuggucccccacagacucagagagaacccgccaccAUGUUCGUGUUCCUGGUGCUGCUGCCC UCUGGUGUCCAGCCAGUGUGUGAACCUGAUCACCAGAACACAGUCAUACACCAACAGCUUUACCAGAGGC GUGUACUACCCCGACAAGGUGUUCAGAUCCAGCGUGCUGCACUCUACCCAGGACCUGUUCCUGCCUUUCU UCAGCAACGUGACCUGGUUCCACGCCAUCUCCGGCACCAAUGGCACCAAGAGAUUCGACAACCCCGUGCU GCCCUUCAACGACGGGGUGUACUUUGCCAGCACCGAGAAGUCCAACAUCAUCAGAGGCUGGAUCUUCGGC ACCACACUGGACAGCAAGACCCAGAGCCUGCUGAUCGUGAACAACGCCACCAACGUGGUCAUCAAAGUGU

	GCGAGUUCCAGUUCUGCAACGACCCCUUCCUGGACGUCUACUACCACAAGAACAACAAGAGCUGGAUGGA
	AAGCGAGUUCCGGGUGUACAGCAGCGCCAACAACUGCACCUUCGAGUACGUGUCCCAGCCUUUCCUGAUG
	GACCUGGAAGGCAAGCAGGGCAACUUCAAGAACCUGCGCGAGUUCGUGUUUAAGAACAUCGACGGCUACU
	UCAAGAUCUACAGCAAGCACACCCCUAUCAACCUCGGCCGGGAUCUGCCUCAGGGCUUCUCUGCUCUGGA
	ACCCCUGGUGGAUCUGCCCAUCGGCAUCAACAUCACCCGGUUUUCAGACACUGCUGGCCCUGCACAGAAGC
	UACCUGACACCUGGCGAUAGCAGCGGAUGGACAGCUGGUGCCGCCGCUUACUAUGUGGGCUACCUGC
	AGCCUAGAACCUUCCUGCUGAAGUACAACGAGAACGGCACCAUCACCGACGCCGUGGAUUGUGCUCUGGA
	UCCUCUGAGCGAGACAAAGUGCACCCUGAAGUCCUUCACCGUGGAAAAGGGCAUCUACCAGACCAGCAAC
	UUCCGGGUGCAGCCCACCGAAUCCAUCGUGCGGUUCCCCAAUAUCACCAAUCUGUGCCCCUUCGACGAGG
	UGUUCAAUGCCACCACCUUCGCCUCUGUGUACGCCUGGAACCGGAAGCGGAUCAGCAAUUGCGUGGCCGA
	CUACUCCGUGCUGUACAACUUCGCCCCCUUCUUCGCAUUCAAGUGCUACGGCGUGUCCCCUACCAAGCUG
	AACGACCUGUGCUUCACAAACGUGUACGCCGACAGCUUCGUGAUCCGGGGAAACGAAGUGUCACAGAUUG
	CCCCUGGACAGACAGGCAACAUCGCCGACUACAACUACAAGCUGCCCGACGACUUCACCGGCUGUGUGAU
	UGCCUGGAACAGCAACAAGCUGGACUCCACCGUCGGCGGCAACUACAAUUACAGGUACCGGCUGUUCCGG
	AAGUCCAAGCUGAAGCCCUUCGAGCGGGACAUCUCCACCGAGAUCUAUCAGGCCGGCAACAAGCCUUGUA
	ACGGCGUGGCAGGCGUGAACUGCUACUUCCCACUGCAGUCCUACGGCUUUAGGCCCACAUACGGCGUGGG
	CCACCAGCCCUACAGAGUGGUGGUGCUGAGCUUCGAACUGCUGCAUGCCCCUGCCACAGUGUGCGGCCCU
	AAGAAAAGCACCAAUCUCGUGAAGAACAAAUGCGUGAACUUCAACUUCAACGGCCUGACCGGCACCGGCGU
	GCUGACAGAGAGCAACAAGAAGUUCCUGCCAUUCCAGCAGUUUGGCCGGGAUAUCGCCGAUACCACAGAC
	GCCGUUAGAGAUCCCCAGACACUGGAAAUCCUGGACAUCACCCCUUGCAGCUUCGGCGGAGUGUCUGUGA
	UCACCCCUGGCACCAACACCAGCAAUCAGGUGGCAGUGCUGUACCAGGGCGUGAACUGUACCGAAGUGCC
	CGUGGCCAUUCACGCCGAUCAGCUGACACCUACAUGGCGGGUGUACUCCACCGGCAGCAAUGUGUUUCAG
	ACCAGAGCCGGCUGUCUGAUCGGAGCCGAGUACGUGAACAAUAGCUACGAGUGGCGACAUCCCCCAUCGGCG
	CUGGAAUCUGCGCCAGCUACCAGACACAGACAAAGAGCCACCGGAGAGGCCAGAAGCGUGGCCAGCCAGAG
	CAUCAUUGCCUACACAAUGUCUCUGGGCGCCGAGAACAGCGUGGCCUACUCCAACAACUCUAUCGCUAUC
	CCCACCAACUUCACCAUCAGCGUGACCACAGAGAUCCUGCCUGUGUCCAUGACCAAGACCAGCGUGGACUG
	CACCAUGUACAUCUGCGGCGAUUCCACCGAGUGCUCCAACCUGCUGCUGCAGUACGGCAGCUUCUGCACC

		CAGCUGAAAAGAGCCCUGACAGGGAUCGCCGUGGAACAGGACAAGAACACCCAAGAGGUGUUCGCCCAAG
		UGAAGCAGAUCUACAAGACCCCUCCUAUCAAGUACUUCGGCGCGCUUCAAUUUCAGCCAGAUUCUGCCCGA
		UCCUAGCAAGCCCAGCAAGCGGAGCUUCAUCGAGGACCUGCUGUUCAACAAAGUGACACUGGCCGACGCC
		GGCUUCAUCAAGCAGUAUGGCGAUUGUCUGGGCGACAUUGCCGCCAGGGAUCUGAUUUGCGCCCAGAAG
		UUUAACGGACUGACAGUGCUGCCUCCUCUGCUGACCGAUGAGAUGAUCGCCCAGUACACAUCUGCCCUGC
		UGGCCGGCACAAUCACAAGCGGCUGGACAUUUGGAGCAGGCGCCGCUCUGCAGAUCCCCUUUGCUAUGCA
		GAUGGCCUACCGGUUCAACGGCAUCGGAGUGACCCAGAAUGUGCUGUACGAGAACCAGAAGCUGAUCGCC
		AACCAGUUCAACAGCGCCAUCGGCAAGAUCCAGGACAGCCUGAGCAGCACAGCAAGCGCCCUGGGAAAGCU
		GCAGGACGUGGUCAACCACAAUGCCCAGCACUGAACACCCUGGUCAAGCAGCUGUCCUCCAAGUUCGGC
		GCCAUCAGCUCUGUGCUGAACGAUAUCCUGAGCAGACUGGACCCUCCUGAGGCCGAGGUGCAGAUCGACA
		GACUGAUCACAGGCAGACUGCAGAGCCUCCAGACAUACGUGACCCAGCAGCUGAUCAGAGCCGCCGAGAU
		UAGAGCCUCUGCCAAUCUGGCCGCCACCAAGAUGUCUGAGUGUGUGCUGGGCCAGAGCAAGAGAGUGGAC
		UUUUGCGGCAAGGGCUACCACCUGAUGAGCUUCCCUCAGUCUGCCCCUCACGGCGUGGUGUUUCUGCAC
		GUGACAUAUGUGCCCGCUCAAGAGAAGAAUUUCACCACCGCUCCAGCCAUCUGCCACGACGGCAAAGCCCA
		CUUUCCUAGAGAAGGCGUGUUCGUGUCCAACGGCACCCAUUGGUUCGUGACACAGCGGAACUUCUACGAG
		CCCCAGAUCAUCACCACCGACAACACCUUCGUGUCUGGCAACUGCGACGUCGUGAUCGGCAUUGUGAACA
		AUACCGUGUACGACCCUCUGCAGCCCGAGCUGGACAGCUUCAAAGAGGAACUGGACAAGUACUUUAAGAA
		CCACACAAGCCCCGACGUGGACCUGGGCGAUAUCAGCGGAAUCAAUGCCAGCGUCGUGAACAUCCAGAAA
		GAGAUCGACCGGCUGAACGAGGUGGCCAAGAAUCUGAACGAGAGCCUGAUCGACCUGCAAGAACUGGGGA
		AGUACGAGCAGUACAUCAAGUGGCCCUGGUACAUCUGGCUGGGCUUUAUCGCCGGACUGAUUGCCAUCG
		UGAUGGUCACAAUCAUGCUGUGUUGCAUGACCAGCUGCUGUAGCUGCCUGAAGGGCUGUUGUAGCUGUG
		GCAGCUGCUGCAAGUUCGACGAGGACGAUUCUGAGCCCGUGCUGAAGGGCGUGAAACUGCACUACACAUG
		AUGAcucgagcugguacugcaugcaaugcuagcugcccuuucccguccuggguaccccgagucucccccgaccucgggguc
		ccagguaugcucccaccuccaccugcccacucaccaccucugcuaguuccagacaccucccaagcacgcagcaaugcagcucaaaa
		cgcuuagccuagccacaccccacgggaaacagcagugauuaaccuuuagcaauaaacgaaaguuuaacuaagcuauaccuaaccc
		caggguuggucaauuucgugccagccacacccuggagcuagcaaa

104	Full length DNA construct encoding a SARS-CoV-2 S protein from an Omicron BQ.1.1 variant	AgaataaactagtattcttctggtcccacagactcagaggaacccgccaccATGTTCGTGTTCCTGGTGCTGCTCCTCTGG
		TGTCCAGCCAGTGTGTGAACCTGATCACCAGAACACAGTCATACACCAACAGCTTTACCAGAGGCGTGTACT
		ACCCCGACAAGGTGTTCAGATCCAGCGTGCTGCACTCTACCCAGGACCTGTTCCTGCCTTTCTTCAGCAACG
		TGACCTGGTTCCACGCCATCTCCGGCACCAATGGCACCAAGAGATTCGACAACCCCGTGCTGCCCTTCAACG
		ACGGGGTGTACTTTGCCAGCACCGAGAAGTCCAACATCATCAGAGGCTGGATCTTCGGCACCACACTGGACA
		GCAAGACCCAGAGCCTGCTGATCGTGAACAACGCCACCAACGTGGTCATCAAAGTGTGCGAGTTCCAGTTCT
		GCAACGACCCCTTCCTGGACGTCTACTACCACAAGAACAACAAGAGCTGGATGGAAAGCGAGTTCCGGGTGT
		ACAGCAGCGCCAACAACTGCACCTTCGAGTACGTGTCCCAGCCTTTCCTGATGGACCTGGAAGGCAAGCAGG
		GCAACTTCAAGAACCTGCGCGAGTTCGTGTTTAAGAACATCGACGGCTACTTCAAGATCTACAGCAAGCACA
		CCCCTATCAACCTCGGCCGGGATCTGCCTCAGGGCTTCTCTGCTCTGGAACCCCTGGTGGATCTGCCCATCG
		GCATCAACATCACCCGGTTTCAGACACTGCTGGCCCTGCACAGAAGCTACCTGACACCTGGCGATAGCAGCA
		GCGGATGGACAGCTGGTGCCGCCGCTTACTATGTGGGCTACCTGCAGCCTAGAACCTTCCTGCTGAAGTAC
		AACGAGAACGGCACCATCACCGACGCCGTGGATTGTGCTCTGGATCCTCTGAGCGAGACAAAGTGCACCCT
		GAAGTCCTTCACCGTGGAAAAGGGCATCTACCAGACCAGCAACTTCCGGGTGCAGCCCACCGAATCCATCGT
		GCGGTTCCCCAATATCACCAATCTGTGCCCCTTCGACGAGGTGTTCAATGCCACCACCTTCGCCTCTGTGTA
		CGCCTGGAACCGGAAGCGGATCAGCAATTGCGTGGCCGACTACTCCGTGCTGTACAACTTCGCCCCCTTCTT
		CGCATTCAAGTGCTACGGCGTGTCCCCTACCAAGCTGAACGACCTGTGCTTCACAAACGTGTACGCCGACAG
		CTTCGTGATCCGGGGGAAACGAAGTGTCACAGATTGCCCCTGGACAGACAGGCAACATCGCCGACTACAACTA
		CAAGCTGCCCGACGACTTCACCGGCTGTGTGATTGCCTGGAACAGCAACAAGCTGGACTCCAAGGTCGGCG
		GCAACTACAATTACAGGTACCGGCTGTTCCGGAAGTCCAAGCTGAAGCCCTTCGAGCGGGACATCTCCACCG
		AGATCTATCAGGCCGGCAACAAGCCTTGTAACGGCGTGGCAGGCGTGAACTGCTACTTCCCACTGCAGTCCT
		ACGGCTTTAGGCCCACATACGGCGTGGGCCACCAGCCCTACAGAGTGGTGGTGCTGAGCTTCGAACTGCTG
		CATGCCCCTGCCACAGTGTGCGGCCCTAAGAAAAGCACCAATCTCGTGAAGAACAAATGCGTGAACTTCAAC
		TTCAACGGCCTGACCGGCACCGGCGTGCTGACAGAGAGCAACAAGAAGTTCCTGCCATTCCAGCAGTTTGG
		CCGGGATATCGCCGATACCACAGACGCCGTTAGAGATCCCCAGACACTGGAAATCCTGGACATCACCCCTTG
		CAGCTTCGGCGGAGTGTCTGTGATCACCCCTGGCACCAACACCAGCAATCAGGTGGCAGTGCTGTACCAGG
		GCGTGAACTGTACCGAAGTGCCCGTGGCCATTCACGCCGATCAGCTGACACCTACATGGCGGGTGTACTCC

	ACCGGCAGCAATGTGTTTCAGACCAGAGCCGGCTGTCTGATCGGAGCCGAGTACGTGAACAATAGCTACGA
	GTGCGACATCCCCATCGGCGCTGGAATCTGCGCCAGCTACCAGACACAGACACAAAGAGCCACCGGAGAGCCA
	GAAGCGTGGCCAGCCAGAGCATCATTGCCTACACAATGTCTCTGGGCGCCGAGAACAGCGTGGCCTACTCC
	AACAACTCTATCGCTATCCCCACCAACTTCACCATCAGCGTGACCACAGAGATCCTGCCTGTGTCCATGACCA
	AGACCAGCGTGGACTGCACCATGTACATCTGCGGCGATTCCACCGAGTGCTCCAACCTGCTGCTGCAGTACG
	GCAGCTTCTGCACCCAGCTGAAAAGAGCCCTGACAGGGATCGCCGTGGAACAGGACAAGAACACCCAAGAG
	GTGTTCGCCCAAGTGAAGCAGATCTACAAGACCCCTCCTATCAAGTACTTCGGCGGCTTCAATTTCAGCCAG
	ATTCTGCCCGATCCTAGCAAGCCCAGCAAGCGGAGCTTCATCGAGGACCTGCTGTTCAACAAAGTGACACTG
	GCCGACGCCGGCTTCATCAAGCAGTATGGCGATTGTCTGGGCGACATTGCCGCCAGGGATCTGATTTGCGC
	CCAGAAGTTTAACGGACTGACAGTGCTGCCTCCTCTGCTGACCGATGAGATGATCGCCCAGTACACATCTGC
	CCTGCTGGCCGGCACAATCACAAGCGGCTGGACATTTGGAGCAGGCGCCGCTCTGCAGATCCCCCTTTGCTA
	TGCAGATGGCCTACCGGTTCAACGGCATCGGAGTGACCCAGAATGTGCTGTACGAGAACCAGAAGCTGATC
	GCCAACCAGTTCAACAGCGCCATCGGCAAGATCCAGGACAGCCTGAGCAGCACAGCAAGCGCCCTGGGAAA
	GCTGCAGGACGTGGTCAACCACAATGCCCAGGCACTGAACACCCTGGTCAAGCAGCTGTCCTCCAACTTCGG
	CGCCATCAGCTCTGTGCTGAACGATATCCTGAGCAGACTGGACCCTCCTGAGGCCGAGGTGCAGATCGACA
	GACTGATCACAGGCAGACTGCAGAGCCTCCAGACATACGTGACCCAGCAGCTGATCAGAGCCGCCGAGATT
	AGAGCCTCTGCCAATCTGGCCGCCACCAAGATGTCTGAGTGTGTGCTGGGCCAGAGCAAGAGAGTGGACTT
	TTGCGGCAAGGGCTACCACCTGATGAGCTTCCCTCAGTCTGCCCCTCACGGCGTGGTGTTTCTGCACGTGAC
	ATATGTGCCCGCTCAAGAGAAGAATTTCACCACCGCTCCAGCCATCTGCCACGACGGCAAAGCCCACTTTCC
	TAGAGAAGGCGTGTTCGTGTCCAACGGCACCCATTGGTTCGTGACACAGCGGAACTTCTACGAGCCCCAGA
	TCATCACCACCGACAACACCTTCGTGTCTGGCAACTGCGACGTCGTGATCGGCATTGTGAACAATACCGTGT
	ACGACCCTCTGCAGCCCGAGCTGGACAGCTTCAAAGAGGAACTGGACAAGTACTTTAAGAACCACACAAGCC
	CCGACGTGGACCTGGGCGATATCAGCGGAATCAATGCCAGCGTCGTGAACATCCAGAAAGAGATCGACCGG
	CTGAACGAGGTGGCCAAGAATCTGAACGAGAGCCTGATCGACCTGCAAGAACTGGGGAAGTACGAGCAGTA
	CATCAAGTGGCCCTGGTACATCTGGCTGGGCTTTATCGCCGGACTGATTGCCATCGTGATGGTCACAATCAT
	GCTGTGTTGCATGACCAGCTGCTGTAGCTGCCTGAAGGGCTGTTGTAGCTGTGGCAGCTGCTGCAAGTTCG
	ACGAGGACGATTCTGAGCCCGTGCTGAAGGGCGTGAAACTGCACTACACATGATGActcgagctggtactgcatgc

	acgcaatgctagctgccccttcccgtcctgggtaccccgagtctccccgacctcgggtcccaggtatgctcccacctccacctgccccactca ccacctctgctagttccagacacctcccaagcacgcagcaatgcagctcaaaacgcttagcctagccacaccccacgggaaacagcagtga ttaacctttagcaataaacgaaagtttaactaagctatactaaccccagggttggtcaatttcgtgccagccacaccctggagctagcaaaaaa aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaaaaa

Table 16A. Sequence of one embodiment of an exemplary Omicron XBB.1.5-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
158	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron XBB.1.5 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 982 and 983 of SEQ ID NO: 158)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPALPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYQKNNKSWM ESEFRVYSSANNCTFEYVSQPFLMDLEGKEGNFKNLREFVFKNIDGYFKIYSKHTPINLERDLPQGFSALEPLVDL PIGINITRFQTLLALHRSYLTPVDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS FTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVIYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKPSGNYNYLYRL FRKSKLKPFERDISTEIYQAGNKPCNGVAGPNCYSPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
159	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.1.5 variant	auguucguguuccuggugcugcugccucuggugcuccagccagugugugaaccugaucaccagaacacagucauacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccuggcuuccacgccauccacgcuguccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgac ggggcuguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacguggucaucaaagugugcgaguuccaguucugcaacgaccccuuccuggacgucuacca gaagaacaacaagagcuggauggaaagcgaguuccgggcuguacagcagcgccaacaacugcaccuucgaguacgugucccagccu uuccugauggaccuggaaggcaaggagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaag aucuacagcaagcacaccccuaucaaccucgagcgggaucugccucagggcuucucugcucuggaaccccuggcuggaucugccca

		ucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacaccuguggauaggcagcggauggac
		agcuggugccgcccgcuuacuauguggguaccugcagccuagaaccuucccugcugaaguacaacgagaacggcaccaucaccgac
		gccguggauuugcucuggauccucugagcgagacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagacca
		gcaacuuccgggugcagcccaccgaauccaucgugcgguucccaauaucaccaauucugugcccccuuccacgagguguucaaugcc
		accaccuucgccucuguguacgccuggaacggaagcggaucagcaauugcguggccgacuaccuccgugaucuacaacuucgccc
		ccuucuucgcauucaagugcuacggcguguccccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgu
		gauccgggaaacgaagugucacagaauugccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuuc
		accggcuguguguugaauugccuggaacagcaacaagcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccgga
		aguccaagcugaagccccuucgagcgggacaucuccaccgagaucuaucaggccggcaacaagccuuguaacggcguggcaggccc
		caacugcuacagcccacugcaguccuacggcuuuaggcccacauacggcgugggccaccagcccuacagagugguggugcugagc
		uucgaacugcugcaugccccugccacaguugugcggccuaagaaaagcaccaaucucgugaagaacaaaugcgugaacuucaacu
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		uaccacagacgccguuagagaucccagacacuggaaauccuggacaucaccccuugcagcuucggcggaguucugugaucacc
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		gcuauccccaccaacuucaccaucagcgugaccacagagauccugccuguguccaugaccaagaccagcguggacugcaccaugua
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		aucgccguggaacaggacaagaacacccaagagguguuucgcccaagugaagcagaucuacaagacccccuccuaucaaguacuucg
		gcggcuucaauuucagccagauucugcccgauccuagcaagcccagcaagcggagcuucaucgaggaccugcuguucaacaaagu
		gacacuggccgacgccggcuucaucaagcaguauggcgauugucuggggcgacauugccgccagggaucugauuugcgcccagaa
		guuuaacggacugacagugcugccucccucugcugaccgaugagaugaucgcccaguacacaucugcccugcuggccggcacaauc
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		cccucagucugccccucacggcguggguguuucugcacgugacauauguggcccgcucaagagaagaauuucaccaccgcuccagcc
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		cugggcgauaucagcggaaucaaugccagcgucgugaacauccagaaagagaucgaccggcugaacgagguggccaagaaucug
		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggccccugguacaucuggcuggcuuuauc
		gccggacugauugccaucgugauggucacaaucaugcugguuugcaugaccagcugcuguagccugcuggaagggcuguuguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagccccgugcugaagggcgugaaacugcacuacacaugauga
160	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.1.5 variant	atgttcgtgttcctggtgctgctgcctctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactaccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgccttctttcagcaacgtgacctggttccacgc
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		cagcagccgccaacaactgcaccttcgagtacgtgtcccagccttcctgatggacctggaaggcaagggagggcaacttcaagaacctgcgcg
		agttcgtgtttaagaacatcgacggctacttcaagatctacagcaagcacaccctatcaacctcgagcgggatctgcctcagggcttctctgct
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		agcagcagcggatggacagctggtgccgccgcttactatgtgggctacctgcagcctagaacctttcctgctgaagtacaacgagaacggcac
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		tcgcctctgtgtacgcctggaaccggaagcggatcagcaattgcgtggccgactactccgtgatctacaacttcgccccttcttcgcattcaag
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		cggcgtgggccaccagccctacagagtggtggtgctgagcttcgaactgctgcatgcccctgccacagtgtgcggccctaagaaaagcacc

	aatctcgtgaagaacaaatgcgtgaacttcaacttcaaccggcctgaccggcaccggcgtgctgacagaggagcaacaagaagttcctgccatt
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	ccaccgacaacaccttcgtgtctggcaactgcgacgtcgtgatcggcattgtgaacaataccgtgtacgacgccctctgcagcccgagctggaca
	gcttcaaagaggaactggacaagtacttaagaaccacacaagccccgacgtggacctgggcgatatcagcggaatcaatgcccagcgtcgt
	gaacatccagaaagagatcgaccggctgaacgaggtggccaagaatctgaacgagagcctgatcgacctgcaagaactgggggaagtacg
	agcagtacatcaagtggccctggtacatctggctgggctttatcgccggactgattgccatcgtgatggtcacaatcatgctgtgttgcatgacc
	agctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagccgtgctgaagggcgtgaa
	actgcactacacatgatga

161	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.1.5 variant	Agaauaaacuaguauucuucugguccccacagacucagagagaaacccgccaccauguucguguuccuggugcugccucugg uguccagccaguguguugaaccugaucaccagaacacagucauacaccaacagcuuuaccagaggcguguacuaccccgacaaggu guucagauccagcgugcugcacucuaccccaggaccuguuccugccuuucuucagcaacgugaccugguuccacgccauccacgug uccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgacgggguguacuuugccagcaccgagaaguccaa caucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcugcugaucgugaacaacgccaccaacgugguc aucaaagugugcgaguuccaguucugcaacgaccccuucuccuggacgucuaccagaagaacaacaagagcuggaugaaagcgag uuccggguguacagcagcgccaacaacaacugcaccuucgaguacgugucccagccuuuccugauggaccuggaaggcaaggagggca acuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccuaucaaccucga gcgggaucugccucagggcuucucugcucuggaaccccuggugaucugcccaucggcaucaacaucacccgguuucagacacug cuggcccugcacagaagcuaccugacaccuguggauagcagcagcggaugggacagcuggugccgccgcgcuuuacuauguggguacc ugcagccuagaaacccuucccugcugaaguacaacgagaacggcaccaucaccgacgccguggaauugugcucuggaauccucugagcga gacaaagugcaccccugaaguccuucaccguggaaaagggcaucuaccagaccaacuuccgggugcagcccaccgaauccaucg ugcgguucccaauaucaccaaucugugcccccuuccacgagguguucaaugccaccaccuucgccucugugcuacgccuggaaccgg aagcggaucagcaauugcguggccgacuacucccgugaucuacaacuucgccccccuucucgcauucaagugcuacggcguguccc cuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugaucccgggaaacgaagugucacagauugcccc uggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccuggaacagcaacaag cuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggacaucu ccaccgagaucuaucaggccggcaacaagccuuguaacggcguggcaggccccaacugcuacagcccaccagucccaacggcuuu aggcccacauacggcgugggccaccagcccuacagagugguggugcugagcuucgaacugcugcaugccccugccacaguguggcg gcccuaagaaaagcaccaauccucgugaagaacaaauggcgugaacuucaacuucaacggccugaccggcacccggcgugcugacaga gagcaacaagaaguuccugccaauuccagcaguuuuggccgggauaucgccgauaccacagacgccguuuagagaucccccagacacug gaaauccuggacaucacccccuugcagcuucggcggaguucugugaucaccccuggcaccaacaccagcaaucaggugguggcagugc uguaccagggcgugaacuguaccgaagugcccguggccaauucacgccgaucagcugacaccuacaauggcgggugguacuccaccgg cagcaauguguuucagacgagccggcugucugaucgguccgaguacgugaacaauagcuacgagugcgacaucccccaucggc gcuggaaucugccgccagcuaccagacacagaaagagccaccggagagccaggaagcguggccagccagagcaucauugccuacac aaugucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuauccccaccaacuucaccaucagcgugaccacag agauccugccuguguccaugaccaagaccagcguggacugcaccauguacaucugcggcgauuccaccgagugcuccaaccugcu

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		uuagcaauaaacgaaaguuuuaacuaagcuauacuaaccccagggguuggucaauuucgugccagccacaccccuggagcuagcaaa
		aaaa

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	aaaaaaaaaaaaaaa

Table 16B. Sequence of one embodiment of an exemplary Omicron XBB.1.16-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
163	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron XBB.1.16 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 982 and 983 of SEQ ID NO: 163)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPALPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYQKNNKSWM ESEFRVYSSANNCTFEYVSQPFLMDLVGKEGNFKNLREFVFKNIDGYFKIYSKHTPINLERDLPQGFSALEPLVDL PIGINITRFQTLLALHRSYLTPVDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS FTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVIYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKPSGNYNYLYRL FRKSKLKPFERDISTEIYQAGNRPCNGVAGPNCYSPLQSYGFRPTYGVGHQPYRVVVLSFELLHAPATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
164	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.1.16 variant	Auguucguguuccuggugcugcugccucugguguccagccagugugugaaccugaucaccagaacacagucauacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccuggcuuccacgccauccacguguccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgac ggggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacguggucaucaaagugugcgaguuccaguucugcaacgaccccuuccuggacgucuacca gaagaacaacaagagcuggauggaaagcgaguuccgggguguacagcagcgccaacaacugcaccuucgaguacgugucccagccu uuccugauggaccugGUGggcaaggagggcaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaa gaucuacagcaagcacaccccuaucaaccucgagcgggaucugccucagggcuucucugcucuggaaccccugguggaucugccc

		aucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacaccuguggauagcagcggauugga
		cagcuggugccgccgcuuacuauguggguaccugcagccuagaaccuucccugcugaaguacaacgagaacggcaccaucaccga
		cgccguggauuguguccuggaucccucgagcgagacaaaguugcacccugaaguccuucaccguggaaaagggcaucuaccagacc
		agcaacuucccgggugcagcccaccgaauccaucgugcgguucccaauaucaccaauucugugcccuucccacgagguguucaaugc
		caccaccuucgccucuguguacgccuggaaccggaagcggaucagcaauugcguggccgacuacuccgugaucuacaacuucgcc
		cccuucuucgcauucaaguguacggcguguccccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucg
		ugauccgggaaacgaagugucacagauugccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuu
		caccggcuguguguuguggaacagcaacaagcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccgg
		aaguccaagcugaagccuucgagcgggacaucuccaccgagaucuaucaggccggcaacAGGccuuguaacggcguggcaggc
		cccaacugcuacagcccaccugcaguccuacggcuuuaggcccacauacggcgugggccaccagcccuacagaguggugguga
		gcuucgaacugcugcaugccccugccacaguugugcggcccuaagaaaagcaccaaucucgugaagaacaaaugcgugaacuucaa
		cuucaacggccugaccggcaccggcgugcugacagagagcaacaagaaguuccugccauuccagcaguuuggccgggauaucgcc
		gauaccacagacgccguuagagaucccccagacacuggaaauccuggacaucacccuugcagcuucggcggagugucugugauca
		ccccuggcaccaacaccagcaaucagguggcagugcuguaccagggcgugaacuguaccgaagugcccguggccauucacgccga
		ucagcugacaccuacaugggcggguguacuccaccggcagcaauguguuucagaccagagccggcugucugaucggagccgaguac
		gugaacaauagcuacgagugcgacauccccaucggcgcuggaaucugcgccagcuaccagacacagacaaagagccaccggagag
		ccagaagcguggccagccagagcaucauugccuacacaaugucucugggcgccgagaacagcguggccuacuccaacaacucuau
		cgcuaucccccaccaacuucaccaucagcgugaccacagagauccugccuguguccaugaccaagaccagcguggacugcaccaugu
		acaucugcggcgauuccaccgagugcuccaaccugcugcugcaguacggcagcuucugcacccagcugaaaagagcccugacagg
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		cacaagcggcuggacauuuggagcaggccgccgcucugcagauccccuuugcuaugcagauggccuaccggcuucaacggcaucgga
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		gcagcacagcaagcgccccuggaaagcugcaggacgugugucaaccacacaaugcccaggcacugaacacccccuggucaagcagcugucc
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		ugaucacaggcagacugcagaggccuccagacacuacgugacccagcagcugaucagagccgccgagauuagaggccucugccaaucu
		ggccgccaccaagaugucugaguguguugcugggccagaagcaagagaguggacuauuugcggcaagggcuaccaccugaugagcuu
		cccucagucugccccucacggcgugguguuuucugcacgugacauaugugcccgcucaagagaagaauuucaccaccgcuccagcc
		aucugccacgacggcaaagcccacuuuccuagagaaggcguguucgugucccaacggcacccauugguucgugacacagcggaacu
		ucuacgagccccagaucaucaccaccgacaacaccuucguguucuggcaacugcgacgucgugaucgugcauuguugaacaauaccgu
		guacgacccucugcagcccgagcuggacagcuucaaagaggaacuggacaaguacuuuaagaaccacacaagcccgacguggac
		cugggcgauaucagcggaaucaaugccagcgucgugaacauccagaaagagaucgaccggcugaacgaggugggccaagaaucug
		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggcccugguacaucuggcugggcuuuauc
		gccggacugauugccaucgugaugucacaaucaugcugugguugcaugaccagcugcuguagccugaagggcguuguuagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggcgugaaacugcacuacacaugauga
165	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.1.16 variant	Atgttcgtgttcctggtgctgctgcctctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactaccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgc
		catccacgtgtccggcaccaatggcaccaagagattcgacaaccccgccctgcccttcaacgacgggtgtactttgccagcaccgagaagt
		ccaacatcatcagaggctggatcttcggcaccacactggacagcaagacccagagcctgctgatcgtgaacaacgccaccaacgtggtcatc
		aaagtgtgcgagttccagttctgcaacgaccccttcctggacgtctaccagaagaacacaagagctggatggaaagcgagttccgggtgta
		cagcagcgccaacacaactgcaccttcgagtacgtgtcccagccttcctgatggacctgGTGggcaaggagggcaacttcaagaacctgcgc
		gagttcgtgtttaagaacatcgacggctacttcaagatctacagcaagcacaccctatcaacctgagcgggatctgcctcagggcttctctg
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		agaacacccaagaggtgttcgcccaagtgaagcagatctacaagaccccctcctatcaagtacttcggcggcttcaatttcagccagattctgcc
		cgatcctagcaagcccagcaagcggagcttcatgaggacctgctgttcaacaaagtgacactggccgacgccggcttcatcaagcagtatg
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		atcggcaagatccaggacagcctgagcagcacagcaagcgccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaa
		caccctggtcaagcagctgtcctccaagttcggcgccatcagctctgtgctgaacgatatctctgagcagactggaccctcctgaggccgaggt
		gcagatcgacagactgatcacaggcagactgcagagcctccagacatacgtgacccagcagctgatcagagccgccgagattagaggcctct
		gccaatctggccgccaccaagatgtctgagtgtgtgctgggccagagcaagagagtggactttttgcggcaagggctaccacctgatgagctt
		ccctcagtctgccctcacggcgtggtgtttctgcacgtgacatatgtgcccgctcaagagaagaatttcaccaccgctccagccatctgccacg
		acggcaaagcccacttctagagaaggcgttcgtgtccaacggcacccattggttcgtgacacagcggaacttctacgagccccagatca
		tcaccaccgacaacaccttcgtgtctggcaactgcgacgtcgtgatcggcattgtgaacaataccgtgtacgaccctctgcagcccgagctgg
		acagcttcaaagaggaactggacaagtactttaagaaccacacaagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgt
		cgtgaacatccagaaagagatcgaccggctgaacgaggtggccaagaatctgaacgagagcctgatcgacctgcaagaactgggaagt
		acgagcagtacatcaagtggccctggtacatctggctgggcttttatcgccggactgattgccatcgtgatggtcacaatcatgctgttgttgcatg
		accagctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgt
		gaaactgcactacacatgatga

166	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.1.16 variant	Agaauaaacuaguauuucuucugguccccacagacucagagagaaacccgccaccauguucguguuccuggugcugccucugg uguccagccaguguugugaaccugaucaccagaacacagucauacacaacagcuuuaccagaggcguguacuaccccgacaaggu guucagauccagcgugcugcacucuaccccaggaccuguuccugccuuucuucagcaacgugaccugguuccacgccauccacgug uccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgacgggguguacuuugccagcaccgagaaguccaa caucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcugaucgugaacaacgccaccaacguggguc aucaaagugugccgaguuccaguucugcaacgacccccuuccuggacgucuaccagaagaacaacaagagcuggaaagcgag uuccggguguacagcagcgccaacaacaacugcaccuucgaguacguguccccagccuuuccugauggaccugGUGggcaaggagggc aacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacaccccuaucaaccucg agcgggaucugccucagggcuucucugcucuggugguggaucugcccaucacgacaucaacaucacccgguuucagacacu gcuggcccugcacagaagcuaccugacaccuggaauggacagcuggugccgccgcuuacuauguggggcua ccugcagccuagaaaccuuccugcugaaguacaacgagaacggcaccaucaccgacgccguggaauugugcucuggaauccucugagc gagacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagacaccaacuuccgggugcagcccaccgaaucca ucgugcgguucccccaauaucaccaaucugugcccccuuccacgagguguucaaugccaccgccaccuucgcccucugugcgccuggaa ccggaagcggaucagcaauugcgugggccgacuacuccgugaucuacaacuucgccccccuucuucgcauucaagugcuacggcgug uccccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugaucccgggggaaacgaaguguucacagauug ccccuggacagacaggcaacaucgccgacuacuacaacuacaagcugcccgacgacuucaccggcugugugaauugccuggaacagcaac aagcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggaca ucucccaccgagaucuaucaggccggcaacAGGccuuguaaacggcgcuggcaggcccccaacugcuacagcccacugcaguccuacgg cuuuaggcccacauacggcguggggccacccagcccuacagaguggguggugcugagcuucgaacugcugcaugccccugccacagug ugcggcccuaagaaaagcaccaaucucgugaagaacaaaaugcgugaacuucaacaauccgaccggccugacccggcgcacggcuga cagagagcaacaagaaguuccugccauuccagcaguuuggccgggauaucgccgauaccacagacgccguuagagauccccagac acuggaaauccuggacaucacccccuugcagcuucggcggagugucugugaucacccccuggcaccaacaccagcaaucagguggca gugcuguaccagggcgugaacuguaccgaaguugcccguggccauucacgccgaucagcugcacaccuacaauggcgggguguacucca ccggcagcaauguguuucagaccagagccggcugucugaucggagccgaguacgugaacaauagcuacgagugcgacaucccccau cggcgcuggaaucugccgccagcuaccagacacagacaaagagccaccggagagccagaagcguggccagccagagcaucauugcc uacacaaugucucugggcgccgagaacagcguggccuacuccaacaacucuauucgcuauccccaccaacuucaccaucagcgugac cacagagauccugccuguguccaugaccaagaccagcguggacugcaccauguacaucugcggcgauuccaccgagugcuccaac

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		agguguucgcccaagugaagcagaucuacaagacccccuccuaucaaguacuucggcggcuucaaauuucagccagauucugcccga
		uccuagcaagcccagcaagcggagcuucaucgaggaccugcuguucaacaaagugacacuggccgacgccggcuucaucaagcag
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		auucugagcccgugcugaagggcgugaaacugcacuacacaugaugacucgagcugguacugcaugcaaugcuagcugcc
		ccuuucccguccuggguaccccgagucucccccgaccucgggucccagguaugcucccaccucccaccucccacucaccaccucug
		cuaguuccagacaccucccaagcacgcagcaaugcagcucaaaacgcuuagccuagccacaccccccacgggaaacagcagugauua
		accuuuagcaauaaacgaaaguuuaacuaagcuauacuaaccccagggcuuggucaauuucgugccagccacaccccuggagcuagc
		aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
		aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
		aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
167	Full length DNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.1.16 variant	Agaataaactagtattcttctggtcccacagactcagagagaacccgccaccatgttcgtgttcctggtgctgctcctggtgtccagccag
		tgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagaggcgtgtactaccccgacaaggtgttcagatccagcgtgctg
		cactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgccatccacgtgtccggcaccaatggcaccaagagattcga

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	ccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaacacctggtcaagcagctgtcctccaagttcggcgccatcagc
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	gacatacgtgacccagcagctgatcagagccgccgagattagagcctctgccaatctggccgccaccaagatgtctgagtgtgtgctgggcc
	agagcaagagagtggactttgcggcaagggctaccacctgatgagcttccctcagtctgcccctcacggcgtggtgtttctgcacgtgacata
	tgtgcccgctcaagagaagaatttcaccaccgctccagccatctgccacgacggcaaagcccacttcctagagaaggcgtgttcgtgtccaa
	cggcacccattggttcgtgacacagcggaacttctacgagcccagatcatcaccaccgacaacacctttcgtgtctggcaactgcgacgtcgt
	gatcggcattgtgaacaataccgtgtacgaccctctgcagcccgagctggacagcttcaaagaggaactggacaagtactttaagaaccaca
	caagccccgacgtggacctgggcgatatcagcggaatcaatgccagcgtcgtgaacatccagaaaagagatcgaccggctgaacgaggtgg
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	gctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgtgaaactgcactacacatgatgactcgagctggtactgcatgca
	cgcaatgctagctgcccctttcccgtcctgggtacccgagtctcccccgacctcgggtcccaggtatgctcccacctccacctgccccactcacc
	acctctgctagttccagacacctcccaagcacgcagcaatgcagctcaaaacgcttagcctagccacaccccacgggaaacagcagtgatt
	aacctttagcaataaacgaaagtttaactaagctatactaacccagggttggtcaatttcgtgccagccacaccctggagctagcaaaaaaa
	aaaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
	aaaaaaaaaaaaaaaaa

Table 16C. Sequence of one embodiment of an exemplary Omicron XBB.2.3-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
168	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron XBB.2.3 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 982 and 983 of SEQ ID NO: 168)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPALPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYQKNNKSWM ESEFRVYSSANNCTFEYVSQPFLMDLEGKEGNFKNLREFVFKNIDGYFKIYSKHTPINLERDLPQGFSALEPLVDL PIGINITRFQTLLALHRSYLTPGGSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS FTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVIYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKPSGNYNYLYRL FRKSKLKPFERDISTEIYQAGNKPCNGVAGPNCYSPLQSYGFRPTYGVGHQPYRVVVLSFELLHASATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
169	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3 variant	auguucguguuccuggugcugcucugguguccagccaguguggugaaccugaucaccagaacacagucaucaacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccuggguuccacgccauccacgugucccggcaccaauggcaccaagagauucgacaacccccgcccugccccuucaacgac gggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacguggucaucaaaguguucgagauuccaguucugcaacgacccccuuccuggacgucuacca gaagaacacaagagcuggaauggaaagcgaguucccggguguacagcagccgccaacaacugcaccuucgaguacguguucccagccu uuccugauggaccuggaaggcaaggagggcaacuucaagaaccugcgcgaguucgugguuuaagaacaucgacggcuacuucaag

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		ucggcaucaacaucacccgguuucagacacugcuggccccugcacagaagcuaccugacaccuggcggcagcagcgaggauggac
		agcugguccgccgcuuacuauguggguaccugcagccuagaaccuuccugcugaaguacaacgagaacggcaccaucaccgac
		gccguggauugugcucuggaauccucugagcgagacaaagugcacccugaaguccuucaccguggaaaagggcaucuaccagacca
		gcaacuuccgggugcagcccaccgaauccaucgugcgguucccaauaucaccaaucugugccccuuccacgagguguucaaugcc
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		gauccgggaaacgaaguucacagaauugcccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuuc
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		uaccacagacgccguuagagaucccagacacuggaaauccuggacaucacccccuugcagcuucggcggaguucugugaucacc
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		ggccgccaccaagaugucugaguguggugcugggccagagcaagagaguggacuuuugcggcaagggcuaccaccugaugagcuu
		cccucagucugccccucacggcguggguuuucugcacgugacauauguggcccgcucaagagaagaauuucaccaccgcuccagcc
		aucugccacgacggcaaagcccacuuuccuagagaaggcguguucguguccaacggcacccauugguucgugacacagcggaacu
		ucuacgagccccagaucaucaccaccgacaacaccuucgugucuggcaacugcgacgucgugaucggcauugugaacaauaccgu
		guacgacccucugcagcccgagcuggacagcuucaaagaggaacuggacaaguacuuuaagaaccacacaagccccgacguggac
		cugggcgauaucagcggaaucaaugccagcgucgugaacauccagaaagagaucgaccggcugaacgagguggccaagaaucug
		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggcccuggguacaucuggcugggcuuuauc
		gccggacugauugccaucgugaugucacaaucaugcuguguugcaugaccagcugcuguagccugcugaagggcuguuguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggcgugaaacugcacuacacaugauga
170	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3 variant	atgttcgtgttcctggtgctgctgccucgtgtccagccagugugaacctgaucaccagaacacagucauacaccaacagcuuuaccagagg
		cgugucuacaccccgacaaggugucaguccuacagcgugcugcacucuaccaggacuucugguccuucuucaacaacgugacuuggu
		catccacgugucccggcaccaaugacaagagauucgacaaccccgccugccuucaacgacgggguguacuucgccagcaccgagaagu
		ccaacaucaucagaggcugcuucaucgaccgcaucaacgagguguucgugcgcgugggcgaccugaaccacgugaacaacgaccuga
		aaagugugcgaguucgaccaccccaucaccgacaucgccgaggagcccgacaccuucccuagcgacaacgaccuggugcccaagaucg
		cagcagcgccaacaacugcaccuucgaguacgugcaccagcccuucuugaccgacgaccacgugcacaccaugcugcagcccaagacc
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	gcttcaaagaggaactggacaagtactttaagaaccacacaagcccccgacgtggacctgggcgatatcagcggaatcaatgccagcgtcgt
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	agcagtacatcaagtggccctggtacatctggctgggctttatcgccggactgattgccatcgtgatggtcacaatcatgctgtgttgcatgacc
	agctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgtgaa
	actgcactacacatgatga

171	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3 variant	Agaauaaaacuaguauucuucugguccccacagacucagagagaacccgccaccauguucguguuccuggugcugccuccugg uguccagccagugugugaaccugaucaccagaacacagucauacaccaacagcuuuaccagaggcguguacuaccccgacaaaggu guucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuucagcaacgugaccugguuccacgccauccacgug uccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgacgggguguacuuugccagcaccgagaaguccaa caucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagccugcugaucguguacaacgccaccaacguggguc aucaaagugugcgaguuccaguucugcaacgaccccuucuccuggacgucuaccagaagaacacaagagcuggaugguaaagcgag uuccggguguacagcagcgccaacaacugccaccuucgaguacgugucccagccuuuccugauggaccuggaaggcaaggagggca acuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacaccccuaucaaccucga gcgggaucugccucagggcuucucugcucuggaacccuggguggaucugcccaucggcaucaacaucaccgguuucagacacug cuggcccugcacagaagcuaccugacaccuggcggcagcagcggauggacagcuggugccgccgcuuacuauguggcuacc ugcagccuagaaccuucccugcugaaguacaacgagaacggcaccaucaccgacgccguggaauugugcucuggaguccucugagcga gacaaagugcacccugaaguccuucaccguggaaaagggcaucuaccagaccagcaacuucgggugcagcccaccgaauccaucg ugcgguucccaauaucaccaaucugugcccccuuccacgagguguucaaugccaccaccuucgccucuguguacgccuggaaccgg aagcggaucagcaauugcguggccgacuacuccgugauucuacaacuucgcccccuucuucgcauucaagugcuacggcgugucccc cuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugauccgggggaaacgaaguguucacagauugcccc uggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugauugccuggaacagcaacaag cuggacuccaaacccagcggcaacuacaauaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggacaucu ccaccgagaucuaucaggccggcaacaagccuuguaacggcgugggcaggcccccaacugcuacagcccacugcaguccuacggcuuu aggcccacauacggcgugggccaccagcccuacagaguggugugcugagcuucgaacugcugcaugccucagccacagugugcg gcccuaagaaaagcaccaauucucgugaagaacaaaugcgugaaacuucaacuucaacggccugaccggcacccggcgugcugacaga gagcaacaagaaguuccugccaauccagcaguuuggcccgggauauucgccgauaccacagacgccguuagagauccccagacacug gaaauccuggacaucacccccuugcagcuucggcggagugucugugaucacccccuggcaccaacacccagcaaucagguggcagugc uguaccagggcgugaacuguaccgaaguggcccguuggccaauucacgccgaucagcugacaccuacauggcgggugguacuccaccgg cagcaauguguuucagaccagagccggcugucugaucggagccgaguacgugaacaauagcuacgagugcgacaucccccaucggc gcuggaaucugcgccagcuaccagacacagacaaagagccaccggagagccagaagcguggccagccagagcaucauugccuacac aaugucucugggcgccgagaacagcguggccuacuccaacaacucuaucgcuauccccaccaacuucaccaucagcgugaccacag agauccugccuguguccaugaccaagaccagcuggacugcaccauguacaucugcggcgauuccaccgagugcucccaaccugcu

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		agagcaagagaguggacuuuugcggcaagggcuaccaccugaugagcuuccucagucugccccucacggcgugguguuucugc
		acgugacauaugugcccgcucaagagaagaauuucaccaccgcuccagccaucugccacgacggcaaagcccacuuuccuagagaa
		ggcguguucguccaacggcacccauuggguucgugacacagcggaacuucuacgagcccagaucaucaccaccgacaacaccu
		ucgugucuggcaacugcgacgucgugaucggcauugugaacaauaccguguacgacccucugcagcccgagcuggacagcuucaa
		agaggaacuggacaaguacuuuaagaaccacacaagcccgacguggaccuggggcgauaucagcggaaucaaugccagcgucgu
		gaacauccagaaagagaucgaccggcugaacgagguggccaagaaucugaacgagagccugaucgaccugcaagaacuggggaa
		guacgagcaguacaucaagugggcccuggguacaucuggcuggcuuuaucgccggacugauugccaucgugauggucacaaucau
		gcuguguugcaugaccagcugcuguagccugaagggcuguuguagcuguggcagcugcugcaaguucgacgaggacgauu
		cugagcccgugcugaagggcgugaaacugcacuacacaugaugacucgagcugguacugcaugcacgcaaugcuagcugccccuu
		ucccguccuggguaccccgagucucccccgaccucgggucccagguaugcucccaccuccacccugcccacucacccaccucugcuag
		uuccagacaccucccaagcacgcagcaaugcagcucaaaacgcuuagccuagccacaccccccacgggaaacagcagugauuaaccu
		uuagcaauaaacgaaagguuuaacuaagcuauacuaaccccagggcuuggucaauucguggccagccacacccuggagcuagcaaa
		aaaa

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	ccctgggaaagctgcaggacgtggtcaaccacaatgcccaggcactgaacaccctggtcaagcagctgtcctccaagttcggcgccatcagc
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	cggcacccattggttcgtgacacagcggaacttctacgagccccagatcatcaccaccgacaacacctttcgtgtctggcaactgcgacgtcgt
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	aaaaaaaaaaaaaaaaaaaaagcatatgactaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
	aaaaaaaaaaaaaaaaa

Table 16D. Sequence of one embodiment of an exemplary Omicron XBB.2.3.2-specific RNA vaccine

SEQ ID NO.	Brief Description	Sequence
173	Amino acid sequence of RNA-encoded SARS-CoV-2 S protein from an Omicron XBB.2.3.2 variant (with PRO mutations at positions corresponding to K986P and V987P of SEQ ID NO: 1; i.e., PRO mutations at positions 982 and 983 of SEQ ID NO: 173)	MFVFLVLLPLVSSQCVNLITRTQSYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKR FDNPALPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLDVYQKNNKSWM ESEFRVYSSANNCTFEYVSQPFLMDLEGKEVNFKNLREFVFKNIDGYFKIYSKHTPINLERDLPQGFSALEPLVDL PIGINITRFQTLLALHRSYLTPGGSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKS FTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFHEVFNATTFASVYAWNRKRISNCVADYSVIYNFAPFFAFKCYG VSPTKLNDLCFTNVYADSFVIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKPSGNYNYLYRL FRKSKLKPFERDISTEIYQAGNKPCNGVAGPNCYSPLQSYGFRPTYGVGHQPYRVVVLSFELLHASATVCGPKKS TNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTS NQVAVLYQGVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEYVNNSYECDIPIGAGICASYQTQTK SHRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQ YGSFCTQLKRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKYFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADA GFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRF NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNHNAQALNTLVKQLSSKFGAISSVLNDIL SRLDPPEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSA PHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVI GIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKY EQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT
174	RNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3.2 variant	auguucguguuccuggugcugcugccucugguguccagccagugugugaaccugaucaccagaacacagucauacaccaacagc uuuaccagaggcguguacuaccccgacaagguguucagauccagcgugcugcacucuacccaggaccuguuccugccuuucuuca gcaacgugaccugguuccacgccauccacguguccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgac ggggguguacuuugccagcaccgagaaguccaacaucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcc ugcugaucgugaacaacgccaccaacguggucaucaaagugugcgaguuccaguucugcaacgaccccuuccuggacgucuacca gaagaacaacaagagcuggauggaaagcgaguuccggguguacagcagcgccaacaacugcaccuucgaguacgugucccagccu uuccugauggaccuggaaggcaaggaggugaacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaag aucuacagcaagcacaccccuaucaaccucgagcgggaucugccucagggcuucucugcucuggaaccccugguggaucugccca

	ucggcaucaacaucacccgguuucagacacugcuggcccugcacagaagcuaccugacaccuggcggcagcagcggauggac
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	gccguggaauuguguccuggauccucugagcgagacaaaguugcacccugaaguccuucaccgugguaaaagggcaucuaccagacca
	gcaacuuccgggugcagcccaccgaauccaucgugcgguuccccaauaucaccaauucugugcccccuuccacgaggugguucaaugcc
	accaccuucgccucuguguacgccuggaaccggaagcggaucagcaauugcguggccgacuacucccgugaucuacaacuucgccc
	ccuucuucgcauucaagugcuacggcguguccccuaccaagcugaacgaccugugcuucacaaacgguacgccgacagcuucgu
	gauccggggaaacgaagugucacagauugccccuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuuc
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	uaccacagacgccguuagagaucccagacacuggaaauccuggacaucacccccuugcagcuucggcggagugucugugaucacc
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	aucgccguggaacaggacaagaacacccaagagguguucgcccaaguguacagaagcagaucuacaagaccccuccuaucaaguacuucg
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	acaagcggcuggacauuuggagcaggcgccgcucugcagauccccuuugcuaugcagauggccuaccggcuucaacggcaucgga
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	gcagcacagcaagcgcccuggaaagcugcaggacgugggucaaccacaaugcccaggcacugaacacccuggucaagcagcugucc
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		ggccgccaccaagauucugagugugugcugggccagagcaagaagaguggacuuuuugcggcaaggcuaccaccugaugagcuu
		cccucagucugccccucacggcgugguguuucugcacgugacauaugugcccgcucaagagaagaauuucaccaccgcuccagcc
		aucugccacgacggcaaagcccaccacuuuccuagagaagcguguucguccaacggcacccauuggguucgugacacagcggaacu
		ucuacgagcccagaucaucaccaccgacaacaccuucguguucuggcaacugcgacgucgugaucggcauugugaacaauaccgu
		guacgacccucugcagcccgagcuggacagcuucaaagaggaacuggacaaguacuuuaagaaccacacaagccccgacguggac
		cugggcgauaucagcggaaucaaugccagcgucgugaacaucccagaaagagaucgaccggcugaacgagguggccaagaaucug
		aacgagagccugaucgaccugcaagaacuggggaaguacgagcaguacaucaaguggcccugguacaucuggcuggggcuuuauc
		gccggacugauugccaucgugauggucacaaucaugcugugugcaugaccagcugcuguagccugaagggcuguuguagc
		uguggcagcugcugcaaguucgacgaggacgauucugagcccgugcugaagggcgugaaacugcacuacacaugauga
175	DNA sequence encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3.2 variant	atgttcgtgttcctggtgctgctgcctctggtgtccagccagtgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagagg
		cgtgtactaccccgacaaggtgttcagatccagcgtgctgcactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgc
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		ccaccgacaacaccttcgtgtctggcaactgcgacgtcgtgatcggcattgtgaacaataccgtgtacgacctctgcagcccgagctggaca
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		agctgctgtagctgcctgaagggctgttgtagctgtggcagctgctgcaagttcgacgaggacgattctgagcccgtgctgaagggcgtgaa
		actgcactacacatgatga

176	Full length RNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3.2 variant	Agaauaaacuaguauucuucuggucccccacagacucagagagaaacccgccaccauguucguguuccuggugcugccuccucugg uguccagccaguguguugaaccugaucaccagaacacagucauacaccaacagcuuuaccagaggcguguacuaccccgacaaaggu guucagauccagcgugcugcacucuacccaggaccuguuccugccuuuucuucagcaacgugaccugguuccacgccaucccacgug uccggcaccaauggcaccaagagauucgacaaccccgcccugcccuucaacgacgggguguacuuugccagcaccgagaagucccaa caucaucagaggcuggaucuucggcaccacacuggacagcaagacccagagcugcugaucgugaacaacgccaccaacguggguc aucaaagugugcgaguuccaguucugcaacgacccccuuccuggacgucuaccagaagaacacaagagcuggauggaaagcgag uuccggguguacagcagcgccaacaacugcaccuucgaguacgugucccagccuuuccugauggaccuggaaggcaaggaggug aacuucaagaaccugcgcgaguucguguuuaagaacaucgacggcuacuucaagaucuacagcaagcacacccccuaucaaccucg agcgggaucugccucagggcuucucugcucuggaaccccuggugaucugcccaucggcaucaacaucacccgguuucagacacu gcuggcccugcacagaagcuaccugacaccuggcggcagcagcggauggacagcuggugccgccgccguuacuauguggguuac cugcagccuagaaccuucccugcugaaguacaacgagaacggcaccaucaccgacgccguggaauugugcucuggaucccucugagcg agacaaagugcacccugaaguccuucaccgugggaaaagggcaucuaccagacaacuuccgggugcagcccacccgaauccaauc gugcgguucccaauaucaccaaucugugcccccuuccacgagguguucaaugccaccaccuucgccucuguguacgccuggaaccg gaagcggaucagcaauugcguggccgacuaccuccgugaucuacaacuucgcccccuucucgcauucaagugcuacggcgugucc ccuaccaagcugaacgaccugugcuucacaaacguguacgccgacagcuucgugaucccgggaaacgaagugucacagauugccc cuggacagacaggcaacaucgccgacuacaacuacaagcugcccgacgacuucaccggcugugugaauugccuggaacagcaacaa gcuggacuccaaacccagcggcaacuacaauuaccuguaccggcuguuccggaaguccaagcugaagcccuucgagcgggacauc uccaccgagaucuaucaggccggcaacaagccuuguaacggcgugggcaggcccccaacugcuacagcccacugcaguccuacggcuu uaggcccacauacggcguggggccaccagcccuacagagugguggugcugagcuucgaacugcugcaugccucagccacagugugc ggcccuaagaaaagcaccaaucucgugaagaacaaaugcgugaacuucaacuucaacggccugaccggcacccggcgugcugacag agagcaacaagaaguuccugccaauucccagcaguuuggcccgggauaucgccgauaccacagacgccguuagagauccccagacacu ggaaauccuggacaucacccccuugcagcuucggcggaguucugugaucacccccuggcaccaacaccagcaaucaggugggcagug cuguaccagggcgugaacuguuaccgaagugcccguggccaauccacgccgaucugacaccuacaugggcgggguguacuccaccg gcagcaauguguuucagaccagagcccggcugucugaucggagccgaguacgugaacaauagcuacgagugcgacaucccccaucg gcgcuggaaucugcgccagcuaccagacacagacaaagagccaccgggagccagaagcgugggccagccagagcaucauuugccua cacaaugucucugggcgccgagaacagcguggccuacuccaacucuaucgcuauccccacaacuucaccaucagcgugacca cagagauccugccugugucaaugaccaagacccagcguggacugcaccauguacaucugcggcgaauuccaccggagugcuccaaccu

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		cuagcaagcccagcaagcggagcuucaucgaggaccugcuguucaacaaagugacacuggccgacgccggcuucaucaagcagua
		uggcgauugucuggggcgacauugccgccagggaucugauuugcgcccagaaguuuaacggacugacagugcugccuccuucugcu
		gaccgaugagaugaucgcccaguacacaucugccccugcuggccggcacaaucacaagcggcuggacauuuggagcaggcgccgcu
		cugcagauccccuuugcuaugcagauggccuacccgguucaacggcaucgggagugacccagaauugugcuguacgagaaaccagaagc
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		aguacgagcaguacaucaagugggcccugguacaucuggcuuuaucgccggacugauugccaucgugauggucacaauca
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		guuccagacaccucccaagcacgcagcaaugcagcucaaaacgcuuagccuagccacaccccacgggaaacagcagugauuaacc
		uuuagcaauaaacgaaaguuuaacuaagcuauacuaaccccaggguuggucaauuucguggccagccacacccuggagcuagcaa
		aaaaaaaaaaaaaaaaaaaaaaaaaaagcauaugacuaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa
		aaaaaaaaaaaaaaaaaaaaaaa
177	Full length DNA construct encoding a SARS-CoV-2 S protein from an Omicron XBB.2.3.2 variant	Agaataaactagtattcttctgtgtccccacagactcagagagaacccgccaccatgttcgtgttctgctgcctctggtgtccagccag tgtgtgaacctgatcaccagaacacagtcatacaccaacagctttaccagaggcgtgtactaccccgacaaggtgttcagatccagcgtgctg cactctacccaggacctgttcctgccttttcttcagcaacgtgacctggttccacgccatccacgtgtccggcaccaatggcaccaagagattcga

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	aaaaaaaaaaaaaaaa

Tables 8, 9, 12-14, and 16-16D show amino acid sequences of SARS-CoV-2 S proteins encoded by RNAs described herein from different variants with 2 proline substitutions at positions corresponding to K986P and V987P of SEQ ID NO: 1. In some embodiments, an RNA described herein encodes a SARS-CoV-2 S protein as described herein, for example, in some embodiments, as described in Tables 8, 9, 12-14, and 16-16D, without the 2 proline substitutions at positions corresponding to K986P and V987P of SEQ ID NO: 1. In some embodiments, such an RNA described herein encodes a SARS-CoV-2 S protein comprising one or more mutations characteristic of a variant described herein, and further comprising at least four (including, e.g., at least five, at least six, or more) proline mutations. In some embodiments, at least four of such proline mutations include mutations at positions corresponding to residues 817, 892, 899, and 942 of SEQ ID NO: 1, e.g., as described in WO 2021243122 A2, the entire contents of which are incorporated herein by reference in its entirety. In some embodiments, such a SARS-CoV-2 S protein comprising proline substitutions at positions corresponding to residues 817, 892, 899, and 942 of SEQ ID NO: 1, may further comprise proline substitutions at positions corresponding to residues 986 and 987 of SEQ ID NO: 1.

Self-amplifying RNA (saRNA)

[0624] The active principle of a self-amplifying RNA (saRNA) drug substance is a single-stranded RNA, which self-amplifies upon entering a cell, and a coronavirus vaccine antigen is translated thereafter. In contrast to uRNA and modRNA that preferably code for a single protein, the coding region of saRNA contains two open reading frames (ORFs). The 5'-ORF encodes an RNA-dependent RNA polymerase such as Venezuelan equine encephalitis virus (VEEV) RNA-dependent RNA polymerase (replicase). The replicase ORF is followed 3' by a subgenomic promoter and a second ORF encoding an antigen. Furthermore, saRNA UTRs contain 5' and 3' conserved sequence elements (CSEs) required for self-amplification. The saRNA contains common structural elements optimized for maximal efficacy of the RNA as the uRNA (including, e.g., 5'-cap, 5'-UTR, 3'-UTR, poly(A)-tail). In some embodiments, the saRNA preferably contains uridine. In some embodiments, the saRNA comprises one or more nucleoside modifications as described herein. The preferred 5' cap structure is beta-S-ARCA(D1) ($m_2^{7,2'-O}$GppSpG).

[0625] Cytoplasmic delivery of saRNA initiates an alphavirus-like life cycle. However, saRNA does not encode for alphaviral structural proteins required for genome packaging or cell entry, therefore generation of replication competent viral particles is very unlikely or not possible. Replication does not involve any intermediate steps that generate DNA. The use/uptake of saRNA therefore poses no risk of genomic integration or other permanent genetic modification within the target cell. Furthermore, the saRNA itself prevents its persistent replication by effectively activating innate immune response via recognition of dsRNA intermediates.

[0626] Different embodiments of this platform are as follows:

[0627] **RBS004.1 (SEQ ID NO: 24; SEQ ID NO: 7)**

Structure beta-S-ARCA(D1)-replicase-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0628] **RBS004.2 (SEQ ID NO: 25; SEQ ID NO: 7)**

Structure beta-S-ARCA(D1)-replicase-S1S2-PP-FI-A30L70

Encoded antigen Viral spike protein (S protein) of the SARS-CoV-2 (S1S2 full-length protein, sequence variant)

[0629] **BNT162c1; RBS004.3 (SEQ ID NO: 26; SEQ ID NO: 5)**

Structure beta-S-ARCA(D1)-replicase-RBD-GS-Fibritin-FI-A30L70

Encoded antigen Viral spike protein (S protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein)

[0630] **RBS004.4 (SEQ ID NO: 27; SEQ ID NO: 28)**

Structure beta-S-ARCA(D1)-replicase-RBD-GS-Fibritin-TM-FI-A30L70

Encoded antigen Viral spike protein (S protein) of the SARS-CoV-2 (partial sequence, Receptor Binding Domain (RBD) of S1S2 protein)

[0631] Figure 3 schematizes the general structure of the antigen-encoding RNAs.

[0632] In some embodiments, vaccine RNA described herein comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 16, 17, 19, 20, 21, 24, 25, 26, 27, 30, and 32.

[0633] In some embodiments, RNA described herein is formulated in lipid nanoparticles, lipoplex, polyplexes (PLX), lipidated polyplexes (LPLX), liposomes, or polysaccharide nanoparticles. In some embodiments, RNA described herein is preferably formulated in lipid nanoparticles (LNP). In one embodiment, LNP comprise a cationic lipid, a neutral lipid, a steroid, a polymer conjugated lipid; and RNA. In one embodiment, the cationic lipid is ALC-0315, the neutral lipid is DSPC, the steroid is cholesterol, and the polymer conjugated lipid is ALC-0159. The preferred mode of administration is intramuscular administration, more preferably in aqueous cryoprotectant buffer for intramuscular administration. Drug product is a preferably a preservative-free, sterile dispersion of RNA formulated in lipid nanoparticles (LNP) in aqueous cryoprotectant buffer for intramuscular administration.

[0634] In different embodiments, drug product comprises the components shown below, preferably at the proportions or concentrations shown below:

Component	**Function**	**Proportion (mol%)**
ALC-0315 [1]	Functional lipid	47.5
ALC-0159 [2]	Functional lipid	1.8
DSPC [3]	Structural lipid	10.0
Cholesterol, synthetic	Structural lipid	40.7

Component	**Function**	**Concentration (mg/mL)**
Drug Substance	Active	0.5
ALC-0315 [1]	Functional lipid	7.17
ALC-0159 [2]	Functional lipid	0.89
DSPC [3]	Structural lipid	1.56
Cholesterol, synthetic	Structural lipid	3.1
Sucrose	Cryoprotectant	102.69
NaCl	Buffer	6.0
KCl	Buffer	0.15
Na_2HPO_4	Buffer	1.08
KH_2PO_4	Buffer	0.18
Water for injection	Solvent/Vehicle	q.s.

Component	**Function**	**Concentration (mg/mL)**

Drug Substance	Active	1.0
ALC-0315 [1]	Functional lipid	13.56
ALC-0159 [2]	Functional lipid	1.77
DSPC [3]	Structural lipid	3.11
Cholesterol, synthetic	Structural lipid	6.20
Sucrose	Cryoprotectant	102.69
NaCl	Buffer	6.0
KCl	Buffer	0.15
Na2HPO4	Buffer	1.08
KH2PO4	Buffer	0.15
Water for injection	Solvent/Vehicle	q.s.

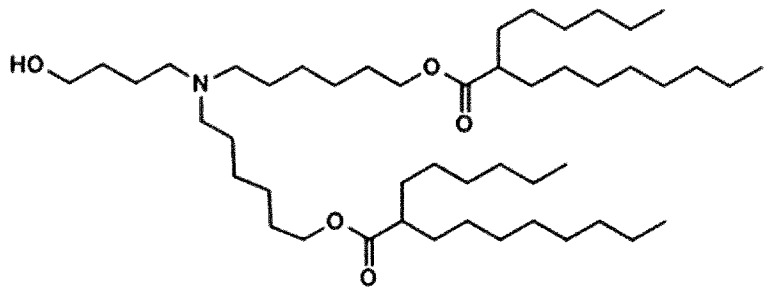
[1] ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) / 6-[N-6-(2-hexyldecanoyloxy)hexyl-N-(4-hydroxybutyl)amino]hexyl 2-hexyldecanoate

[2] ALC-0159 = 2-[(polyethylene glycol)-2000]-*N,N*-ditetradecylacetamide / 2-[2-(ω-methoxy (polyethyleneglycol2000) ethoxy]-N,N-ditetradecylacetamide

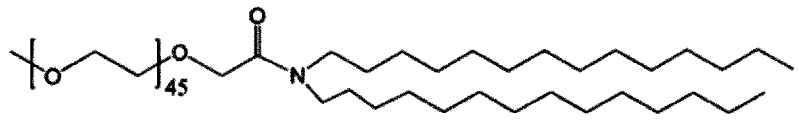
[3] DSPC = 1,2-Distearoyl-*sn*-glycero-3-phosphocholine

q.s. = quantum satis (as much as may suffice)

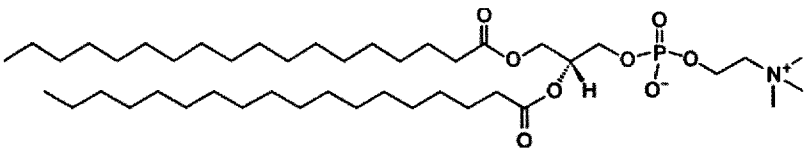
[0635] ALC-0315:



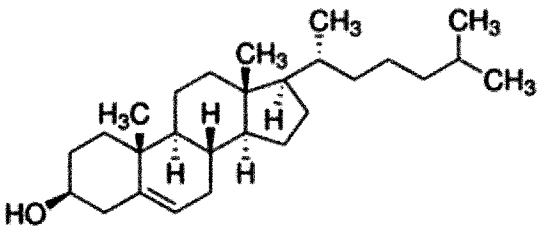
[0636] ALC-0159:



[0637] DSPC:



[0638] Cholesterol:



[0639] In some embodiments, particles disclosed herein are formulated in a solution comprising 10 mM Tris and 10% sucrose, and optionally having a pH of about 7.4. In some embodiments, particles disclosed herein are formulated in a solution comprising about 103 mg/ml sucrose, about 0.20 mg/ml tromethamine (Tris base), and about 1.32 mg/ml Tris.

[0640] In some embodiments, a composition comprises:

(a) about 0.1 mg/mL RNA comprising an open reading frame encoding a polypeptide that comprises a SARS-CoV-2 protein or an immunogenic fragment or variant thereof,

(b) about 1.43 mg/ml ALC-0315,

(c) about 0.18 mg/ml ALC-0159,

(d) about 0.31 mg/ml DSPC,

(e) about 0.62 mg/ml cholesterol,

(f) about 103 mg/ml sucrose,

(g) about 0.20 mg/ml tromethamine (Tris base),

(h) about 1.32 mg/ml Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl), and

(i) q.s. water.

[0641] In one embodiment, the ratio of RNA (e.g., mRNA) to total lipid (N/P) is between 6.0 and 6.5 such as about 6.0 or about 6.3.

Nucleic acid containing particles

[0642] Nucleic acids described herein, such as RNA encoding a vaccine antigen, may be administered formulated as particles.

[0643] In the context of the present disclosure, the term "particle" relates to a structured entity formed by molecules or molecule complexes. In one embodiment, the term "particle" relates to a micro- or nano-sized structure, such as a micro- or nano-sized compact structure dispersed in a medium. In one embodiment, a particle is a nucleic acid containing particle such as a particle comprising DNA, RNA or a mixture thereof.

[0644] Electrostatic interactions between positively charged molecules such as polymers and lipids and negatively charged nucleic acid are involved in particle formation. This results in complexation and spontaneous formation of nucleic acid particles. In one embodiment, a nucleic acid particle is a nanoparticle.

[0645] As used in the present disclosure, "nanoparticle" refers to a particle having an average diameter suitable for parenteral administration.

[0646] A "nucleic acid particle" can be used to deliver nucleic acid to a target site of interest (e.g., cell, tissue, organ, and the like). A nucleic acid particle may be formed from at least one cationic or cationically ionizable lipid or lipid-like material, at least one cationic polymer such as protamine, or a mixture thereof and nucleic acid. In some embodiments, exemplary nanoparticles include lipid nanoparticles, polyplexes (PLX), lipidated polyplexes (LPLX), liposomes, or polysaccharide nanoparticles.

[0647] In some embodiments, RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic

variant thereof is formulated as LNPs. In some embodiments, LNPs comprise one or more cationically ionizable lipids; one or more neutral lipids (e.g., in some embodiments sterol such as, e.g., cholesterol; and/or phospholipids), and one or more polymer-conjugated lipids. In some embodiments, the formulation comprises ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), cholesterol, sucrose, trometamol (Tris), trometamol hydrochloride and water.

[0648] RNA particles described herein include nanoparticles. In some embodiments, exemplary nanoparticles include lipid nanoparticles, lipoplex, polyplexes (PLX), lipidated polyplexes (LPLX), liposomes, or polysaccharide nanoparticles.

[0649] Polyplexes (PLX), polysaccharide nanoparticles, and liposomes, are all delivery technologies that are well known to a person of skill in the art. See, e.g., Lächelt, Ulrich, and Ernst Wagner. "Nucleic acid therapeutics using polyplexes: a journey of 50 years (and beyond)" Chemical reviews 115.19 (2015): 11043-11078; Plucinski, Alexander, Zan Lyu, and Bernhard VKJ Schmidt, "Polysaccharide nanoparticles: from fabrication to applications." Journal of Materials Chemistry B (2021); and Tenchov, Rumiana, et al. "Lipid Nanoparticles– From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement," ACS nano 15.11 (2021): 16982-17015, respectively, the contents of each of which are hereby incorporated by reference herein in their entirety.

[0650] In some embodiments, the concentration of RNA in a pharmaceutical RNA preparation is about 0.1 mg/ml. In some embodiments, the concentration of RNA in a pharmaceutical RNA preparation is about 30 µg/ml to about 100 µg/ml. In some embodiments, the concentration of RNA in a pharmaceutical RNA preparation is about 50 µg/ml to about 100 µg/ml.

[0651] Without intending to be bound by any theory, it is believed that the cationic or cationically ionizable lipid or lipid-like material and/or the cationic polymer combine together with the nucleic acid to form aggregates, and this aggregation results in colloidally stable particles.

[0652] In one embodiment, particles described herein further comprise at least one lipid or lipid-like material other than a cationic or cationically ionizable lipid or lipid-like material, at least one polymer other than a cationic polymer, or a mixture thereof

[0653] In some embodiments, nucleic acid particles comprise more than one type of nucleic acid molecules, where the molecular parameters of the nucleic acid molecules may be similar or different from each other, like with respect to molar mass or fundamental structural elements such as molecular architecture, capping, coding regions or other features.

[0654] Nucleic acid particles described herein may have an average diameter that in one embodiment ranges from about 30 nm to about 1000 nm, from about 50 nm to about 800 nm, from about 70 nm to about 600 nm, from about 90 nm to about 400 nm, or from about 100 nm to about 300 nm.

[0655] Nucleic acid particles described herein may exhibit a polydispersity index less than about 0.5, less than about 0.4, less than about 0.3, or about 0.2 or less. By way of example, the nucleic acid particles can exhibit a polydispersity index in a range of about 0.1 to about 0.3 or about 0.2 to about 0.3.

[0656] With respect to RNA lipid particles, the N/P ratio gives the ratio of the nitrogen groups in the lipid to the number of phosphate groups in the RNA. It is correlated to the charge ratio, as the nitrogen atoms (depending on the pH) are usually positively charged and the phosphate groups are negatively charged. The N/P ratio, where a charge equilibrium exists, depends on the pH. Lipid formulations are frequently formed at N/P ratios larger than four up to twelve, because positively charged nanoparticles are considered favorable for transfection. In that case, RNA is considered to be completely bound to nanoparticles.

[0657] Nucleic acid particles described herein can be prepared using a wide range of methods that may involve obtaining a colloid from at least one cationic or cationically ionizable lipid or lipid-like material and/or at least one cationic polymer and mixing the colloid with nucleic acid to obtain nucleic acid particles.

[0658] The term "colloid" as used herein relates to a type of homogeneous mixture in which dispersed particles do not settle out. The insoluble particles in the mixture are microscopic, with particle sizes between 1 and 1000 nanometers. The mixture may be termed a colloid or a colloidal suspension. Sometimes the term "colloid" only refers to the particles in the mixture and not the entire suspension.

[0659] For the preparation of colloids comprising at least one cationic or cationically ionizable lipid or lipid-like material and/or at least one cationic polymer methods are applicable herein that are conventionally used for preparing liposomal vesicles and are appropriately adapted. The most commonly used methods for preparing liposomal vesicles share the following fundamental stages: (i) lipids dissolution in organic solvents, (ii) drying of the resultant solution, and (iii) hydration of dried lipid (using various aqueous media).

[0660] In the film hydration method, lipids are firstly dissolved in a suitable organic solvent, and dried down to yield a thin film at the bottom of the flask. The obtained lipid film is hydrated using an appropriate aqueous medium to produce a liposomal dispersion. Furthermore, an additional downsizing step may be included.

[0661] Reverse phase evaporation is an alternative method to the film hydration for preparing liposomal vesicles that involves formation of a water-in-oil emulsion between an aqueous phase and an organic phase containing lipids. A brief sonication of this mixture is required for system homogenization. The removal of the organic phase under reduced pressure yields a milky gel that turns subsequently into a liposomal suspension.

[0662] The term "ethanol injection technique" refers to a process, in which an ethanol solution comprising lipids is rapidly injected into an aqueous solution through a needle. This action disperses the lipids throughout the solution and promotes lipid structure formation, for example lipid vesicle formation such as liposome formation. Generally, the RNA lipoplex particles described herein are obtainable by adding RNA to a colloidal liposome dispersion. Using the ethanol injection technique, such colloidal liposome dispersion is, in one embodiment, formed as follows: an ethanol solution comprising lipids, such as cationic lipids and additional lipids, is injected into an aqueous solution under stirring. In one embodiment, the RNA lipoplex particles described herein are obtainable without a step of extrusion.

[0663] The term "extruding" or "extrusion" refers to the creation of particles having a fixed, cross-sectional profile. In particular, it refers to the downsizing of a particle, whereby the particle is forced through filters with defined pores.

[0664] Other methods having organic solvent free characteristics may also be used according to the present disclosure for preparing a colloid.

[0665] LNPs typically comprise four components: ionizable cationic lipids, neutral lipids such as phospholipids, a steroid such as cholesterol, and a polymer conjugated lipid such as polyethylene glycol (PEG)-lipids. Each component is responsible for payload protection, and enables effective intracellular delivery. LNPs may be prepared by mixing lipids dissolved in ethanol rapidly with nucleic acid in an aqueous buffer.

[0666] The term "average diameter" refers to the mean hydrodynamic diameter of particles as measured by dynamic laser light scattering (DLS) with data analysis using the so-called cumulant algorithm, which provides as results the so-called $Z_{average}$ with the dimension of a length, and the polydispersity index (PI), which is dimensionless (Koppel, D., J. Chem. Phys. 57, 1972, pp 4814-4820, ISO 13321). Here "average diameter", "diameter" or "size" for particles is used synonymously with this value of the $Z_{average}$.

[0667] The "polydispersity index" is preferably calculated based on dynamic light scattering measurements by the so-called cumulant analysis as mentioned in the definition of the "average diameter". Under certain prerequisites, it can be taken as a measure of the size distribution of an ensemble of nanoparticles.

[0668] Different types of nucleic acid containing particles have been described previously to be suitable for delivery of nucleic acid in particulate form (e.g. Kaczmarek, J. C. et al., 2017, Genome Medicine 9, 60). For non-viral nucleic acid delivery vehicles, nanoparticle encapsulation of nucleic acid physically protects nucleic acid from degradation and, depending on the specific chemistry, can aid in cellular uptake and endosomal escape.

[0669] The present disclosure describes particles comprising nucleic acid, at least one cationic or cationically ionizable lipid or lipid-like material, and/or at least one cationic polymer which associate with nucleic acid to form nucleic acid particles and compositions comprising such particles. The nucleic acid particles may comprise nucleic acid which is complexed in different forms by non-covalent interactions to the particle. The particles described herein are not viral particles, in particular infectious viral particles, i.e., they are not able to virally infect cells.

[0670] Suitable cationic or cationically ionizable lipids or lipid-like materials and cationic polymers are those that form nucleic acid particles and are included by the term "particle forming components" or "particle forming agents". The term "particle forming components" or "particle forming agents" relates to any components which associate with nucleic acid to form nucleic acid particles. Such components include any component which can be part of nucleic acid particles.

[0671] In some embodiments, a nucleic acid containing particle (e.g., a lipid nanoparticle (LNP)) comprises two or more RNA molecules, each comprising a different nucleic acid sequence. In some embodiments, a nucleic acid containing particle comprises two or more RNA molecules, each encoding a different immunogenic polypeptide or immunogenic fragment thereof. In some embodiments, two or more RNA molecules present in a nucleic acid containing particle comprise: a first RNA molecule encodes an immunogenic polypeptide or immunogenic fragment thereof from a coronavirus and a second RNA molecule encodes an immunogenic polypeptide or immunogenic fragment thereof from an infectious disease pathogen (e.g., virus, bacteria, parasite, etc.). For example, in some embodiments, two or more RNA molecules present in a nucleic acid containing particle comprise: a first RNA molecule encoding an immunogenic polypeptide or immunogenic fragment thereof from a coronavirus (e.g., in some embodiments SARS-CoV-2 Wuhan strain or a variant thereof, e.g., a SARS-CoV-2 having one or more mutations characteristic of an Omicron variant) and a second RNA molecule encoding an immunogenic polypeptide or immunogenic fragment thereof from an influenza virus. In some embodiments, two or more RNA molecules present in a nucleic acid containing particle comprise: a first RNA molecule encoding an immunogenic polypeptide or immunogenic fragment thereof from a first coronavirus (e.g., as described herein) and a second RNA molecule encoding an immunogenic polypeptide or immunogenic fragment thereof from a second coronavirus (e.g., as described herein). In some embodiments, a first coronavirus is different from a second coronavirus. In some embodiments, a first and/or second coronavirus is independently from a SARS-CoV-2 Wuhan strain or a variant thereof, e.g., a SARS-CoV-2 having one or more mutations characteristic of an Omicron variant.

[0672] In some embodiments, two or more RNA molecules present in a nucleic acid containing particle each encode an immunogenic polypeptide or an immunogenic fragment thereof from the same and/or different strains and/or variants of coronavirus (e.g., in some embodiments SARS-CoV-2 strains or variants). For example, in some embodiments, two or more RNA molecules present in a nucleic acid containing particle each encode a different immunogenic polypeptide or immunogenic fragment thereof from a coronavirus membrane protein, a coronavirus nucleocapsid protein, a coronavirus spike protein, a coronavirus non-structural protein and/or a coronavirus accessory protein. In some embodiments, such immunogenic polypeptides or immunogenic fragments thereof may be from the same or a different coronavirus (e.g., in some embodiments a SARS-CoV-2 Wuhan strain or variants thereof, for example, in some embodiments a variant having one or more mutations characteristic of a prevalent variant such as an Omicron variant). In some embodiments, a nucleic acid containing particle comprises a first RNA molecule encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a first strain or variant, and

a second RNA molecule encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a second strain or variant, wherein the second strain or variant is different from the first strain or variant.

[0673] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises a first RNA molecule encoding a SARS-CoV-2 S protein from a Wuhan strain and a second RNA molecule encoding a SARS-CoV-2 S protein comprising one or more mutations that are characteristic of an Omicron variant (e.g., a BA.1, BA.2, BA.3, BA.4/5, XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant).

[0674] In some embodiments, a nucleic acid containing particle comprises a first RNA molecule encoding a SARS-CoV-2 S protein from a first Omicron variant and a second RNA molecule encoding a SARS-CoV-2 S protein comprising one or more mutations that are characteristic of a second Omicron variant.

[0675] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises three or more RNA molecules, each encoding a SARS-CoV-2 S protein comprising mutations of a different SARS-CoV-2 variant.

[0676] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprising two or more RNA molecules, comprises each RNA molecule in the same amount (i.e., at a 1:1 ratio).

[0677] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprising two or more RNA molecules, comprises a different amount of each RNA molecule. For example, in some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, where the first RNA molecule is present in an amount that is 0.01 to 100 times that of the second RNA molecule (e.g., wherein the amount of the first RNA molecule is 0.01 to 50, 0.01 to 4, 0.01 to 30, 0.01 to 25, 0.01 to 20, 0.01 to 15, 0.01 to 10, 0.01 to 9, 0.01 to 8, 0.01 to 7, 0.01 to 6, 0.01 to 5, 0.01 to 4, 0.01 to 3, 0.01 to 2, 0.01 to 1.5, 1 to 50, 1 to 4, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1 to 1.5 times higher than the second RNA molecule). In some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, wherein the concentration of the first RNA molecule is 1 to 10 times that of the second RNA molecule. In some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, wherein the concentration of the first RNA molecule is 1 to 5 times that of the second RNA molecule. In some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, wherein the concentration of the first RNA molecule is 1 to 3 times that of the second RNA molecule. In some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, wherein the concentration of the first RNA molecule is 2 times that of the second RNA molecule. In some embodiments, a nucleic acid containing particle comprises a first RNA molecule and a second RNA molecule, wherein the concentration of the first RNA molecule is 3 times that of the second RNA molecule.

[0678] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprising three RNA molecules, comprises each RNA molecule in the same amount (i.e., at a 1:1:1 ratio).

[0679] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprising three RNA molecules, comprises a different amount of each RNA molecule. For example, in some embodiments, the ratio of first RNA molecule: second RNA molecule: third RNA molecule is 1: 0.01-100: 0.01-100 (e.g., 1: 0.01-50: 0.01-50; 1: 0.01-40: 0.01-40; 1: 0.01-30: 0.01-25; 1: 0.01-25: 0.01-25; 1: 0.01-20: 0.01-20; 1: 0.01-15: 0.01-15; 1: 0.01-10: 0.01-9; 1: 0.01-9: 0.01-9; 1: 0.01-8: 0.01-8; 1: 0.01-7: 0.01-7; 1: 0.01-6: 0.01-6; 1: 0.01-5: 0.01-5; 1: 0.01-4: 0.01-4; 1: 0.01-3: 0.01-3; 1: 0.01-2: 0.01-2; or 1: 0.01-1.5: 0.01-1.5). In some embodiments, the ratio of first RNA molecule: second RNA molecule: third RNA molecule is 1:1:3. In some embodiments, the ratio of first RNA molecule: second RNA molecule: third RNA molecule is 1:3:3.

[0680] In some embodiments, a first RNA molecule encoding a SARS-CoV-2 S protein from a Wuhan strain comprises a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 7. In some embodiments, a first RNA molecule encoding a SARS-CoV-2 S protein from a Wuhan strain comprises a nucleotide sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 9. In some embodiments, a first RNA molecule encoding a SARS-COV-2 S protein from a Wuhan strain comprises a nucleotide sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 20. In some embodiments, a first RNA molecule encoding a SARS-COV-2 S protein from a Wuhan strain comprises a nucleotide sequence that encodes an amino acid sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 7.

[0681] In some embodiments, a second RNA molecule encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant comprises a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 69. In some embodiments, a second RNA molecule encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 70. In some embodiments, a second RNA molecule encoding a SARS-COV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 72. In some embodiments, a second RNA molecule encoding a SARS-COV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that encodes an amino acid sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 69.

[0682] In some embodiments, a second RNA molecule encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant comprises a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 74. In some embodiments, a second RNA molecule encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical) to SEQ ID NO: 75. In some embodiments, a second RNA molecule encoding a SARS-COV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 77. In some embodiments, a second RNA molecule encoding a SARS-COV-2 S protein comprising one or more mutations characteristic of an Omicron variant comprises a nucleotide sequence that encodes an amino acid sequence that is at least 80% identical to (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to) SEQ ID NO: 74.

[0683] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 7 or an amino acid sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at

least 99% or higher) identical to SEQ ID NO: 7); and a second RNA molecule comprising a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 69. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 69 or a sequence that is at least 80% identical to SEQ ID NO: 69 is 1:1. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 69 or a sequence that is at least 80% identical to SEQ ID NO: 69 is 1:2. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 69 or a sequence that is at least 80% identical to SEQ ID NO: 69 is 1:3.

[0684] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 9); and a second RNA molecule comprising a nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 70. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 70 or a sequence that is at least 80% identical to SEQ ID NO: 70 is 1:1. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 70 or a sequence that is at least 80% identical to SEQ ID NO: 70 is 1:2. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 70 or a sequence that is at least 80% identical to SEQ ID NO: 70 is 1:3.

[0685] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence of SEQ ID NO: 20 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 20; and a second RNA molecule comprising a nucleotide sequence of SEQ ID NO: 72 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 72. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 72 or a sequence that is at least 80% identical to SEQ ID NO: 72 is 1:1. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 72 or a sequence that is at least 80% identical to SEQ ID NO: 72 is 1:2. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a

sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 72 or a sequence that is at least 80% identical to SEQ ID NO: 72 is 1:3.

[0686] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 7 or an amino acid sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 7); and a second RNA molecule comprising a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 74 or an amino acid sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 74. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 74 or a sequence that is at least 80% identical to SEQ ID NO: 74 is 1:1. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 74 or a sequence that is at least 80% identical to SEQ ID NO: 74 is 1:2. In some embodiments, the ratio of the first RNA molecule that encodes the amino acid sequence of SEQ ID NO: 7 or a sequence that is at least 80% identical to SEQ ID NO: 7 to the second RNA molecule that encodes the amino acid sequence of SEQ ID NO: 74 or a sequence that is at least 80% identical to SEQ ID NO: 74 is 1:3.

[0687] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 9); and a second RNA molecule comprising a nucleotide sequence of SEQ ID NO: 75 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 75. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 75 or a sequence that is at least 80% identical to SEQ ID NO: 75 is 1:1. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 75 or a sequence that is at least 80% identical to SEQ ID NO: 75 is 1:2. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 9 or a sequence that is at least 80% identical to SEQ ID NO: 9 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 75 or a sequence that is at least 80% identical to SEQ ID NO: 75 is 1:3.

[0688] In some embodiments, a nucleic acid containing particle (e.g., in some embodiments an LNP as described herein) comprises: a first RNA molecule comprising a nucleotide sequence of SEQ ID NO: 20 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 20; and a second RNA molecule comprising a nucleotide sequence of SEQ ID NO: 77 or a nucleotide sequence that is at least 80% (e.g., at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher) identical to SEQ ID NO: 77. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a

nucleotide sequence of SEQ ID NO: 77 or a sequence that is at least 80% identical to SEQ ID NO: 77 is 1:1. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 77 or a sequence that is at least 80% identical to SEQ ID NO: 77 is 1:2. In some embodiments, the ratio of the first RNA molecule comprising the nucleotide sequence of SEQ ID NO: 20 or a sequence that is at least 80% identical to SEQ ID NO: 20 to the second RNA molecule that comprises a nucleotide sequence of SEQ ID NO: 77 or a sequence that is at least 80% identical to SEQ ID NO: 77 is 1:3.

[0689] In some embodiments, a particle (e.g., in some embodiments an LNP) containing nucleic acids (e.g., RNAs) encoding different polypeptides can be formed by mixing a plurality of (e.g., at least two, at least three, or more) RNA molecules with particle-forming components (e.g., lipids). In some embodiments, nucleic acids (e.g., RNAs) encoding different polypeptides can be mixed (e.g., in some embodiments in substantially equal proportions, e.g., in some embodiments at a 1:1 ratio when two RNA molecules are present) prior to mixing with particle-forming components (e.g., lipids).

[0690] In some embodiments, two or more RNA molecules each encoding a different polypeptide (e.g., as described herein) can be mixed with particle-forming agents to form nucleic acid containing particles as described above. In alternative embodiments, two or more RNA molecules each encoding a different polypeptide (e.g., as described herein) can be formulated into separate particle compositions, which are then mixed together. For example, in some embodiments, individual populations of nucleic acid containing particles, each population comprising an RNA molecule encoding a different immunogenic polypeptide or immunogenic fragment thereof (e.g., as described herein), can be separately formed and then mixed together, for example, prior to filling into vials during a manufacturing process, or immediately prior to administration (e.g., by an administering health-care professional)). Accordingly, in some embodiments, described herein is a composition comprises two or more populations of particles (e.g., in some embodiments, lipid nanoparticles), each population comprising at least one RNA molecule encoding a different immunogenic polypeptide or immunogenic fragment thereof (e.g., a SARS-CoV-2 S protein, or fragments thereof, from a different variant). In some embodiments, each population may be provided in a composition at a desirable proportion (e.g., in some embodiments, each population may be provided in a composition in an amount that provides the same amount of RNA molecules).

[0691] Cationic polymer

[0692] Given their high degree of chemical flexibility, polymers are commonly used materials for nanoparticle-based delivery. Typically, cationic polymers are used to electrostatically condense the negatively charged nucleic acid into nanoparticles. These positively charged groups often consist of amines that change their state of protonation in the pH range between 5.5 and 7.5, thought to lead to an ion imbalance that results in endosomal rupture. Polymers such as poly-L-lysine, polyamidoamine, protamine and polyethyleneimine, as well as naturally occurring polymers such as chitosan have all been applied to nucleic acid delivery and are suitable as cationic polymers herein. In addition, some investigators have synthesized polymers specifically for nucleic acid delivery. Poly(β-amino esters), in particular, have gained widespread use in nucleic acid delivery owing to their ease of synthesis and biodegradability. Such synthetic polymers are also suitable as cationic polymers herein.

[0693] A "polymer," as used herein, is given its ordinary meaning, i.e., a molecular structure comprising one or more repeat units (monomers), connected by covalent bonds. The repeat units can all be identical, or in some cases, there can be more than one type of repeat unit present within the polymer. In some cases, the polymer is biologically derived, i.e., a biopolymer such as a protein. In some cases, additional moieties can also be present in the polymer, for example targeting moieties such as those described herein.

[0694] If more than one type of repeat unit is present within the polymer, then the polymer is said to be a "copolymer." It is to be understood that the polymer being employed herein can be a copolymer. The repeat units

forming the copolymer can be arranged in any fashion. For example, the repeat units can be arranged in a random order, in an alternating order, or as a "block" copolymer, i.e., comprising one or more regions each comprising a first repeat unit (e.g., a first block), and one or more regions each comprising a second repeat unit (e.g., a second block), etc. Block copolymers can have two (a diblock copolymer), three (a triblock copolymer), or more numbers of distinct blocks.

[0695] In certain embodiments, the polymer is biocompatible. Biocompatible polymers are polymers that typically do not result in significant cell death at moderate concentrations. In certain embodiments, the biocompatible polymer is biodegradable, i.e., the polymer is able to degrade, chemically and/or biologically, within a physiological environment, such as within the body.

[0696] In certain embodiments, polymer may be protamine or polyalkyleneimine, in particular protamine.

[0697] The term "protamine" refers to any of various strongly basic proteins of relatively low molecular weight that are rich in arginine and are found associated especially with DNA in place of somatic histones in the sperm cells of various animals (as fish). In particular, the term "protamine" refers to proteins found in fish sperm that are strongly basic, are soluble in water, are not coagulated by heat, and yield chiefly arginine upon hydrolysis. In purified form, they are used in a long-acting formulation of insulin and to neutralize the anticoagulant effects of heparin.

[0698] According to the present disclosure, the term "protamine" as used herein is meant to comprise any protamine amino acid sequence obtained or derived from natural or biological sources including fragments thereof and multimeric forms of said amino acid sequence or fragment thereof as well as (synthesized) polypeptides which are artificial and specifically designed for specific purposes and cannot be isolated from native or biological sources.

[0699] In one embodiment, the polyalkyleneimine comprises polyethylenimine and/or polypropylenimine, preferably polyethyleneimine. A preferred polyalkyleneimine is polyethyleneimine (PEI). The average molecular weight of PEI is preferably $0.75 \cdot 10^2$ to 10^7 Da, preferably 1000 to 10^5 Da, more preferably 10000 to 40000 Da, more preferably 15000 to 30000 Da, even more preferably 20000 to 25000 Da.

[0700] Preferred according to the present disclosure is linear polyalkyleneimine such as linear polyethyleneimine (PEI).

[0701] Cationic polymers (including polycationic polymers) contemplated for use herein include any cationic polymers which are able to electrostatically bind nucleic acid. In one embodiment, cationic polymers contemplated for use herein include any cationic polymers with which nucleic acid can be associated, e.g. by forming complexes with the nucleic acid or forming vesicles in which the nucleic acid is enclosed or encapsulated.

[0702] Particles described herein may also comprise polymers other than cationic polymers, i.e., non-cationic polymers and/or anionic polymers. Collectively, anionic and neutral polymers are referred to herein as non-cationic polymers.

[0703] Lipid and lipid-like material

[0704] The terms "lipid" and "lipid-like material" are broadly defined herein as molecules which comprise one or more hydrophobic moieties or groups and optionally also one or more hydrophilic moieties or groups. Molecules comprising hydrophobic moieties and hydrophilic moieties are also frequently denoted as amphiphiles. Lipids are usually poorly soluble in water. In an aqueous environment, the amphiphilic nature allows the molecules to self-assemble into organized structures and different phases. One of those phases consists of lipid bilayers, as they are present in vesicles, multilamellar/unilamellar liposomes, or membranes in an aqueous environment. Hydrophobicity can be conferred by the inclusion of apolar groups that include, but are not limited to, long-chain saturated and unsaturated aliphatic hydrocarbon groups and such groups substituted by one or more aromatic, cycloaliphatic, or heterocyclic group(s). The hydrophilic groups may comprise polar and/or charged groups and include carbohydrates, phosphate, carboxylic, sulfate, amino, sulfhydryl, nitro, hydroxyl, and other like groups.

[0705] As used herein, the term "amphiphilic" refers to a molecule having both a polar portion and a non-polar portion. Often, an amphiphilic compound has a polar head attached to a long hydrophobic tail. In some embodiments, the polar portion is soluble in water, while the non-polar portion is insoluble in water. In addition, the polar portion may have either a formal positive charge, or a formal negative charge. Alternatively, the polar portion may have both a formal positive and a negative charge, and be a zwitterion or inner salt. For purposes of the present disclosure, the amphiphilic compound can be, but is not limited to, one or a plurality of natural or non-natural lipids and lipid-like compounds.

[0706] The term "lipid-like material", "lipid-like compound" or "lipid-like molecule" relates to substances that structurally and/or functionally relate to lipids but may not be considered as lipids in a strict sense. For example, the term includes compounds that are able to form amphiphilic layers as they are present in vesicles, multilamellar/unilamellar liposomes, or membranes in an aqueous environment and includes surfactants, or synthesized compounds with both hydrophilic and hydrophobic moieties. Generally speaking, the term refers to molecules, which comprise hydrophilic and hydrophobic moieties with different structural organization, which may or may not be similar to that of lipids. As used herein, the term "lipid" is to be construed to cover both lipids and lipid-like materials unless otherwise indicated herein or clearly contradicted by context.

[0707] Specific examples of amphiphilic compounds that may be included in an amphiphilic layer include, but are not limited to, phospholipids, aminolipids and sphingolipids.

[0708] In certain embodiments, the amphiphilic compound is a lipid. The term "lipid" refers to a group of organic compounds that are characterized by being insoluble in water, but soluble in many organic solvents. Generally, lipids may be divided into eight categories: fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, polyketides (derived from condensation of ketoacyl subunits), sterol lipids and prenol lipids (derived from condensation of isoprene subunits). Although the term "lipid" is sometimes used as a synonym for fats, fats are a subgroup of lipids called triglycerides. Lipids also encompass molecules such as fatty acids and their derivatives (including tri-, di-, monoglycerides, and phospholipids), as well as sterol-containing metabolites such as cholesterol.

[0709] Fatty acids, or fatty acid residues are a diverse group of molecules made of a hydrocarbon chain that terminates with a carboxylic acid group; this arrangement confers the molecule with a polar, hydrophilic end, and a nonpolar, hydrophobic end that is insoluble in water. The carbon chain, typically between four and 24 carbons long, may be saturated or unsaturated, and may be attached to functional groups containing oxygen, halogens, nitrogen, and sulfur. If a fatty acid contains a double bond, there is the possibility of either a cis or trans geometric isomerism, which significantly affects the molecule's configuration. Cis-double bonds cause the fatty acid chain to bend, an effect that is compounded with more double bonds in the chain. Other major lipid classes in the fatty acid category are the fatty esters and fatty amides.

[0710] Glycerolipids are composed of mono-, di-, and tri-substituted glycerols, the best-known being the fatty acid triesters of glycerol, called triglycerides. The word "triacylglycerol" is sometimes used synonymously with "triglyceride". In these compounds, the three hydroxyl groups of glycerol are each esterified, typically by different fatty acids. Additional subclasses of glycerolipids are represented by glycosylglycerols, which are characterized by the presence of one or more sugar residues attached to glycerol via a glycosidic linkage.

[0711] The glycerophospholipids are amphipathic molecules (containing both hydrophobic and hydrophilic regions) that contain a glycerol core linked to two fatty acid-derived "tails" by ester linkages and to one "head" group by a phosphate ester linkage. Examples of glycerophospholipids, usually referred to as phospholipids (though sphingomyelins are also classified as phospholipids) are phosphatidylcholine (also known as PC, GPCho or lecithin), phosphatidylethanolamine (PE or GPEtn) and phosphatidylserine (PS or GPSer).

[0712] Sphingolipids are a complex family of compounds that share a common structural feature, a sphingoid base backbone. The major sphingoid base in mammals is commonly referred to as sphingosine. Ceramides (N-acyl-

sphingoid bases) are a major subclass of sphingoid base derivatives with an amide-linked fatty acid. The fatty acids are typically saturated or mono-unsaturated with chain lengths from 16 to 26 carbon atoms. The major phosphosphingolipids of mammals are sphingomyelins (ceramide phosphocholines), whereas insects contain mainly ceramide phosphoethanolamines and fungi have phytoceramide phosphoinositols and mannose-containing headgroups. The glycosphingolipids are a diverse family of molecules composed of one or more sugar residues linked via a glycosidic bond to the sphingoid base. Examples of these are the simple and complex glycosphingolipids such as cerebrosides and gangliosides.

[0713] Sterol lipids, such as cholesterol and its derivatives, or tocopherol and its derivatives, are an important component of membrane lipids, along with the glycerophospholipids and sphingomyelins.

[0714] Saccharolipids describe compounds in which fatty acids are linked directly to a sugar backbone, forming structures that are compatible with membrane bilayers. In the saccharolipids, a monosaccharide substitutes for the glycerol backbone present in glycerolipids and glycerophospholipids. The most familiar saccharolipids are the acylated glucosamine precursors of the Lipid A component of the lipopolysaccharides in Gram-negative bacteria. Typical lipid A molecules are disaccharides of glucosamine, which are derivatized with as many as seven fatty-acyl chains. The minimal lipopolysaccharide required for growth in E. coli is Kdo2-Lipid A, a hexa-acylated disaccharide of glucosamine that is glycosylated with two 3-deoxy-D-manno-octulosonic acid (Kdo) residues.

[0715] Polyketides are synthesized by polymerization of acetyl and propionyl subunits by classic enzymes as well as iterative and multimodular enzymes that share mechanistic features with the fatty acid synthases. They comprise a large number of secondary metabolites and natural products from animal, plant, bacterial, fungal and marine sources, and have great structural diversity. Many polyketides are cyclic molecules whose backbones are often further modified by glycosylation, methylation, hydroxylation, oxidation, or other processes.

[0716] According to the present disclosure, lipids and lipid-like materials may be cationic, anionic or neutral. Neutral lipids or lipid-like materials exist in an uncharged or neutral zwitterionic form at a selected pH.

Cationic or cationically ionizable lipids or lipid-like materials

[0717] The nucleic acid particles described herein may comprise at least one cationic or cationically ionizable lipid or lipid-like material as particle forming agent. Cationic or cationically ionizable lipids or lipid-like materials contemplated for use herein include any cationic or cationically ionizable lipids or lipid-like materials which are able to electrostatically bind nucleic acid. In one embodiment, cationic or cationically ionizable lipids or lipid-like materials contemplated for use herein can be associated with nucleic acid, e.g. by forming complexes with the nucleic acid or forming vesicles in which the nucleic acid is enclosed or encapsulated.

[0718] As used herein, a "cationic lipid" or "cationic lipid-like material" refers to a lipid or lipid-like material having a net positive charge. Cationic lipids or lipid-like materials bind negatively charged nucleic acid by electrostatic interaction. Generally, cationic lipids possess a lipophilic moiety, such as a sterol, an acyl chain, a diacyl or more acyl chains, and the head group of the lipid typically carries the positive charge.

[0719] In certain embodiments, a cationic lipid or lipid-like material has a net positive charge only at certain pH, in particular acidic pH, while it has preferably no net positive charge, preferably has no charge, i.e., it is neutral, at a different, preferably higher pH such as physiological pH. This ionizable behavior is thought to enhance efficacy through helping with endosomal escape and reducing toxicity as compared with particles that remain cationic at physiological pH.

[0720] For purposes of the present disclosure, such "cationically ionizable" lipids or lipid-like materials are comprised by the term "cationic lipid or lipid-like material" unless contradicted by the circumstances.

[0721] In one embodiment, the cationic or cationically ionizable lipid or lipid-like material comprises a head group which includes at least one nitrogen atom (N) which is positive charged or capable of being protonated.

[0722] Examples of cationic lipids include, but are not limited to 1,2-dioleoyl-3-trimethylammonium propane (DOTAP); N,N-dimethyl-2,3-dioleyloxypropylamine (DODMA), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA), 3-(N—(N',N'-dimethylaminoethane)-carbamoyl)cholesterol (DC-Chol), dimethyldioctadecylammonium (DDAB); 1,2-dioleoyl-3-dimethylammonium-propane (DODAP); 1,2-diacyloxy-3-dimethylammonium propanes; 1,2-dialkyloxy-3-dimethylammonium propanes; dioctadecyldimethyl ammonium chloride (DODAC), 1,2-distearyloxy-N,N-dimethyl-3-aminopropane (DSDMA), 2,3-di(tetradecoxy)propyl-(2-hydroxyethyl)-dimethylazanium (DMRIE), 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine (DMEPC), I,2-dimyristoyl-3-trimethylammonium propane (DMTAP), 1,2-dioleyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DORIE), and 2,3-dioleoyloxy- N-[2(spermine carboxamide)ethyl]-N,N-dimethyl-I-propanamium trifluoroacetate (DOSPA), 1,2-dilinoleyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), dioctadecylamidoglycyl spermine (DOGS), 3-dimethylamino-2-(cholest-5-en-3-beta-oxybutan-4-oxy)-1-(cis,cis-9,12-oc-tadecadienoxy)propane (CLinDMA), 2-[5'-(cholest-5-en-3-beta-oxy)-3'-oxapentoxy)-3-dimethyl-1-(cis,cis-9',12'-octadecadienoxy)propane (CpLinDMA), N,N-dimethyl-3,4-dioleyloxybenzylamine (DMOBA), 1,2-N,N'-dioleylcarbamyl-3-dimethylaminopropane (DOcarbDAP), 2,3-Dilinoleoyloxy-N,N-dimethylpropylamine (DLinDAP), 1,2-N,N'-Dilinoleylcarbamyl-3-dimethylaminopropane (DLincarbDAP), 1,2-Dilinoleoylcarbamyl-3-dimethylaminopropane (DLinCDAP), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-K-XTC2-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate (DLin-MC3-DMA), N-(2-Hydroxyethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (DMRIE), (±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(cis-9-tetradecenyloxy)-1-propanaminium bromide (GAP-DMORIE), (±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(dodecyloxy)-1-propanaminium bromide (GAP-DLRIE), (±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (GAP-DMRIE), N-(2-Aminoethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide (βAE-DMRIE), N-(4-carboxybenzyl)-N,N-dimethyl-2,3-bis(oleoyloxy)propan-1-aminium (DOBAQ), 2-({8-[(3β)-cholest-5-en-3-yloxy]octyl}oxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-1-amine (Octyl-CLinDMA), 1,2-dimyristoyl-3-dimethylammonium-propane (DMDAP), 1,2-dipalmitoyl-3-dimethylammonium-propane (DPDAP), N1-[2-((1S)-1-[(3-aminopropyl)amino]-4-[di(3-amino-propyl)amino]butylcarboxamido)ethyl]-3,4-di[oleyloxy]-benzamide (MVL5), 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (DOEPC), 2,3-bis(dodecyloxy)-N-(2-hydroxyethyl)-N,N-dimethylpropan-1-amonium bromide (DLRIE), N-(2-aminoethyl)-N,N-dimethyl-2,3-bis(tetradecyloxy)propan-1-aminium bromide (DMORIE), di((Z)-non-2-en-1-yl) 8,8'-((((2(dimethylamino)ethyl)thio)carbonyl)azanediyl)dioctanoate (ATX), N,N-dimethyl-2,3-bis(dodecyloxy)propan-1-amine (DLDMA), N,N-dimethyl-2,3-bis(tetradecyloxy)propan-1-amine (DMDMA), Di((Z)-non-2-en-1-yl)-9-((4-(dimethylaminobutanoyl)oxy)heptadecanedioate (L319), N-Dodecyl-3-((2-dodecylcarbamoyl-ethyl)-{2-[(2-dodecylcarbamoyl-ethyl)-2-{(2-dodecylcarbamoyl-ethyl)-[2-(2-dodecylcarbamoyl-ethylamino)-ethyl]-amino}-ethylamino)propionamide (lipidoid $98N_{12}$-5), 1-[2-[bis(2-hydroxydodecyl)amino]ethyl-[2-[4-[2-[bis(2 hydroxydodecyl)amino]ethyl]piperazin-1-yl]ethyl]amino]dodecan-2-ol (lipidoid C12-200).

[0723] In some embodiments, the cationic lipid may comprise from about 10 mol % to about 100 mol %, about 20 mol % to about 100 mol %, about 30 mol % to about 100 mol %, about 40 mol % to about 100 mol %, or about 50 mol % to about 100 mol % of the total lipid present in the particle.

Additional lipids or lipid-like materials

[0724] Particles described herein may also comprise lipids or lipid-like materials other than cationic or cationically ionizable lipids or lipid-like materials, i.e., non-cationic lipids or lipid-like materials (including non-cationically ionizable lipids or lipid-like materials). Collectively, anionic and neutral lipids or lipid-like materials are referred to herein as non-cationic lipids or lipid-like materials. Optimizing the formulation of nucleic acid particles

by addition of other hydrophobic moieties, such as cholesterol and lipids, in addition to an ionizable/cationic lipid or lipid-like material may enhance particle stability and efficacy of nucleic acid delivery.

[0725] An additional lipid or lipid-like material may be incorporated which may or may not affect the overall charge of the nucleic acid particles. In certain embodiments, the additional lipid or lipid-like material is a non-cationic lipid or lipid-like material. The non-cationic lipid may comprise, e.g., one or more anionic lipids and/or neutral lipids. As used herein, an "anionic lipid" refers to any lipid that is negatively charged at a selected pH. As used herein, a "neutral lipid" refers to any of a number of lipid species that exist either in an uncharged or neutral zwitterionic form at a selected pH. In preferred embodiments, the additional lipid comprises one of the following neutral lipid components: (1) a phospholipid, (2) cholesterol or a derivative thereof; or (3) a mixture of a phospholipid and cholesterol or a derivative thereof. Examples of cholesterol derivatives include, but are not limited to, cholestanol, cholestanone, cholestenone, coprostanol, cholesteryl-2'-hydroxyethyl ether, cholesteryl-4'-hydroxybutyl ether, tocopherol and derivatives thereof, and mixtures thereof.

[0726] Specific phospholipids that can be used include, but are not limited to, phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidic acids, phosphatidylserines or sphingomyelin. Such phospholipids include in particular diacylphosphatidylcholines, such as distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dimyristoylphosphatidylcholine (DMPC), dipentadecanoylphosphatidylcholine, dilauroylphosphatidylcholine, dipalmitoylphosphatidylcholine (DPPC), diarachidoylphosphatidylcholine (DAPC), dibehenoylphosphatidylcholine (DBPC), ditricosanoylphosphatidylcholine (DTPC), dilignoceroylphatidylcholine (DLPC), palmitoyloleoyl-phosphatidylcholine (POPC), 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC) and phosphatidylethanolamines, in particular diacylphosphatidylethanolamines, such as dioleoylphosphatidylethanolamine (DOPE), distearoyl-phosphatidylethanolamine (DSPE), dipalmitoyl-phosphatidylethanolamine (DPPE), dimyristoyl-phosphatidylethanolamine (DMPE), dilauroyl-phosphatidylethanolamine (DLPE), diphytanoyl-phosphatidylethanolamine (DPyPE), and further phosphatidylethanolamine lipids with different hydrophobic chains.

[0727] In certain preferred embodiments, the additional lipid is DSPC or DSPC and cholesterol.

[0728] In certain embodiments, the nucleic acid particles include both a cationic lipid and an additional lipid.

[0729] In one embodiment, particles described herein include a polymer conjugated lipid such as a pegylated lipid. The term "pegylated lipid" refers to a molecule comprising both a lipid portion and a polyethylene glycol portion. Pegylated lipids are known in the art.

[0730] Without wishing to be bound by theory, the amount of the at least one cationic lipid compared to the amount of the at least one additional lipid may affect important nucleic acid particle characteristics, such as charge, particle size, stability, tissue selectivity, and bioactivity of the nucleic acid. Accordingly, in some embodiments, the molar ratio of the at least one cationic lipid to the at least one additional lipid is from about 10:0 to about 1:9, about 4:1 to about 1:2, or about 3:1 to about 1:1.

[0731] In some embodiments, the non-cationic lipid, in particular neutral lipid, (e.g., one or more phospholipids and/or cholesterol) may comprise from about 0 mol % to about 90 mol %, from about 0 mol % to about 80 mol %, from about 0 mol % to about 70 mol %, from about 0 mol % to about 60 mol %, or from about 0 mol % to about 50 mol %, of the total lipid present in the particle.

Lipoplex Particles

[0732] In certain embodiments of the present disclosure, the RNA described herein may be present in RNA lipoplex particles.

[0733] In the context of the present disclosure, the term "RNA lipoplex particle" relates to a particle that contains lipid, in particular cationic lipid, and RNA. Electrostatic interactions between positively charged liposomes and negatively charged RNA results in complexation and spontaneous formation of RNA lipoplex particles. Positively charged liposomes may be generally synthesized using a cationic lipid, such as DOTMA, and additional lipids, such as DOPE. In one embodiment, a RNA lipoplex particle is a nanoparticle.

[0734] In certain embodiments, the RNA lipoplex particles include both a cationic lipid and an additional lipid. In an exemplary embodiment, the cationic lipid is DOTMA and the additional lipid is DOPE.

[0735] In some embodiments, the molar ratio of the at least one cationic lipid to the at least one additional lipid is from about 10:0 to about 1:9, about 4:1 to about 1:2, or about 3:1 to about 1:1. In specific embodiments, the molar ratio may be about 3:1, about 2.75:1, about 2.5:1, about 2.25:1, about 2:1, about 1.75:1, about 1.5:1, about 1.25:1, or about 1:1. In an exemplary embodiment, the molar ratio of the at least one cationic lipid to the at least one additional lipid is about 2:1.

[0736] RNA lipoplex particles described herein have an average diameter that in one embodiment ranges from about 200 nm to about 1000 nm, from about 200 nm to about 800 nm, from about 250 to about 700 nm, from about 400 to about 600 nm, from about 300 nm to about 500 nm, or from about 350 nm to about 400 nm. In specific embodiments, the RNA lipoplex particles have an average diameter of about 200 nm, about 225 nm, about 250 nm, about 275 nm, about 300 nm, about 325 nm, about 350 nm, about 375 nm, about 400 nm, about 425 nm, about 450 nm, about 475 nm, about 500 nm, about 525 nm, about 550 nm, about 575 nm, about 600 nm, about 625 nm, about 650 nm, about 700 nm, about 725 nm, about 750 nm, about 775 nm, about 800 nm, about 825 nm, about 850 nm, about 875 nm, about 900 nm, about 925 nm, about 950 nm, about 975 nm, or about 1000 nm. In an embodiment, the RNA lipoplex particles have an average diameter that ranges from about 250 nm to about 700 nm. In another embodiment, the RNA lipoplex particles have an average diameter that ranges from about 300 nm to about 500 nm. In an exemplary embodiment, the RNA lipoplex particles have an average diameter of about 400 nm.

[0737] The RNA lipoplex particles and compositions comprising RNA lipoplex particles described herein are useful for delivery of RNA to a target tissue after parenteral administration, in particular after intravenous administration. The RNA lipoplex particles may be prepared using liposomes that may be obtained by injecting a solution of the lipids in ethanol into water or a suitable aqueous phase. In one embodiment, the aqueous phase has an acidic pH. In one embodiment, the aqueous phase comprises acetic acid, e.g., in an amount of about 5 mM. Liposomes may be used for preparing RNA lipoplex particles by mixing the liposomes with RNA. In one embodiment, the liposomes and RNA lipoplex particles comprise at least one cationic lipid and at least one additional lipid. In one embodiment, the at least one cationic lipid comprises 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and/or 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP). In one embodiment, the at least one additional lipid comprises 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE), cholesterol (Chol) and/or 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC). In one embodiment, the at least one cationic lipid comprises 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and the at least one additional lipid comprises 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE). In one embodiment, the liposomes and RNA lipoplex particles comprise 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE).

[0738] Spleen targeting RNA lipoplex particles are described in WO 2013/143683, herein incorporated by reference. It has been found that RNA lipoplex particles having a net negative charge may be used to preferentially target spleen tissue or spleen cells such as antigen-presenting cells, in particular dendritic cells. Accordingly, following administration of the RNA lipoplex particles, RNA accumulation and/or RNA expression in the spleen occurs. Thus, RNA lipoplex particles of the present disclosure may be used for expressing RNA in the spleen. In an

embodiment, after administration of the RNA lipoplex particles, no or essentially no RNA accumulation and/or RNA expression in the lung and/or liver occurs. In one embodiment, after administration of the RNA lipoplex particles, RNA accumulation and/or RNA expression in antigen presenting cells, such as professional antigen presenting cells in the spleen occurs. Thus, RNA lipoplex particles of the present disclosure may be used for expressing RNA in such antigen presenting cells. In one embodiment, the antigen presenting cells are dendritic cells and/or macrophages.

Lipid nanoparticles (LNPs)

[0739] In one embodiment, nucleic acid such as RNA described herein is administered in the form of lipid nanoparticles (LNPs) (e.g., encapsulated within or associated with an LNP). The LNP may comprise any lipid capable of forming a particle to which the one or more nucleic acid molecules are attached, or in which the one or more nucleic acid molecules are encapsulated.

[0740] In one embodiment, the LNP comprises one or more cationic lipids, and one or more stabilizing lipids. Stabilizing lipids include neutral lipids and pegylated lipids.

[0741] In one embodiment, the LNP comprises a cationic lipid, a neutral lipid, a steroid, a polymer conjugated lipid; and the RNA, encapsulated within or associated with the lipid nanoparticle.

[0742] In one embodiment, the LNP comprises from 20 to 60 mol percent, 40 to 55 mol percent, from 40 to 50 mol percent, from 41 to 49 mol percent, from 41 to 48 mol percent, from 42 to 48 mol percent, from 43 to 48 mol percent, from 44 to 48 mol percent, from 45 to 48 mol percent, from 46 to 48 mol percent, from 47 to 48 mol percent, or from 47.2 to 47.8 mol percent of the cationic lipid. In one embodiment, the LNP comprises about 47.0, 47.1, 47.2, 47.3, 47.4, 47.5, 47.6, 47.7, 47.8, 47.9 or 48.0 mol percent of the cationic lipid.

[0743] In one embodiment, the neutral lipid is present in a concentration ranging from 5 to 25 mol percent, 5 to 15 mol percent, from 7 to 13 mol percent, or from 9 to 11 mol percent. In one embodiment, the neutral lipid is present in a concentration of about 9.5, 10 or 10.5 mol percent.

[0744] In one embodiment, the steroid is present in a concentration ranging from 25 to 55 mol percent, 30 to 50 mol percent, from 35 to 45 mol percent or from 38 to 43 mol percent. In one embodiment, the steroid is present in a concentration of about 40, 41, 42, 43, 44, 45 or 46 mol percent.

[0745] In one embodiment, the LNP comprises from 0.5 to 15 mol percent, 1 to 10 mol percent, from 1 to 5 mol percent, or from 1 to 2.5 mol percent of the polymer conjugated lipid.

[0746] In one embodiment, the LNP comprises from 20 to 60 mol percent cationic or lipid, 5 to 25 mol percent non-cationic lipid (e.g., neutral lipid), 25 to 55 mol percent sterol or steroid, and 0.5 to 15 mol percent polymer-conjugated lipid (e.g., PEG-modified lipid).

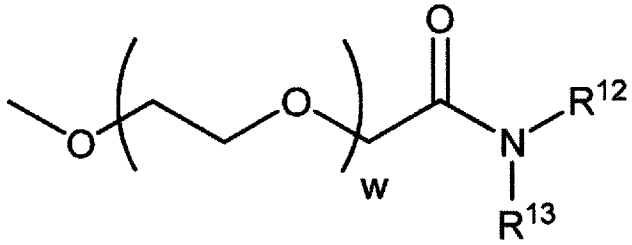
[0747] In one embodiment, the LNP comprises from 40 to 50 mol percent a cationic lipid; from 5 to 15 mol percent of a neutral lipid; from 35 to 45 mol percent of a steroid; from 1 to 10 mol percent of a polymer conjugated lipid; and the RNA, encapsulated within or associated with the lipid nanoparticle.

[0748] In one embodiment, the mol percent is determined based on total mol of lipid present in the lipid nanoparticle.

[0749] In one embodiment, the neutral lipid is selected from the group consisting of DSPC, DPPC, DMPC, DOPC, POPC, DOPE, DOPG, DPPG, POPE, DPPE, DMPE, DSPE, and SM. In one embodiment, the neutral lipid is selected from the group consisting of DSPC, DPPC, DMPC, DOPC, POPC, DOPE and SM. In one embodiment, the neutral lipid is DSPC.

[0750] In one embodiment, the steroid is cholesterol.

[0751] In one embodiment, the polymer conjugated lipid is a pegylated lipid. In one embodiment, the

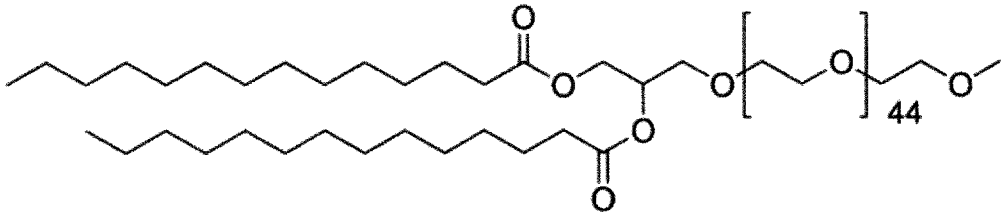


pegylated lipid has the following structure:

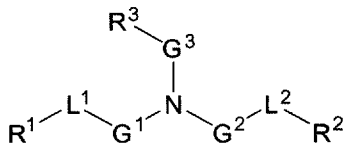
[0752] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

[0753] R^{12} and R^{13} are each independently a straight or branched, saturated or unsaturated alkyl chain containing from 10 to 30 carbon atoms, wherein the alkyl chain is optionally interrupted by one or more ester bonds; and w has a mean value ranging from 30 to 60. In one embodiment, R^{12} and R^{13} are each independently straight, saturated alkyl chains containing from 12 to 16 carbon atoms. In one embodiment, w has a mean value ranging from 40 to 55. In one embodiment, the average w is about 45. In one embodiment, R^{12} and R^{13} are each independently a straight, saturated alkyl chain containing about 14 carbon atoms, and w has a mean value of about 45.

[0754] In one embodiment, the pegylated lipid is DMG-PEG 2000, e.g., having the following structure:



[0755] In some embodiments, the cationic lipid component of the LNPs has the structure of Formula (III):



(III)

or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof, wherein:

one of L^1 or L^2 is –O(C=O)-, -(C=O)O-, -C(=O)-, -O-, -$S(O)_x$-, -S-S-, -C(=O)S-, SC(=O)-, -$NR^aC(=O)$-, -$C(=O)NR^a$-, $NR^aC(=O)NR^a$-, -$OC(=O)NR^a$- or -$NR^aC(=O)O$-, and the other of L^1 or L^2 is –O(C=O)-, -(C=O)O-, -C(=O)-, -O-, -$S(O)_x$-, -S-S-, -C(=O)S-, SC(=O)-, -$NR^aC(=O)$-, -$C(=O)NR^a$-, $NR^aC(=O)NR^a$-, -$OC(=O)NR^a$- or -$NR^aC(=O)O$- or a direct bond;

G^1 and G^2 are each independently unsubstituted C_1-C_{12} alkylene or C_1-C_{12} alkenylene;

G^3 is C_1-C_{24} alkylene, C_1-C_{24} alkenylene, C_3-C_8 cycloalkylene, C_3-C_8 cycloalkenylene;

R^a is H or C_1-C_{12} alkyl;

R^1 and R^2 are each independently C_6-C_{24} alkyl or C_6-C_{24} alkenyl;

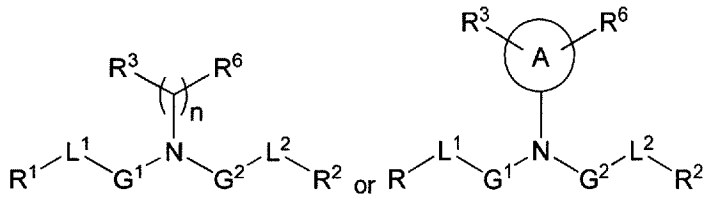
R^3 is H, OR^5, CN, -$C(=O)OR^4$, -$OC(=O)R^4$ or –$NR^5C(=O)R^4$;

R^4 is C_1-C_{12} alkyl;

R^5 is H or C_1-C_6 alkyl; and

x is 0, 1 or 2.

[0756] In some of the foregoing embodiments of Formula (III), the lipid has one of the following structures (IIIA) or (IIIB):



(IIIA) (IIIB)

wherein:

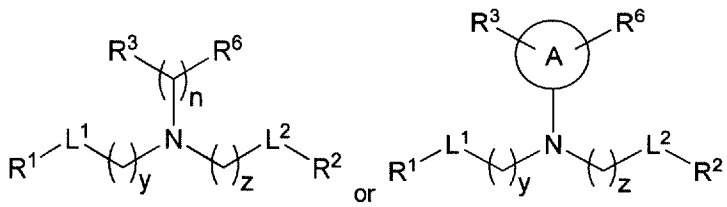
A is a 3 to 8-membered cycloalkyl or cycloalkylene ring;

R^6 is, at each occurrence, independently H, OH or C_1-C_{24} alkyl;

n is an integer ranging from 1 to 15.

[0757] In some of the foregoing embodiments of Formula (III), the lipid has structure (IIIA), and in other embodiments, the lipid has structure (IIIB).

[0758] In other embodiments of Formula (III), the lipid has one of the following structures (IIIC) or (IIID):

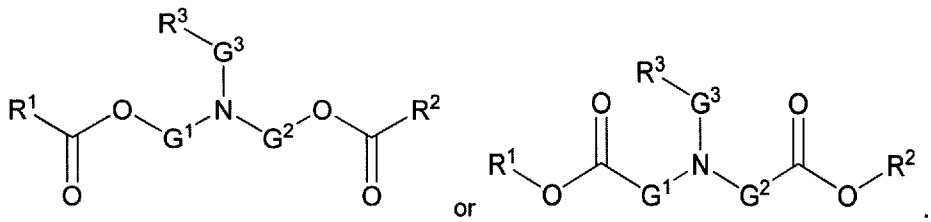


(IIIC) (IIID)

wherein y and z are each independently integers ranging from 1 to 12.

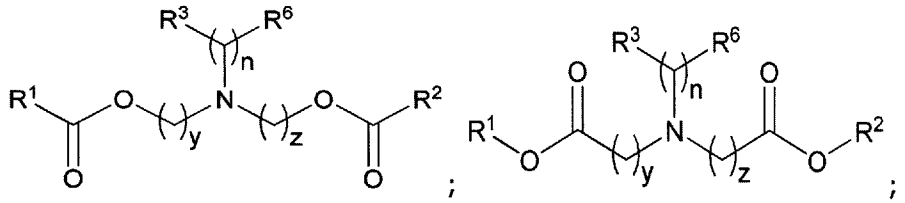
[0759] In any of the foregoing embodiments of Formula (III), one of L^1 or L^2 is -O(C=O)-. For example, in some embodiments each of L^1 and L^2 are -O(C=O)-. In some different embodiments of any of the foregoing, L^1 and L^2 are each independently -(C=O)O- or -O(C=O)-. For example, in some embodiments each of L^1 and L^2 is -(C=O)O-.

[0760] In some different embodiments of Formula (III), the lipid has one of the following structures (IIIE) or (IIIF):

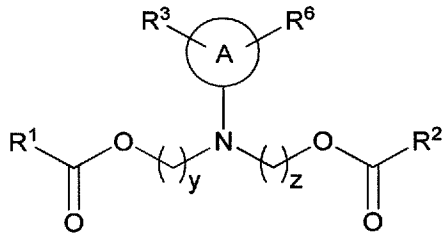


(IIIE) (IIIF)

[0761] In some of the foregoing embodiments of Formula (III), the lipid has one of the following structures (IIIG), (IIIH), (IIII), or (IIIJ):

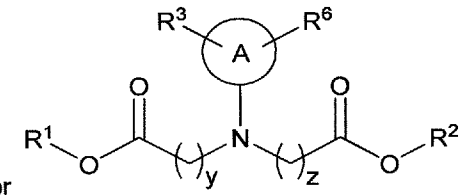


(IIIG) (IIIH)



(IIII)

or



(IIIJ)

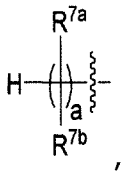
[0762] In some of the foregoing embodiments of Formula (III), n is an integer ranging from 2 to 12, for example from 2 to 8 or from 2 to 4. For example, in some embodiments, n is 3, 4, 5 or 6. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6.

[0763] In some other of the foregoing embodiments of Formula (III), y and z are each independently an integer ranging from 2 to 10. For example, in some embodiments, y and z are each independently an integer ranging from 4 to 9 or from 4 to 6.

[0764] In some of the foregoing embodiments of Formula (III), R^6 is H. In other of the foregoing embodiments, R^6 is C_1-C_{24} alkyl. In other embodiments, R^6 is OH.

[0765] In some embodiments of Formula (III), G^3 is unsubstituted. In other embodiments, G3 is substituted. In various different embodiments, G^3 is linear C_1-C_{24} alkylene or linear C_1-C_{24} alkenylene.

[0766] In some other foregoing embodiments of Formula (III), R^1 or R^2, or both, is C_6-C_{24} alkenyl. For example, in some embodiments, R^1 and R^2 each, independently have the following structure:



,

wherein:

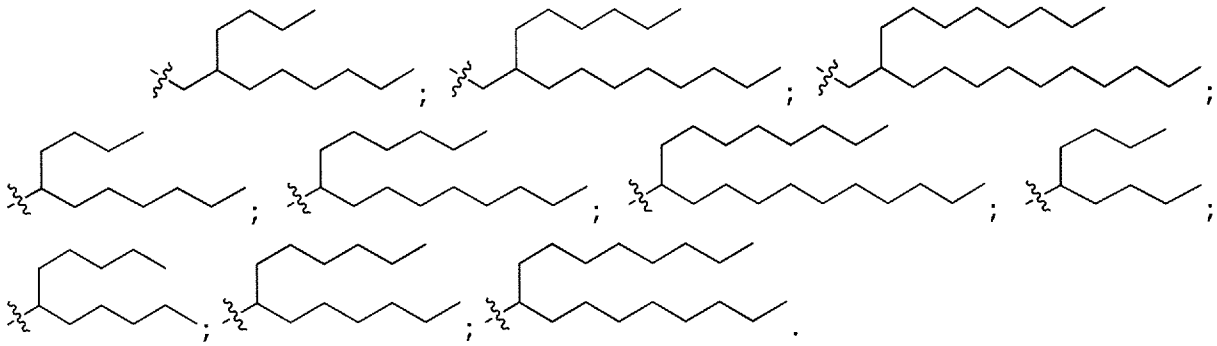
R^{7a} and R^{7b} are, at each occurrence, independently H or C_1-C_{12} alkyl; and

a is an integer from 2 to 12,

wherein R^{7a}, R^{7b} and a are each selected such that R^1 and R^2 each independently comprise from 6 to 20 carbon atoms. For example, in some embodiments a is an integer ranging from 5 to 9 or from 8 to 12.

[0767] In some of the foregoing embodiments of Formula (III), at least one occurrence of R^{7a} is H. For example, in some embodiments, R^{7a} is H at each occurrence. In other different embodiments of the foregoing, at least one occurrence of R^{7b} is C_1-C_8 alkyl. For example, in some embodiments, C_1-C_8 alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-hexyl or n-octyl.

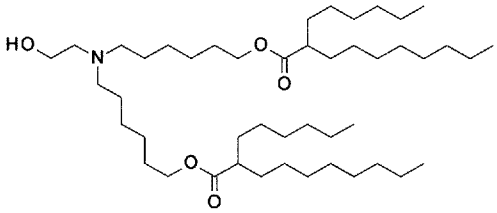
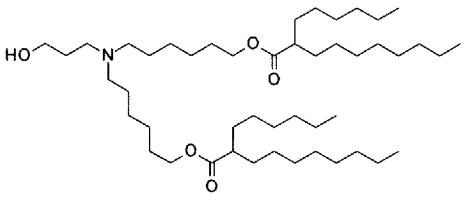
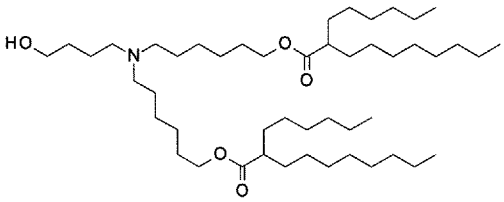
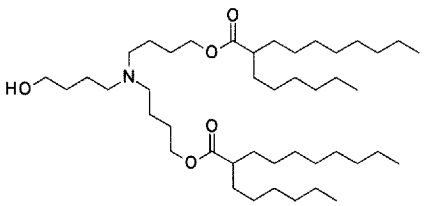
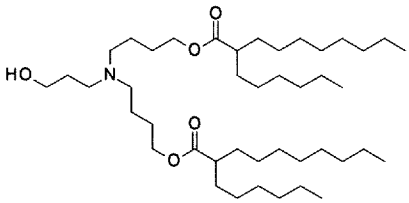
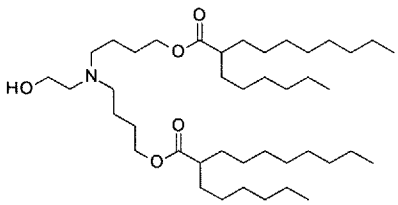
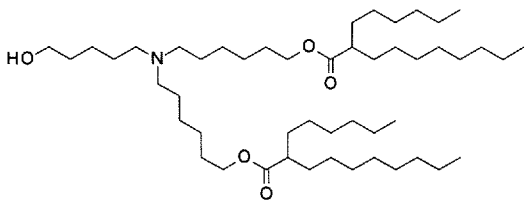
[0768] In different embodiments of Formula (III), R^1 or R^2, or both, has one of the following structures:

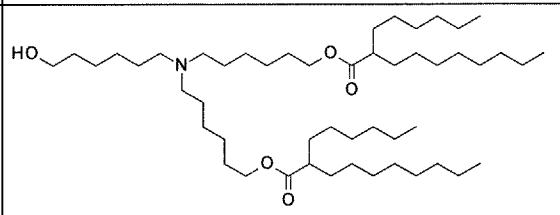
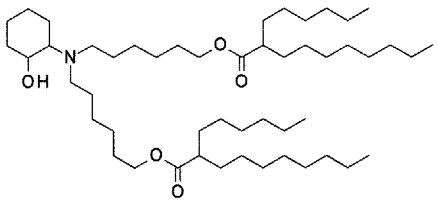
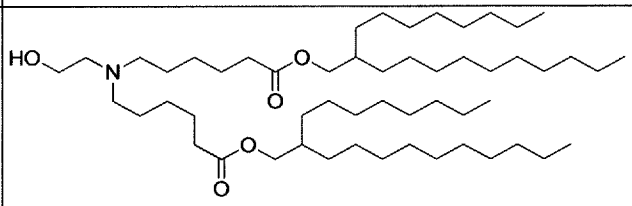
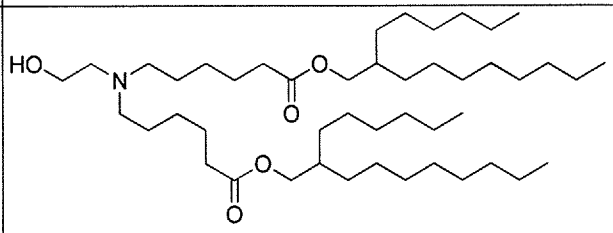
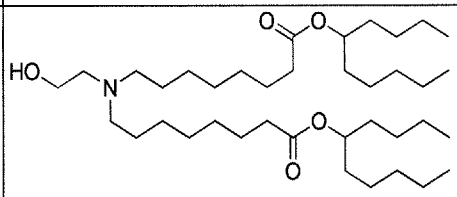
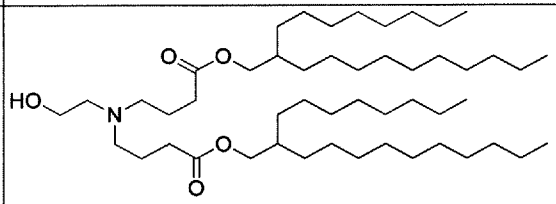
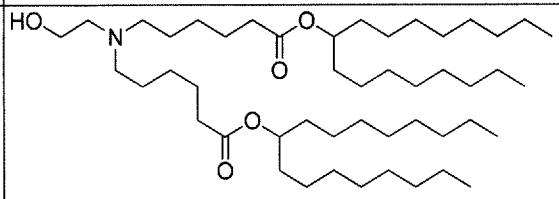
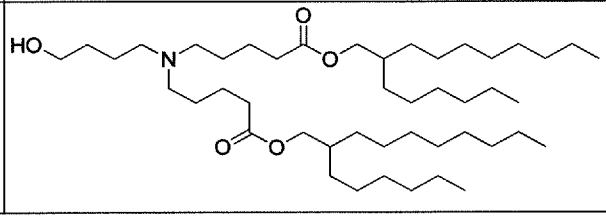


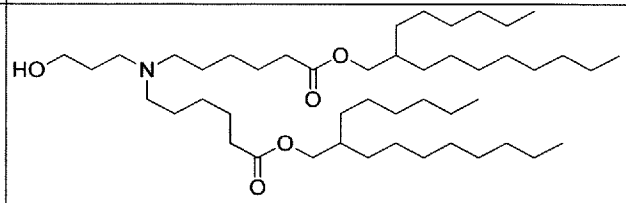
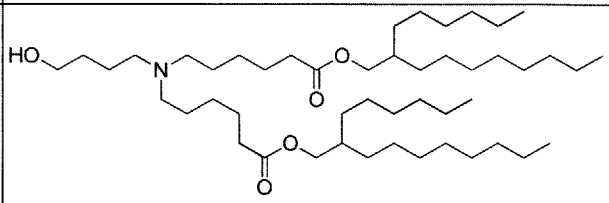
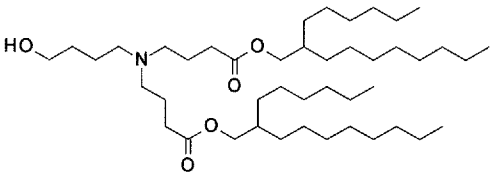
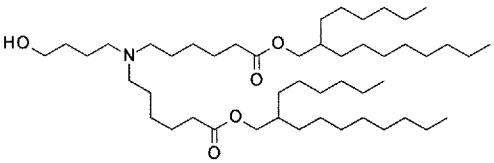
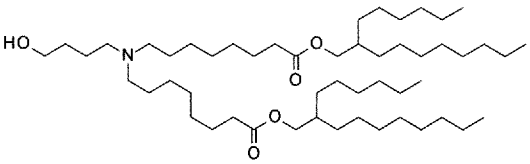
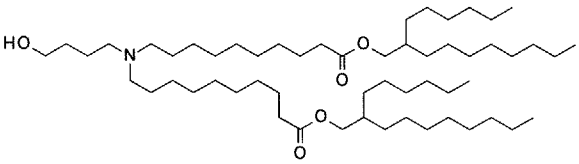
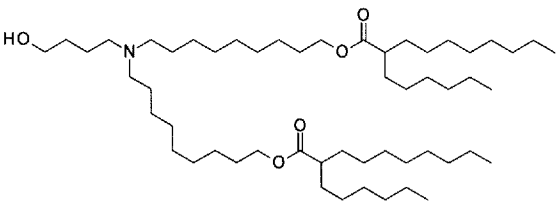
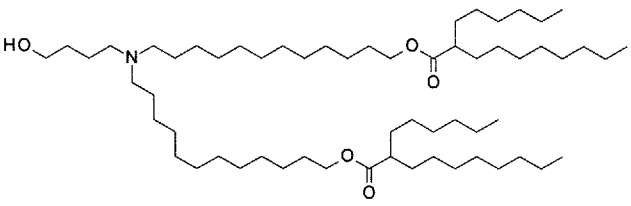
[0769] In some of the foregoing embodiments of Formula (III), R^3 is OH, CN, -C(=O)OR^4, -OC(=O)R^4 or –NHC(=O)R^4. In some embodiments, R^4 is methyl or ethyl.

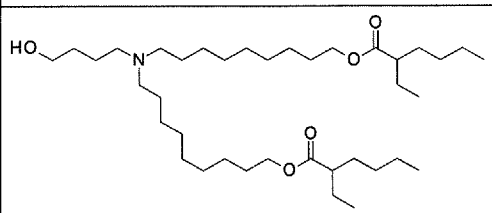
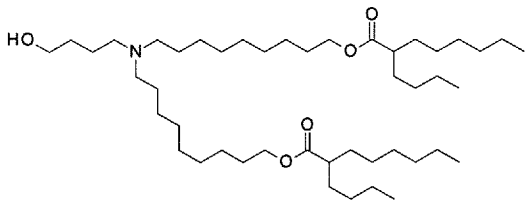
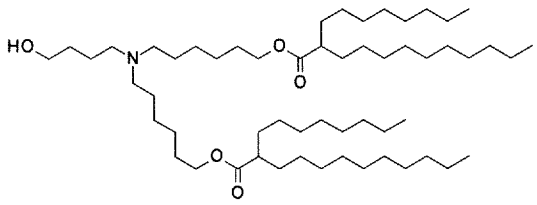
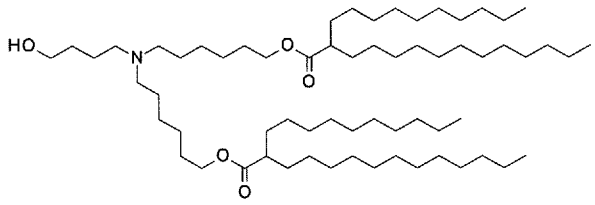
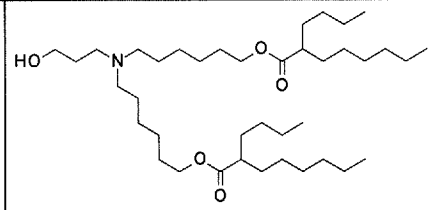
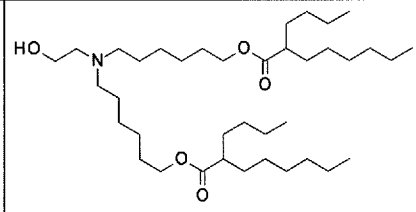
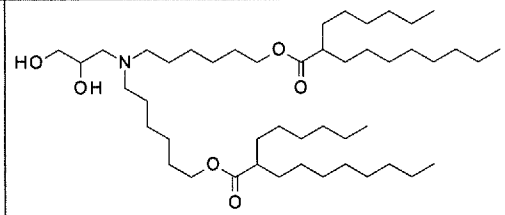
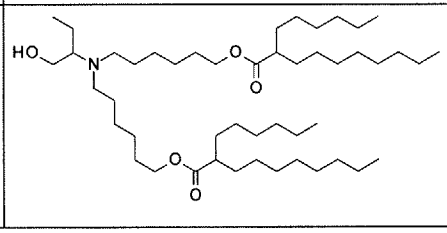
[0770] In various different embodiments, the cationic lipid of Formula (III) has one of the structures set forth in the table below.

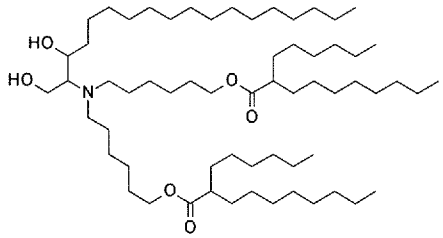
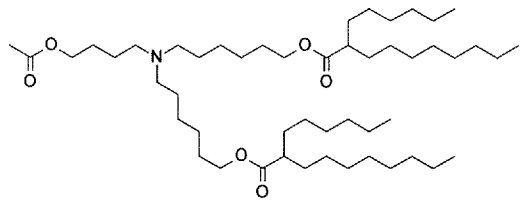
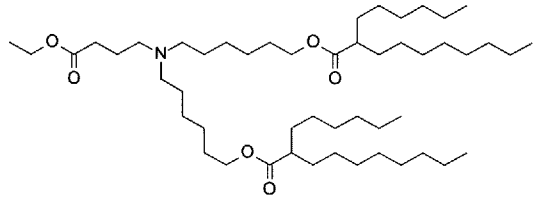
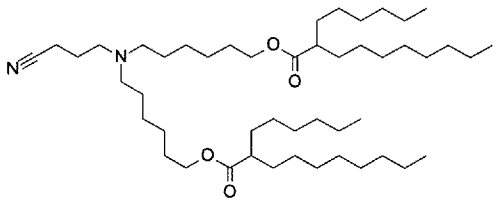
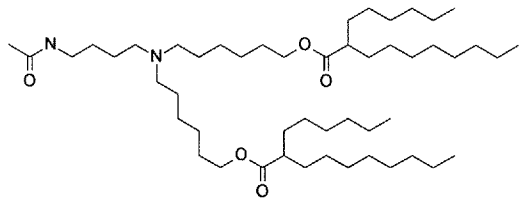
Table 17: Representative Compounds of Formula (III).

No.	Structure
III-1	
III-2	
III-3	
III-4	
III-5	
III-6	
III-7	

No.	Structure
III-8	
III-9	
III-10	
III-11	
III-12	
III-13	
III-14	
III-15	

No.	Structure
III-16	
III-17	
III-18	
III-19	
III-20	
III-21	
III-22	
III-23	

No.	Structure
III-24	
III-25	
III-26	
III-27	
III-28	
III-29	
III-30	
III-31	

No.	Structure
III-32	
III-33	
III-34	
III-35	
III-36	

[0771] In some embodiments, the LNP comprises a lipid of Formula (III), RNA, a neutral lipid, a steroid and a pegylated lipid. In some embodiments, the lipid of Formula (III) is compound III-3. In some embodiments, the neutral lipid is DSPC. In some embodiments, the steroid is cholesterol. In some embodiments, the pegylated lipid is ALC-0159.

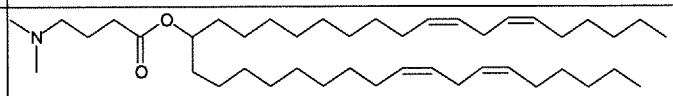
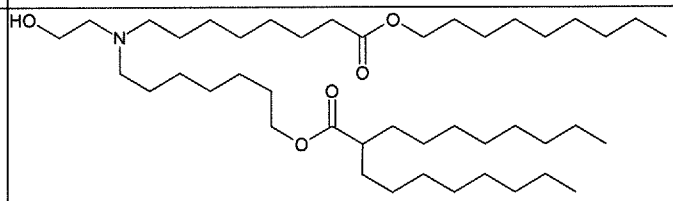
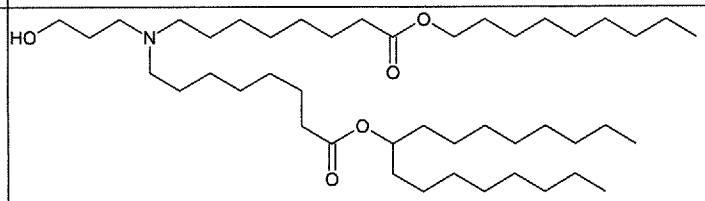
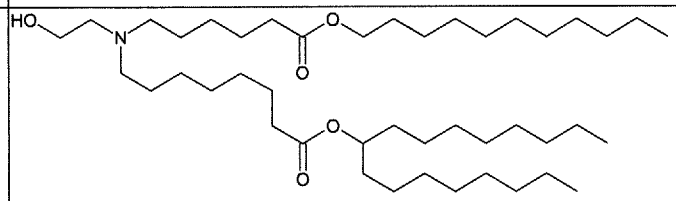
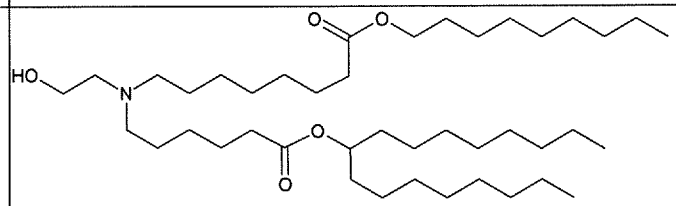
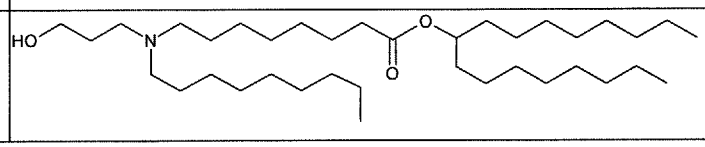
[0772] In some embodiments, the cationic lipid is present in the LNP in an amount from about 40 to about 50 mole percent. In one embodiment, the neutral lipid is present in the LNP in an amount from about 5 to about 15 mole percent. In one embodiment, the steroid is present in the LNP in an amount from about 35 to about 45 mole percent. In one embodiment, the pegylated lipid is present in the LNP in an amount from about 1 to about 10 mole percent.

[0773] In some embodiments, the LNP comprises compound III-3 in an amount from about 40 to about 50 mole percent, DSPC in an amount from about 5 to about 15 mole percent, cholesterol in an amount from about 35 to about 45 mole percent, and ALC-0159 in an amount from about 1 to about 10 mole percent.

[0774] In some embodiments, the LNP comprises compound III-3 in an amount of about 47.5 mole percent, DSPC in an amount of about 10 mole percent, cholesterol in an amount of about 40.7 mole percent, and ALC-0159 in an amount of about 1.8 mole percent.

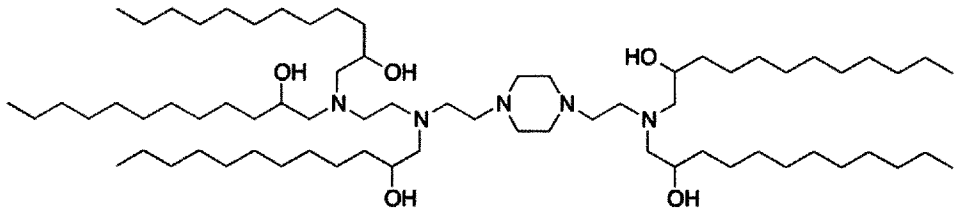
[0775] In various different embodiments, the cationic lipid has one of the structures set forth in the table below.

Table 18: Representative cationic lipids.

No.	Structure
A	
B	
C	
D	
E	
F	

[0776] In some embodiments, the LNP comprises a cationic lipid shown in the above table, e.g., a cationic lipid of Formula (B) or Formula (D), in particular a cationic lipid of Formula (D), RNA, a neutral lipid, a steroid and a pegylated lipid. In some embodiments, the neutral lipid is DSPC. In some embodiments, the steroid is cholesterol. In some embodiments, the pegylated lipid is DMG-PEG 2000.

[0777] In one embodiment, the LNP comprises a cationic lipid that is an ionizable lipid-like material (lipidoid). In one embodiment, the cationic lipid has the following structure:



[0778] The N/P value is preferably at least about 4. In some embodiments, the N/P value ranges from 4 to 20, 4 to 12, 4 to 10, 4 to 8, or 5 to 7. In one embodiment, the N/P value is about 6.

[0779] LNP described herein may have an average diameter that in one embodiment ranges from about 30 nm to about 200 nm, or from about 60 nm to about 120 nm.

RNA Targeting

[0780] Some aspects of the present disclosure involve the targeted delivery of the RNA disclosed herein (e.g., RNA encoding vaccine antigens and/or immunostimulants).

[0781] In one embodiment, the present disclosure involves targeting lung. Targeting lung is in particular preferred if the RNA administered is RNA encoding vaccine antigen. RNA may be delivered to lung, for example, by administering the RNA which may be formulated as particles as described herein, e.g., lipid particles, by inhalation.

[0782] In one embodiment, the present disclosure involves targeting the lymphatic system, in particular secondary lymphoid organs, more specifically spleen. Targeting the lymphatic system, in particular secondary lymphoid organs, more specifically spleen is in particular preferred if the RNA administered is RNA encoding vaccine antigen.

[0783] In one embodiment, the target cell is a spleen cell. In one embodiment, the target cell is an antigen presenting cell such as a professional antigen presenting cell in the spleen. In one embodiment, the target cell is a dendritic cell in the spleen.

[0784] The "lymphatic system" is part of the circulatory system and an important part of the immune system, comprising a network of lymphatic vessels that carry lymph. The lymphatic system consists of lymphatic organs, a conducting network of lymphatic vessels, and the circulating lymph. The primary or central lymphoid organs generate lymphocytes from immature progenitor cells. The thymus and the bone marrow constitute the primary lymphoid organs. Secondary or peripheral lymphoid organs, which include lymph nodes and the spleen, maintain mature naïve lymphocytes and initiate an adaptive immune response.

[0785] RNA may be delivered to spleen by so-called lipoplex formulations, in which the RNA is bound to liposomes comprising a cationic lipid and optionally an additional or helper lipid to form injectable nanoparticle formulations. The liposomes may be obtained by injecting a solution of the lipids in ethanol into water or a suitable aqueous phase. RNA lipoplex particles may be prepared by mixing the liposomes with RNA. Spleen targeting RNA lipoplex particles are described in WO 2013/143683, herein incorporated by reference. It has been found that RNA lipoplex particles having a net negative charge may be used to preferentially target spleen tissue or spleen cells such as antigen-presenting cells, in particular dendritic cells. Accordingly, following administration of the RNA lipoplex particles, RNA accumulation and/or RNA expression in the spleen occurs. Thus, RNA lipoplex particles of the present disclosure may be used for expressing RNA in the spleen. In an embodiment, after administration of the RNA lipoplex particles, no or essentially no RNA accumulation and/or RNA expression in the lung and/or liver occurs. In one embodiment, after administration of the RNA lipoplex particles, RNA accumulation and/or RNA expression in antigen presenting cells, such as professional antigen presenting cells in the spleen occurs. Thus, RNA lipoplex particles of the present disclosure may be used for expressing RNA in such antigen presenting cells. In one embodiment, the antigen presenting cells are dendritic cells and/or macrophages.

[0786] The electric charge of the RNA lipoplex particles of the present disclosure is the sum of the electric charges present in the at least one cationic lipid and the electric charges present in the RNA. The charge ratio is the ratio of the positive charges present in the at least one cationic lipid to the negative charges present in the RNA. The charge ratio of the positive charges present in the at least one cationic lipid to the negative charges present in the RNA is calculated by the following equation: charge ratio=[(cationic lipid concentration (mol)) * (the total number of positive charges in the cationic lipid)] / [(RNA concentration (mol)) * (the total number of negative charges in RNA)].

[0787] The spleen targeting RNA lipoplex particles described herein at physiological pH preferably have a net negative charge such as a charge ratio of positive charges to negative charges from about 1.9:2 to about 1:2, or about 1.6:2 to about 1:2, or about 1.6:2 to about 1.1:2. In specific embodiments, the charge ratio of positive charges to negative charges in the RNA lipoplex particles at physiological pH is about 1.9:2.0, about 1.8:2.0, about 1.7:2.0, about 1.6:2.0, about 1.5:2.0, about 1.4:2.0, about 1.3:2.0, about 1.2:2.0, about 1.1:2.0, or about 1:2.0.

[0788] Immunostimulants may be provided to a subject by administering to the subject RNA encoding an immunostimulant in a formulation for preferential delivery of RNA to liver or liver tissue. The delivery of RNA to such target organ or tissue is preferred, in particular, if it is desired to express large amounts of the immunostimulant and/or if systemic presence of the immunostimulant, in particular in significant amounts, is desired or required.

[0789] RNA delivery systems have an inherent preference to the liver. This pertains to lipid-based particles, cationic and neutral nanoparticles, in particular lipid nanoparticles such as liposomes, nanomicelles and lipophilic ligands in bioconjugates. Liver accumulation is caused by the discontinuous nature of the hepatic vasculature or the lipid metabolism (liposomes and lipid or cholesterol conjugates).

[0790] For *in vivo* delivery of RNA to the liver, a drug delivery system may be used to transport the RNA into the liver by preventing its degradation. For example, polyplex nanomicelles consisting of a poly(ethylene glycol) (PEG)-coated surface and an RNA (e.g., mRNA)-containing core is a useful system because the nanomicelles provide excellent *in vivo* stability of the RNA, under physiological conditions. Furthermore, the stealth property provided by the polyplex nanomicelle surface, composed of dense PEG palisades, effectively evades host immune defenses.

[0791] Examples of suitable immunostimulants for targeting liver are cytokines involved in T cell proliferation and/or maintenance. Examples of suitable cytokines include IL2 or IL7, fragments and variants thereof, and fusion proteins of these cytokines, fragments and variants, such as extended-PK cytokines.

[0792] In another embodiment, RNA encoding an immunostimulant may be administered in a formulation for preferential delivery of RNA to the lymphatic system, in particular secondary lymphoid organs, more specifically spleen. The delivery of an immunostimulant to such target tissue is preferred, in particular, if presence of the immunostimulant in this organ or tissue is desired (e.g., for inducing an immune response, in particular in case immunostimulants such as cytokines are required during T-cell priming or for activation of resident immune cells), while it is not desired that the immunostimulant is present systemically, in particular in significant amounts (e.g., because the immunostimulant has systemic toxicity).

[0793] Examples of suitable immunostimulants are cytokines involved in T cell priming. Examples of suitable cytokines include IL12, IL15, IFN-α, or IFN-β, fragments and variants thereof, and fusion proteins of these cytokines, fragments and variants, such as extended-PK cytokines.

Immunostimulants

[0794] In one embodiment, the RNA encoding vaccine antigen may be non-immunogenic. In this and other embodiments, the RNA encoding vaccine antigen may be co-administered with an immunostimulant or RNA encoding an immunostimulant. The methods and agents described herein are particularly effective if the

immunostimulant is attached to a pharmacokinetic modifying group (hereafter referred to as "extended-pharmacokinetic (PK)" immunostimulant). The methods and agents described herein are particularly effective if the immunostimulant is administered in the form of RNA encoding an immunostimulant. In one embodiment, said RNA is targeted to the liver for systemic availability. Liver cells can be efficiently transfected and are able to produce large amounts of protein.

[0795] An "immunostimulant" is any substance that stimulates the immune system by inducing activation or increasing activity of any of the immune system's components, in particular immune effector cells. The immunostimulant may be pro-inflammatory.

[0796] According to one aspect, the immunostimulant is a cytokine or a variant thereof. Examples of cytokines include interferons, such as interferon-alpha (IFN-α) or interferon-gamma (IFN-γ), interleukins, such as IL2, IL7, IL12, IL15 and IL23, colony stimulating factors, such as M-CSF and GM-CSF, and tumor necrosis factor. According to another aspect, the immunostimulant includes an adjuvant-type immunostimulatory agent such as APC Toll-like Receptor agonists or costimulatory/cell adhesion membrane proteins. Examples of Toll-like Receptor agonists include costimulatory/adhesion proteins such as CD80, CD86, and ICAM-1.

[0797] Cytokines are a category of small proteins (~5–20 kDa) that are important in cell signaling. Their release has an effect on the behavior of cells around them. Cytokines are involved in autocrine signaling, paracrine signaling and endocrine signaling as immunomodulating agents. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells. A given cytokine may be produced by more than one type of cell. Cytokines act through receptors, and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways.

[0798] According to the present disclosure, a cytokine may be a naturally occurring cytokine or a functional fragment or variant thereof. A cytokine may be human cytokine and may be derived from any vertebrate, especially any mammal. One particularly preferred cytokine is interferon-α.

Interferons

[0799] Interferons (IFNs) are a group of signaling proteins made and released by host cells in response to the presence of several pathogens, such as viruses, bacteria, parasites, and also tumor cells. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defenses.

[0800] Based on the type of receptor through which they signal, interferons are typically divided among three classes: type I interferon, type II interferon, and type III interferon.

[0801] All type I interferons bind to a specific cell surface receptor complex known as the IFN-α/β receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains.

[0802] The type I interferons present in humans are IFNα, IFNβ, IFNε, IFNκ and IFNω. In general, type I interferons are produced when the body recognizes a virus that has invaded it. They are produced by fibroblasts and monocytes. Once released, type I interferons bind to specific receptors on target cells, which leads to expression of proteins that will prevent the virus from producing and replicating its RNA and DNA.

[0803] The IFNα proteins are produced mainly by plasmacytoid dendritic cells (pDCs). They are mainly involved in innate immunity against viral infection. The genes responsible for their synthesis come in 13 subtypes that are called IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21. These genes are found together in a cluster on chromosome 9.

[0804] The IFNβ proteins are produced in large quantities by fibroblasts. They have antiviral activity that is involved mainly in innate immune response. Two types of IFNβ have been described, IFNβ1 and IFNβ3. The natural and recombinant forms of IFNβ1 have antiviral, antibacterial, and anticancer properties.

[0805] Type II interferon (IFNγ in humans) is also known as immune interferon and is activated by IL12. Furthermore, type II interferons are released by cytotoxic T cells and T helper cells.

[0806] Type III interferons signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12). Although discovered more recently than type I and type II IFNs, recent information demonstrates the importance of type III IFNs in some types of virus or fungal infections.

[0807] In general, type I and II interferons are responsible for regulating and activating the immune response.

[0808] According to the present disclosure, a type I interferon is preferably IFNα or IFNβ, more preferably IFNα.

[0809] According to the present disclosure, an interferon may be a naturally occurring interferon or a functional fragment or variant thereof. An interferon may be human interferon and may be derived from any vertebrate, especially any mammal.

Interleukins

[0810] Interleukins (ILs) are a group of cytokines (secreted proteins and signal molecules) that can be divided into four major groups based on distinguishing structural features. However, their amino acid sequence similarity is rather weak (typically 15–25% identity). The human genome encodes more than 50 interleukins and related proteins.

[0811] According to the present disclosure, an interleukin may be a naturally occurring interleukin or a functional fragment or variant thereof. An interleukin may be human interleukin and may be derived from any vertebrate, especially any mammal.

Extended-PK group

[0812] Immunostimulant polypeptides described herein can be prepared as fusion or chimeric polypeptides that include an immunostimulant portion and a heterologous polypeptide (i.e., a polypeptide that is not an immunostimulant). The immunostimulant may be fused to an extended-PK group, which increases circulation half-life. Non-limiting examples of extended-PK groups are described infra. It should be understood that other PK groups that increase the circulation half-life of immunostimulants such as cytokines, or variants thereof, are also applicable to the present disclosure. In certain embodiments, the extended-PK group is a serum albumin domain (e.g., mouse serum albumin, human serum albumin).

[0813] As used herein, the term "PK" is an acronym for "pharmacokinetic" and encompasses properties of a compound including, by way of example, absorption, distribution, metabolism, and elimination by a subject. As used herein, an "extended-PK group" refers to a protein, peptide, or moiety that increases the circulation half-life of a biologically active molecule when fused to or administered together with the biologically active molecule. Examples of an extended-PK group include serum albumin (e.g., HSA), Immunoglobulin Fc or Fc fragments and variants thereof, transferrin and variants thereof, and human serum albumin (HSA) binders (as disclosed in U.S. Publication Nos. 2005/0287153 and 2007/0003549). Other exemplary extended-PK groups are disclosed in Kontermann, Expert Opin Biol Ther, 2016 Jul;16(7):903-15 which is herein incorporated by reference in its entirety. As used herein, an "extended-PK" immunostimulant refers to an immunostimulant moiety in combination with an extended-PK group. In one embodiment, the extended-PK immunostimulant is a fusion protein in which an immunostimulant moiety is linked or fused to an extended-PK group.

[0814] In certain embodiments, the serum half-life of an extended-PK immunostimulant is increased relative to the immunostimulant alone (i.e., the immunostimulant not fused to an extended-PK group). In certain embodiments, the serum half-life of the extended-PK immunostimulant is at least 20, 40, 60, 80, 100, 120, 150, 180, 200, 400, 600, 800, or 1000% longer relative to the serum half-life of the immunostimulant alone. In certain embodiments, the serum half-life of the extended-PK immunostimulant is at least 1.5-fold, 2-fold, 2.5-fold, 3-fold, 3.5 fold, 4-fold, 4.5-fold, 5-fold, 6-fold, 7-fold, 8-fold, 10- fold, 12-fold, 13-fold, 15-fold, 17-fold, 20-fold, 22- fold, 25-fold, 27-fold, 30-fold, 35-fold, 40-fold, or 50-fold greater than the serum half-life of the immunostimulant alone. In certain embodiments, the serum half-life of the extended-PK immunostimulant is at least 10 hours, 15 hours, 20 hours, 25 hours, 30 hours, 35 hours, 40 hours, 50 hours, 60 hours, 70 hours, 80 hours, 90 hours, 100 hours, 110 hours, 120 hours, 130 hours, 135 hours, 140 hours, 150 hours, 160 hours, or 200 hours.

[0815] As used herein, "half-life" refers to the time taken for the serum or plasma concentration of a compound such as a peptide or protein to reduce by 50%, *in vivo*, for example due to degradation and/or clearance or sequestration by natural mechanisms. An extended-PK immunostimulant suitable for use herein is stabilized *in vivo* and its half-life increased by, e.g., fusion to serum albumin (e.g., HSA or MSA), which resist degradation and/or clearance or sequestration. The half-life can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art, and may for example generally involve the steps of suitably administering a suitable dose of the amino acid sequence or compound to a subject; collecting blood samples or other samples from said subject at regular intervals; determining the level or concentration of the amino acid sequence or compound in said blood sample; and calculating, from (a plot of) the data thus obtained, the time until the level or concentration of the amino acid sequence or compound has been reduced by 50% compared to the initial level upon dosing. Further details are provided in, e.g., standard handbooks, such as Kenneth, A. et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in Peters et al., Pharmacokinetic Analysis: A Practical Approach (1996). Reference is also made to Gibaldi, M. et al., Pharmacokinetics, 2nd Rev. Edition, Marcel Dekker (1982).

[0816] In certain embodiments, the extended-PK group includes serum albumin, or fragments thereof or variants of the serum albumin or fragments thereof (all of which for the purpose of the present disclosure are comprised by the term "albumin"). Polypeptides described herein may be fused to albumin (or a fragment or variant thereof) to form albumin fusion proteins. Such albumin fusion proteins are described in U.S. Publication No. 20070048282.

[0817] As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a protein such as a therapeutic protein, in particular an immunostimulant. The albumin fusion protein may be generated by translation of a nucleic acid in which a polynucleotide encoding a therapeutic protein is joined in-frame with a polynucleotide encoding an albumin. The therapeutic protein and albumin, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein (e.g., a "therapeutic protein portion" or an "albumin protein portion"). In a highly preferred embodiment, an albumin fusion protein comprises at least one molecule of a therapeutic protein (including, but not limited to a mature form of the therapeutic protein) and at least one molecule of albumin (including but not limited to a mature form of albumin). In one embodiment, an albumin fusion protein is processed by a host cell such as a cell of the target organ for administered RNA, e.g. a liver cell, and secreted into the circulation. Processing of the nascent albumin fusion protein that occurs in the secretory pathways of the host cell used for expression of the RNA may include, but is not limited to signal peptide cleavage; formation of disulfide bonds; proper folding; addition and processing of carbohydrates (such as for example, N- and O-linked glycosylation); specific proteolytic cleavages; and/or assembly into multimeric proteins. An albumin fusion protein is preferably encoded by RNA in a non-processed form which in particular has a signal peptide at its N-terminus

and following secretion by a cell is preferably present in the processed form wherein in particular the signal peptide has been cleaved off. In a most preferred embodiment, the "processed form of an albumin fusion protein" refers to an albumin fusion protein product which has undergone N-terminal signal peptide cleavage, herein also referred to as a "mature albumin fusion protein".

[0818] In preferred embodiments, albumin fusion proteins comprising a therapeutic protein have a higher plasma stability compared to the plasma stability of the same therapeutic protein when not fused to albumin. Plasma stability typically refers to the time period between when the therapeutic protein is administered *in vivo* and carried into the bloodstream and when the therapeutic protein is degraded and cleared from the bloodstream, into an organ, such as the kidney or liver, that ultimately clears the therapeutic protein from the body. Plasma stability is calculated in terms of the half-life of the therapeutic protein in the bloodstream. The half-life of the therapeutic protein in the bloodstream can be readily determined by common assays known in the art.

[0819] As used herein, "albumin" refers collectively to albumin protein or amino acid sequence, or an albumin fragment or variant, having one or more functional activities (e.g., biological activities) of albumin. In particular, "albumin" refers to human albumin or fragments or variants thereof especially the mature form of human albumin, or albumin from other vertebrates or fragments thereof, or variants of these molecules. The albumin may be derived from any vertebrate, especially any mammal, for example human, cow, sheep, or pig. Non-mammalian albumins include, but are not limited to, hen and salmon. The albumin portion of the albumin fusion protein may be from a different animal than the therapeutic protein portion.

[0820] In certain embodiments, the albumin is human serum albumin (HSA), or fragments or variants thereof, such as those disclosed in US 5,876,969, WO 2011/124718, WO 2013/075066, and WO 2011/0514789.

[0821] The terms, human serum albumin (HSA) and human albumin (HA) are used interchangeably herein. The terms, "albumin and "serum albumin" are broader, and encompass human serum albumin (and fragments and variants thereof) as well as albumin from other species (and fragments and variants thereof).

[0822] As used herein, a fragment of albumin sufficient to prolong the therapeutic activity or plasma stability of the therapeutic protein refers to a fragment of albumin sufficient in length or structure to stabilize or prolong the therapeutic activity or plasma stability of the protein so that the plasma stability of the therapeutic protein portion of the albumin fusion protein is prolonged or extended compared to the plasma stability in the non-fusion state.

[0823] The albumin portion of the albumin fusion proteins may comprise the full length of the albumin sequence, or may include one or more fragments thereof that are capable of stabilizing or prolonging the therapeutic activity or plasma stability. Such fragments may be of 10 or more amino acids in length or may include about 15, 20, 25, 30, 50, or more contiguous amino acids from the albumin sequence or may include part or all of specific domains of albumin. For instance, one or more fragments of HSA spanning the first two immunoglobulin-like domains may be used. In a preferred embodiment, the HSA fragment is the mature form of HSA.

[0824] Generally speaking, an albumin fragment or variant will be at least 100 amino acids long, preferably at least 150 amino acids long.

[0825] According to the present disclosure, albumin may be naturally occurring albumin or a fragment or variant thereof. Albumin may be human albumin and may be derived from any vertebrate, especially any mammal.

[0826] Preferably, the albumin fusion protein comprises albumin as the N-terminal portion, and a therapeutic protein as the C-terminal portion. Alternatively, an albumin fusion protein comprising albumin as the C-terminal portion, and a therapeutic protein as the N-terminal portion may also be used. In other embodiments, the albumin fusion protein has a therapeutic protein fused to both the N-terminus and the C-terminus of albumin. In a preferred embodiment, the therapeutic proteins fused at the N- and C-termini are the same therapeutic proteins. In another preferred embodiment, the therapeutic proteins fused at the N- and C-termini are different therapeutic proteins. In one embodiment, the different therapeutic proteins are both cytokines.

[0827] In one embodiment, the therapeutic protein(s) is (are) joined to the albumin through (a) peptide linker(s). A linker peptide between the fused portions may provide greater physical separation between the moieties and thus maximize the accessibility of the therapeutic protein portion, for instance, for binding to its cognate receptor. The linker peptide may consist of amino acids such that it is flexible or more rigid. The linker sequence may be cleavable by a protease or chemically.

[0828] As used herein, the term "Fc region" refers to the portion of a native immunoglobulin formed by the respective Fc domains (or Fc moieties) of its two heavy chains. As used herein, the term "Fc domain" refers to a portion or fragment of a single immunoglobulin (Ig) heavy chain wherein the Fc domain does not comprise an Fv domain. In certain embodiments, an Fc domain begins in the hinge region just upstream of the papain cleavage site and ends at the C-terminus of the antibody. Accordingly, a complete Fc domain comprises at least a hinge domain, a CH2 domain, and a CH3 domain. In certain embodiments, an Fc domain comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, a CH4 domain, or a variant, portion, or fragment thereof. In certain embodiments, an Fc domain comprises a complete Fc domain (i.e., a hinge domain, a CH2 domain, and a CH3 domain). In certain embodiments, an Fc domain comprises a hinge domain (or portion thereof) fused to a CH3 domain (or portion thereof). In certain embodiments, an Fc domain comprises a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof). In certain embodiments, an Fc domain consists of a CH3 domain or portion thereof. In certain embodiments, an Fc domain consists of a hinge domain (or portion thereof) and a CH3 domain (or portion thereof). In certain embodiments, an Fc domain consists of a CH2 domain (or portion thereof) and a CH3 domain. In certain embodiments, an Fc domain consists of a hinge domain (or portion thereof) and a CH2 domain (or portion thereof). In certain embodiments, an Fc domain lacks at least a portion of a CH2 domain (e.g., all or part of a CH2 domain). An Fc domain herein generally refers to a polypeptide comprising all or part of the Fc domain of an immunoglobulin heavy-chain. This includes, but is not limited to, polypeptides comprising the entire CH1, hinge, CH2, and/or CH3 domains as well as fragments of such peptides comprising only, e.g., the hinge, CH2, and CH3 domain. The Fc domain may be derived from an immunoglobulin of any species and/or any subtype, including, but not limited to, a human IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody. The Fc domain encompasses native Fc and Fc variant molecules. As set forth herein, it will be understood by one of ordinary skill in the art that any Fc domain may be modified such that it varies in amino acid sequence from the native Fc domain of a naturally occurring immunoglobulin molecule. In certain embodiments, the Fc domain has reduced effector function (e.g., FcγR binding).

[0829] The Fc domains of a polypeptide described herein may be derived from different immunoglobulin molecules. For example, an Fc domain of a polypeptide may comprise a CH2 and/or CH3 domain derived from an IgG1 molecule and a hinge region derived from an IgG3 molecule. In another example, an Fc domain can comprise a chimeric hinge region derived, in part, from an IgG1 molecule and, in part, from an IgG3 molecule. In another example, an Fc domain can comprise a chimeric hinge derived, in part, from an IgG1 molecule and, in part, from an IgG4 molecule.

[0830] In certain embodiments, an extended-PK group includes an Fc domain or fragments thereof or variants of the Fc domain or fragments thereof (all of which for the purpose of the present disclosure are comprised by the term "Fc domain"). The Fc domain does not contain a variable region that binds to antigen. Fc domains suitable for use in the present disclosure may be obtained from a number of different sources. In certain embodiments, an Fc domain is derived from a human immunoglobulin. In certain embodiments, the Fc domain is from a human IgG1 constant region. It is understood, however, that the Fc domain may be derived from an immunoglobulin of another mammalian species, including for example, a rodent (e.g. a mouse, rat, rabbit, guinea pig) or non- human primate (e.g. chimpanzee, macaque) species.

[0831] Moreover, the Fc domain (or a fragment or variant thereof) may be derived from any immunoglobulin class, including IgM, IgG, IgD, IgA, and IgE, and any immunoglobulin isotype, including IgG1, IgG2, IgG3, and IgG4.

[0832] A variety of Fc domain gene sequences (e.g., mouse and human constant region gene sequences) are available in the form of publicly accessible deposits. Constant region domains comprising an Fc domain sequence can be selected lacking a particular effector function and/or with a particular modification to reduce immunogenicity. Many sequences of antibodies and antibody-encoding genes have been published and suitable Fc domain sequences (e.g. hinge, CH2, and/or CH3 sequences, or fragments or variants thereof) can be derived from these sequences using art recognized techniques.

[0833] In certain embodiments, the extended-PK group is a serum albumin binding protein such as those described in US2005/0287153, US2007/0003549, US2007/0178082, US2007/0269422, US2010/0113339, WO2009/083804, and WO2009/133208, which are herein incorporated by reference in their entirety. In certain embodiments, the extended-PK group is transferrin, as disclosed in US 7,176,278 and US 8,158,579, which are herein incorporated by reference in their entirety. In certain embodiments, the extended-PK group is a serum immunoglobulin binding protein such as those disclosed in US2007/0178082, US2014/0220017, and US2017/0145062, which are herein incorporated by reference in their entirety. In certain embodiments, the extended-PK group is a fibronectin (Fn)-based scaffold domain protein that binds to serum albumin, such as those disclosed in US2012/0094909, which is herein incorporated by reference in its entirety. Methods of making fibronectin-based scaffold domain proteins are also disclosed in US2012/0094909. A non-limiting example of a Fn3-based extended-PK group is Fn3(HSA), i.e., a Fn3 protein that binds to human serum albumin.

[0834] In certain aspects, the extended-PK immunostimulant, suitable for use according to the present disclosure, can employ one or more peptide linkers. As used herein, the term "peptide linker" refers to a peptide or polypeptide sequence which connects two or more domains (e.g., the extended-PK moiety and an immunostimulant moiety) in a linear amino acid sequence of a polypeptide chain. For example, peptide linkers may be used to connect an immunostimulant moiety to a HSA domain.

[0835] Linkers suitable for fusing the extended-PK group to e.g. an immunostimulant are well known in the art. Exemplary linkers include glycine-serine-polypeptide linkers, glycine-proline-polypeptide linkers, and proline-alanine polypeptide linkers. In certain embodiments, the linker is a glycine-serine-polypeptide linker, i.e., a peptide that consists of glycine and serine residues.

[0836] In addition to, or in place of, the heterologous polypeptides described above, an immunostimulant polypeptide described herein can contain sequences encoding a "marker" or "reporter". Examples of marker or reporter genes include β-lactamase, chloramphenicol acetyltransferase (CAT), adenosine deaminase (ADA), aminoglycoside phosphotransferase, dihydrofolate reductase (DHFR), hygromycin-B-hosphotransferase (HPH), thymidine kinase (TK), β-galactosidase, and xanthine guanine phosphoribosyltransferase (XGPRT).

Pharmaceutical compositions

[0837] The agents described herein may be administered in pharmaceutical compositions or medicaments and may be administered in the form of any suitable pharmaceutical composition.

[0838] In one embodiment, the pharmaceutical composition described herein is an immunogenic composition for inducing an immune response against coronavirus in a subject. For example, in one embodiment, the immunogenic composition is a vaccine.

[0839] In one embodiment of all aspects of the present disclosure, the components described herein such as RNA encoding a vaccine antigen may be administered in a pharmaceutical composition which may comprise a pharmaceutically acceptable carrier and may optionally comprise one or more adjuvants, stabilizers etc. In one

embodiment, the pharmaceutical composition is for therapeutic or prophylactic treatments, e.g., for use in treating or preventing a coronavirus infection.

[0840] The term "pharmaceutical composition" relates to a formulation comprising a therapeutically effective agent, preferably together with pharmaceutically acceptable carriers, diluents and/or excipients. Said pharmaceutical composition is useful for treating, preventing, or reducing the severity of a disease or disorder by administration of said pharmaceutical composition to a subject. A pharmaceutical composition is also known in the art as a pharmaceutical formulation.

[0841] The pharmaceutical compositions of the present disclosure may comprise one or more adjuvants or may be administered with one or more adjuvants. The term "adjuvant" relates to a compound which prolongs, enhances or accelerates an immune response. Adjuvants comprise a heterogeneous group of compounds such as oil emulsions (e.g., Freund's adjuvants), mineral compounds (such as alum), bacterial products (such as Bordetella pertussis toxin), or immune-stimulating complexes. Examples of adjuvants include, without limitation, LPS, GP96, CpG oligodeoxynucleotides, growth factors, and cytokines, such as monokines, lymphokines, interleukins, chemokines. The cytokines may be IL1, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IFNα, IFNγ, GM-CSF, LT-a. Further known adjuvants are aluminium hydroxide, Freund's adjuvant or oil such as Montanide® ISA51. Other suitable adjuvants for use in the present disclosure include lipopeptides, such as Pam3Cys.

[0842] The pharmaceutical compositions according to the present disclosure are generally applied in a "pharmaceutically effective amount" and in "a pharmaceutically acceptable preparation".

[0843] The term "pharmaceutically acceptable" refers to the non-toxicity of a material which does not interact with the action of the active component of the pharmaceutical composition.

[0844] The term "pharmaceutically effective amount" or "therapeutically effective amount" refers to the amount which achieves a desired reaction or a desired effect alone or together with further doses. In the case of the treatment of a particular disease, the desired reaction preferably relates to inhibition of the course of the disease. This comprises slowing down the progress of the disease and, in particular, interrupting or reversing the progress of the disease. The desired reaction in a treatment of a disease may also be delay of the onset or a prevention of the onset of said disease or said condition. An effective amount of the compositions described herein will depend on the condition to be treated, the severeness of the disease, the individual parameters of the patient, including age, physiological condition, size and weight, the duration of treatment, the type of an accompanying therapy (if present), the specific route of administration and similar factors. Accordingly, the doses administered of the compositions described herein may depend on various of such parameters. In the case that a reaction in a patient is insufficient with an initial dose, higher doses (or effectively higher doses achieved by a different, more localized route of administration) may be used.

[0845] The pharmaceutical compositions of the present disclosure may contain salts, buffers, preservatives, and optionally other therapeutic agents. In one embodiment, the pharmaceutical compositions of the present disclosure comprise one or more pharmaceutically acceptable carriers, diluents and/or excipients.

[0846] Suitable preservatives for use in the pharmaceutical compositions of the present disclosure include, without limitation, benzalkonium chloride, chlorobutanol, paraben and thimerosal.

[0847] The term "excipient" as used herein refers to a substance which may be present in a pharmaceutical composition of the present disclosure but is not an active ingredient. Examples of excipients, include without limitation, carriers, binders, diluents, lubricants, thickeners, surface active agents, preservatives, stabilizers, emulsifiers, buffers, flavoring agents, or colorants.

[0848] The term "diluent" relates a diluting and/or thinning agent. Moreover, the term "diluent" includes any one or more of fluid, liquid or solid suspension and/or mixing media. Examples of suitable diluents include ethanol, glycerol and water.

[0849] The term "carrier" refers to a component which may be natural, synthetic, organic, inorganic in which the active component is combined in order to facilitate, enhance or enable administration of the pharmaceutical composition. A carrier as used herein may be one or more compatible solid or liquid fillers, diluents or encapsulating substances, which are suitable for administration to subject. Suitable carrier include, without limitation, sterile water, Ringer, Ringer lactate, sterile sodium chloride solution, isotonic saline, polyalkylene glycols, hydrogenated naphthalenes and, in particular, biocompatible lactide polymers, lactide/glycolide copolymers or polyoxyethylene/polyoxy-propylene copolymers. In one embodiment, the pharmaceutical composition of the present disclosure includes isotonic saline.

[0850] Pharmaceutically acceptable carriers, excipients or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R Gennaro edit. 1985).

[0851] Pharmaceutical carriers, excipients or diluents can be selected with regard to the intended route of administration and standard pharmaceutical practice.

[0852] In one embodiment, pharmaceutical compositions described herein may be administered intravenously, intraarterially, subcutaneously, intradermally or intramuscularly. In certain embodiments, the pharmaceutical composition is formulated for local administration or systemic administration. Systemic administration may include enteral administration, which involves absorption through the gastrointestinal tract, or parenteral administration. As used herein, "parenteral administration" refers to the administration in any manner other than through the gastrointestinal tract, such as by intravenous injection. In a preferred embodiment, the pharmaceutical composition is formulated for intramuscular administration. In another embodiment, the pharmaceutical composition is formulated for systemic administration, e.g., for intravenous administration.

[0853] The term "co-administering" as used herein means a process whereby different compounds or compositions (e.g., RNA encoding an antigen and RNA encoding an immunostimulant) are administered to the same patient. The different compounds or compositions may be administered simultaneously, at essentially the same time, or sequentially.

[0854] The pharmaceutical compositions and products described herein may be provided as a frozen concentrate for solution for injection, e.g., at a concentration of 0.50 mg/mL. In one embodiment, for preparation of solution for injection, a drug product is thawed and diluted with isotonic sodium chloride solution (e.g., 0.9% NaCl, saline), e.g., by a one-step dilution process. In some embodiments, bacteriostatic sodium chloride solution (e.g., 0.9% NaCl, saline) cannot be used as a diluent. In some embodiments, a diluted drug product is an off-white suspension. The concentration of the final solution for injection varies depending on the respective dose level to be administered.

[0855] In one embodiment, administration is performed within 6 h after begin of preparation due to the risk of microbial contamination and considering the multiple-dose approach of the preparation process. In one embodiment, in this period of 6 h, two conditions are allowed: room temperature for preparation, handling and transfer as well as 2 to 8°C for storage.

[0856] Compositions described herein may be shipped and/or stored under temperature-controlled conditions, e.g., temperature conditions of about 4-5°C or below, about -20°C or below, - 70°C±10°C (e.g., -80°C to -60°C), e.g., utilizing a cooling system (e.g., that may be or include dry ice) to maintain the desired temperature. In one embodiment, compositions described herein are shipped in temperature-controlled thermal shippers. Such shippers may contain a GPS-enabled thermal sensor to track the location and temperature of each shipment. The compositions can be stored by refilling with, e.g., dry ice.

Treatments

[0857] The present disclosure provides methods and agents for inducing an adaptive immune response against coronavirus in a subject comprising administering an effective amount of a composition comprising RNA encoding a coronavirus vaccine antigen described herein.

[0858] In one embodiment, the methods and agents described herein provide immunity in a subject to coronavirus, coronavirus infection, or to a disease or disorder associated with coronavirus. The present disclosure thus provides methods and agents for treating or preventing the infection, disease, or disorder associated with coronavirus.

[0859] In one embodiment, the methods and agents described herein are administered to a subject having an infection, disease, or disorder associated with coronavirus. In one embodiment, the methods and agents described herein are administered to a subject at risk for developing the infection, disease, or disorder associated with coronavirus. For example, the methods and agents described herein may be administered to a subject who is at risk for being in contact with coronavirus. In one embodiment, the methods and agents described herein are administered to a subject who lives in, traveled to, or is expected to travel to a geographic region in which coronavirus is prevalent. In one embodiment, the methods and agents described herein are administered to a subject who is in contact with or expected to be in contact with another person who lives in, traveled to, or is expected to travel to a geographic region in which coronavirus is prevalent. In one embodiment, the methods and agents described herein are administered to a subject who has knowingly been exposed to coronavirus through their occupation, or other contact. In one embodiment, a coronavirus is SARS-CoV-2. In some embodiments, methods and agents described herein are administered to a subject with evidence of prior exposure to and/or infection with SARS-CoV-2 and/or an antigen or epitope thereof or cross-reactive therewith. For example, in some embodiments, methods and agents described herein are administered to a subject in whom antibodies, B cells, and/or T cells reactive with one or more epitopes of a SARS-CoV-2 spike protein are detectable and/or have been detected.

[0860] For a composition to be useful as a vaccine, the composition must induce an immune response against the coronavirus antigen in a cell, tissue or subject (e.g., a human). In some embodiments, the composition induces an immune response against the coronavirus antigen in a cell, tissue or subject (e.g., a human). In some instances, the vaccine induces a protective immune response in a mammal. The therapeutic compounds or compositions of the present disclosure may be administered prophylactically (i.e., to prevent a disease or disorder) or therapeutically (i.e., to treat a disease or disorder) to subjects suffering from, or at risk of (or susceptible to) developing a disease or disorder. Such subjects may be identified using standard clinical methods. In the context of the present disclosure, prophylactic administration occurs prior to the manifestation of overt clinical symptoms of disease, such that a disease or disorder is prevented or alternatively delayed in its progression. In the context of the field of medicine, the term "prevent" encompasses any activity, which reduces the burden of mortality or morbidity from disease. Prevention can occur at primary, secondary and tertiary prevention levels. While primary prevention avoids the development of a disease, secondary and tertiary levels of prevention encompass activities aimed at preventing the progression of a disease and the emergence of symptoms as well as reducing the negative impact of an already established disease by restoring function and reducing disease-related complications.

[0861] The term "dose" as used herein refers in general to a "dose amount" which relates to the amount of RNA administered per administration, i.e., per dosing.

[0862] In some embodiments, administration of an immunogenic composition or vaccine of the present disclosure may be performed by single administration or boosted by multiple administrations.

[0863] In some embodiments, a regimen described herein includes at least one dose. In some embodiments, a regimen includes a first dose and at least one subsequent dose. In some embodiments, the first dose is the same

amount as at least one subsequent dose. In some embodiments, the first dose is the same amount as all subsequent doses. In some embodiments, the first dose is a different amount as at least one subsequent dose. In some embodiments, the first dose is a different amount than all subsequent doses. In some embodiments, a regimen comprises two doses. In some embodiments, a provided regimen consists of two doses. In some embodiments, a regimen comprises three doses.

[0864] In one embodiment, the present disclosure envisions administration of a single dose. In one embodiment, the present disclosure envisions administration of a priming dose followed by one or more booster doses. The booster dose or the first booster dose may be administered 7 to 28 days or 14 to 24 days following administration of the priming dose. In some embodiments, a first booster dose may be administered 1 week to 3 months (e.g., 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks) following administration of a priming dose. In some embodiments, a subsequent booster dose may be administered at least 1 week or longer, including, e.g., at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, or longer, following a preceding booster dose. In some embodiments, subsequent booster doses may be administered about 5-9 weeks or 6-8 weeks apart. In some embodiments, at least one subsequent booster dose (e.g., after a first booster dose) may be administered at least 3 months or longer, including, e.g., at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, or longer, following a preceding dose.

[0865] In some embodiments, a subsequent dose given to an individual (e.g., as part of a primary regimen or booster regimen) can have the same amount of RNA as previously given to the individual. In some embodiments, a subsequent dose given to an individual (e.g., as part of a primary regimen or booster regimen) can differ in the amount of RNA, as compared to the amount previously given to the individual. For example, in some embodiments, a subsequent dose can be higher or lower than the prior dose, for example, based on consideration of various factors, including, e.g., immunogenicity and/or reactogenicity induced by the prior dose, prevalence of the disease, etc. In some embodiments, a subsequent dose can be higher than a prior dose by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or higher. In some embodiments, a subsequent dose can be higher than a prior dose by at least 1.5-fold, at least 2-fold, at least 2.5 fold, at least 3-fold, or higher. In some embodiments, a subsequent dose can be higher than a prior dose by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or higher. In some embodiments, a subsequent dose can be lower than a prior dose by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70% or lower.In some embodiments, an amount the RNA described herein from 0.1 μg to 300 μg, 0.5 μg to 200 μg, or 1 μg to 100 μg, such as about 1 μg, about 2 μg, about 3 μg, about 10 μg, about 15 μg, about 20 μg, about 25 μg, about 30 μg, about 35 μg, about 40 μg, about 45 μg, about 50 μg, about 55 μg, about 60 μg, about 70 μg, about 80 μg, about 90 μg, or about 100 μg may be administered per dose (e.g., in a given dose).

[0866] In some embodiments, an amount of the RNA described herein of 60 μg or lower, 55 μg or lower, 50 μg or lower, 45 μg or lower, 40 μg or lower, 35 μg or lower, 30 μg or lower, 25 μg or lower, 20 μg or lower, 15 μg or lower, 10 μg or lower, 5 μg or lower, 3 μg or lower, 2.5 μg or lower, or 1 μg or lower may be administered per dose (e.g., in a given dose).

[0867] In some embodiments, an amount of the RNA described herein of at least 0.25 μg, at least 0.5 μg, at least 1 μg, at least 2 μg, at least 3 μg, at least 4 μg, at least 5 μg, at least 10 μg, at least 15 μg, at least 20 μg, at least 25 μg, at least 30 μg, at least 40 μg, at least 50 μg, or at least 60 μg may be administered per dose (e.g., in a given dose). In some embodiments, an amount of the RNA described herein of at least 3 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 10 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of

at least 15 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 20 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 25 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 30 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 50 ug may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of at least 60 ug may be administered in at least one of given doses. In some embodiments, combinations of aforementioned amounts may be administered in a regimen comprising two or more doses (e.g., a prior dose and a subsequent dose can be of different amounts as described herein). In some embodiments, combinations of aforementioned amounts may be administered in a primary regimen and a booster regimen (e.g., different doses can be given in a primary regimen and a booster regimen).

[0868] In some embodiments, a dose (e.g., a dose administered as part of a primary dosing regimen or a booster regimen) comprises about 30 μg of an RNA described herein. In some embodiments, a dose comprising about 30 μg of RNA described herein is administered to a subject who is 12 years or older.

[0869] In some embodiments, a dose (e.g., a dose administered as part of a primary dosing regimen or a booster regimen) comprises about 10 μg of an RNA described herein. In some embodiments, a dose comprising about 10 μg of RNA described herein is administered to a subject who is 5 years to less than 12 years old.

[0870] In some embodiments, a dose (e.g., a dose administered as part of a primary dosing regimen or a booster regimen) comprises about 3 μg of an RNA described herein. In some embodiments, a dose comprising about 3 μg of RNA described herein is administered to a subject who is 6 months to less than 5 years old.

[0871] In some embodiments, an amount of the RNA described herein of 0.25 μg to 60 μg, 0.5 μg to 55 μg, 1 μg to 50 μg, 5 μg to 40 μg, or 10 μg to 30 μg may be administered per dose. In some embodiments, an amount of the RNA described herein of 3 μg to 30 μg may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of 3 μg to 20 μg may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of 3 μg to 15 μg may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of 3 μg to 10 μg may be administered in at least one of given doses. In some embodiments, an amount of the RNA described herein of 10 μg to 30 μg may be administered in at least one of given doses.

[0872] In some embodiments, a regimen administered to a subject may comprise a plurality of doses (e.g., at least two doses, at least three doses, or more). In some embodiments, a regimen administered to a subject may comprise a first dose and a second dose, which are given at least 2 weeks apart, at least 3 weeks apart, at least 4 weeks apart, or more. In some embodiments, such doses may be at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, or more apart. In some embodiments, doses may be administered days apart, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 ,10, 11, 12, 13, 14, 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, 60 or more days apart. In some embodiments, doses may be administered about 1 to about 3 weeks apart, or about 1 to about 4 weeks apart, or about 1 to about 5 weeks apart, or about 1 to about 6 weeks apart, or about 1 to more than 6 weeks apart. In some embodiments, doses may be separated by a period of about 7 to about 60 days, such as for example about 14 to about 48 days, etc. In some embodiments, a minimum number of days between doses may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more. In some embodiments, a maximum number of days between doses may be about 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, or fewer. In some embodiments, doses may be about 21 to about 28 days apart. In some

embodiments, doses may be about 19 to about 42 days apart. In some embodiments, doses may be about 7 to about 28 days apart. In some embodiments, doses may be about 14 to about 24 days. In some embodiments, doses may be about 21 to about 42 days.

[0873] In some embodiments, a vaccination regimen comprises a first dose and a second dose. In some embodiments, a first dose and a second dose are administered by at least 21 days apart. In some embodiments, a first dose and a second dose are administered by at least 28 days apart.

[0874] In some embodiments, a vaccination regimen comprises a first dose and a second dose, wherein the amount of RNA administered in the first dose is the same as the amount of RNA administered in the second dose. In some embodiments, a vaccination regimen comprises a first dose and a second dose wherein the amount of RNA administered in the first dose differs from that administered in the second dose.

[0875] In some embodiments, a vaccination regimen comprises a first dose and a second dose, wherein the amount of RNA administered in the first dose is less than that administered in the second dose. In some embodiments, the amount of RNA administered in the first dose is 10%-90% of the second dose. In some embodiments, the amount of RNA administered in the first dose is 10%-50% of the second dose. In some embodiments, the amount of RNA administered in the first dose is 10%-20% of the second dose. In some embodiments, the first dose and the second dose are administered at least 2 weeks apart, including, at least 3 weeks apart, at least 4 weeks apart, at least 5 weeks apart, at least 6 weeks apart or longer. In some embodiments, the first dose and the second dose are administered at least 3 weeks apart.

[0876] In some embodiments, a first dose comprises less than about 30 ug of RNA and a second dose comprises at least about 30 ug of RNA. In some embodiments, a first dose comprises about 1 to less than about 30 ug of RNA (e.g., about 0.1, about 1, about 3, about 5, about 10, about 15, about 20, about 25, or less than about 30 ug of RNA) and a second dose comprises about 30 to about 100 ug of RNA (e.g., about 30, about 40, about 50, or about 60 ug of RNA). In some embodiments, a first dose comprises about 1 to about 20 ug of RNA, about 1 to about 10 ug of RNA, or about 1 to about 5 ug of RNA and a second dose comprises about 30 to about 60 ug of RNA.

[0877] In some embodiments, a first dose comprises about 1 to about 10 ug of RNA (e.g., about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10 ug of RNA) and a second dose comprises about 30 to about 60 ug of RNA (e.g., about 30, about 35, about 40, about 45, about 50, about 55, or about 60 ug of RNA).

[0878] In some embodiments, a first dose comprises about 1 ug of RNA and a second dose comprises about 30 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 30 ug of RNA. In some embodiments, a first dose comprises about 5 ug of RNA and a second dose comprises about 30 ug of RNA. In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 30 ug of RNA. In some embodiments, a first dose comprises about 15 ug of RNA and a second dose comprises about 30 ug of RNA.

[0879] In some embodiments, a first dose comprises about 1 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 5 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 6 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 15 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 20 ug of RNA and a second dose comprises about 60 ug of RNA. In some embodiments, a first dose comprises about 25 ug of RNA and a second dose comprises

about 60 ug of RNA. In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 60 ug of RNA.

[0880] In some embodiments, a first dose comprises less than about 10 ug of RNA and a second dose comprises at least about 10 ug of RNA. In some embodiments, a first dose comprises about 0.1 to less than about 10 ug of RNA (e.g., about 0.1, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, or less than about 10 ug of RNA) and a second dose comprises about 10 to about 30 ug of RNA (e.g., about 10, about 15, about 20, about 25, or about 30 ug of RNA). In some embodiments, a first dose comprises about 0.1 to about 10 ug of RNA, about 1 to about 5 ug of RNA, or about 0.1 to about 3 ug of RNA and a second dose comprises about 10 to about 30 ug of RNA.

[0881] In some embodiments, a first dose comprises about 0.1 to about 5 ug of RNA (e.g., about 0.1, about 0.5, about 1, about 2, about 3, about 4, about 5ug of RNA) and a second dose comprises about 10 to about 20 ug of RNA (e.g., about 10, about 12, about 14, about 16, about 18, about 20ug of RNA).

[0882] In some embodiments, a first dose comprises about 0.1 ug of RNA and a second dose comprises about 10 ug of RNA. In some embodiments, a first dose comprises about 0.3 ug of RNA and a second dose comprises about 10 ug of RNA. In some embodiments, a first dose comprises about 1 ug of RNA and a second dose comprises about 10 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 10 ug of RNA.

[0883] In some embodiments, a first dose comprises less than about 3 ug of RNA and a second dose comprises at least about 3 ug of RNA. In some embodiments, a first dose comprises about 0.1 to less than about 3 ug of RNA (e.g., about 0.1, about 0.2, about 0.3, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.5, about 2.0, or about 2.5 ug of RNA) and a second dose comprises about 3 to about 10 ug of RNA (e.g., about 3, about 4, about 5, about 6, or about 7, about 8, about 9, or about 10 ug of RNA). In some embodiments, a first dose comprises about 0.1 to about 3 ug of RNA, about 0.1 to about 1 ug of RNA, or about 0.1 to about 0.5 ug of RNA and a second dose comprises about 3 to about 10 ug of RNA.

[0884] In some embodiments, a first dose comprises about 0.1 to about 1.0 ug of RNA (e.g., about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, or about 1.0 ug of RNA) and a second dose comprises about 1 to about 3 ug of RNA (e.g., about 1.0, about 1.5, about 2.0, about 2.5, or about 3.0 ug of RNA).

[0885] In some embodiments, a first dose comprises about 0.1 ug of RNA and a second dose comprises about 3 ug of RNA. In some embodiments, a first dose comprises about 0.3 ug of RNA and a second dose comprises about 3 ug of RNA. In some embodiments, a first dose comprises about 0.5 ug of RNA and a second dose comprises about 3 ug of RNA. In some embodiments, a first dose comprises about 1 ug of RNA and a second dose comprises about 3 ug of RNA.

[0886] In some embodiments, a vaccination regimen comprises a first dose and a second dose, wherein the amount of RNA administered in the first dose is greater than that administered in the second dose. In some embodiments, the amount of RNA administered in the second dose is 10%-90% of the first dose. In some embodiments, the amount of RNA administered in the second dose is 10%-50% of the first dose. In some embodiments, the amount of RNA administered in the second dose is 10%-20% of the first dose. In some embodiments, the first dose and the second dose are administered at least 2 weeks apart, including, at least 3 weeks apart, at least 4 weeks apart, at least 5 weeks apart, at least 6 weeks apart or longer. In some embodiments, the first dose and the second dose are administered at least 3 weeks apart.

[0887] In some embodiments, a first dose comprises at least about 30 ug of RNA and a second dose comprises less than about 30 ug of RNA. In some embodiments, a first dose comprises about 30 to about 100 ug of RNA (e.g., about 30, about 40, about 50, or about 60 ug of RNA) and a second dose comprises about 1 to about

30 ug of RNA (e.g., about 0.1, about 1, about 3, about 5, about 10, about 15, about 20, about 25, or about 30 ug of RNA). In some embodiments, a second dose comprises about 1 to about 20 ug of RNA, about 1 to about 10 ug of RNA, or about 1 to 5 ug of RNA. In some embodiments, a first dose comprises about 30 to about 60 ug of RNA and a second dose comprises about 1 to about 20 ug of RNA, about 1 to about 10 ug of RNA, or about 0.1 to about 3 ug of RNA.

[0888] In some embodiments, a first dose comprises about 30 to about 60 ug of RNA (e.g., about 30, about 35, about 40, about 45, about 50, about 55, or about 60 ug of RNA) and a second dose comprises about 1 to about 10 ug of RNA (e.g., about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10 ug of RNA).

[0889] In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 1 ug of RNA. In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 3 ug of RNA. In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 5 ug of RNA. In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 10 ug of RNA. In some embodiments, a first dose comprises about 30 ug of RNA and a second dose comprises about 15 ug of RNA.

[0890] In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 1 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 3 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 5 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 6 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 10 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 15 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 20 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 25 ug of RNA. In some embodiments, a first dose comprises about 60 ug of RNA and a second dose comprises about 30 ug of RNA.

[0891] In some embodiments, a first dose comprises at least about 10 ug of RNA and a second dose comprises less than about 10 ug of RNA. In some embodiments, a first dose comprises about 10 to about 30 ug of RNA (e.g., about 10, about 15, about 20, about 25, or about 30 ug of RNA) and a second dose comprises about 0.1 to less than about 10 ug of RNA (e.g., about 0.1, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, or less than about 10 ug of RNA). In some embodiments, a first dose comprises about 10 to about 30 ug of RNA, or about 0.1 to about 3 ug of RNA and a second dose comprises about 1 to about 10 ug of RNA, or about 1 to about 5 ug of RNA.

[0892] In some embodiments, a first dose comprises about 10 to about 20 ug of RNA (e.g., about 10, about 12, about 14, about 16, about 18, about 20 ug of RNA) and a second dose comprises about 0.1 to about 5 ug of RNA (e.g., about 0.1, about 0.5, about 1, about 2, about 3, about 4, or about 5 ug of RNA).

[0893] In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 0.1 ug of RNA. In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 0.3 ug of RNA. In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 1 ug of RNA. In some embodiments, a first dose comprises about 10 ug of RNA and a second dose comprises about 3 ug of RNA.

[0894] In some embodiments, a first dose comprises at least about 3 ug of RNA and a second dose comprises less than about 3 ug of RNA. In some embodiments, a first dose comprises about 3 to about 10 ug of RNA (e.g., about 3, about 4, about 5, about 6, or about 7, about 8, about 9, or about 10 ug of RNA) and a second dose comprises 0.1 to less than about 3 ug of RNA (e.g., about 0.1, about 0.2, about 0.3, about 0.5, about 0.6, about

0.7, about 0.8, about 0.9, about 1.0, about 1.5 about 2.0, or about 2.5 ug of RNA). In some embodiments, a first dose comprises about 3 to about 10 ug of RNA and a second dose comprises about 0.1 to about 3 ug of RNA, about 0.1 to about 1 ug of RNA, or about 0.1 to about 0.5 ug of RNA.

[0895] In some embodiments, a first dose comprises about 1 to about 3 ug of RNA (e.g., about 1, about 1.5, about 2.0, about 2.5, or about 3.0 ug of RNA) and a second dose comprises about 0.1 to 0.3 ug of RNA (e.g., about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, or about 1.0 ug of RNA).

[0896] In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 0.1 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 0.3 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 0.6 ug of RNA. In some embodiments, a first dose comprises about 3 ug of RNA and a second dose comprises about 1 ug of RNA.

[0897] In some embodiments, a vaccination regimen comprises at least two doses, including, e.g., at least three doses, at least four doses or more. In some embodiments, a vaccination regimen comprises three doses. In some embodiments, the time interval between the first dose and the second dose can be the same as the time interval between the second dose and the third dose. In some embodiments, the time interval between the first dose and the second dose can be longer than the time interval between the second dose and the third dose, e.g., by days or weeks (including, e.g., at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, or longer). In some embodiments, the time interval between the first dose and the second dose can be shorter than the time interval between the second dose and the third dose, e.g., by days or weeks (including, e.g., at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, or longer). In some embodiments, the time interval between the first dose and the second dose can be shorter than the time interval between the second dose and the third dose, e.g., by at least 1 month (including, e.g., at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, or longer).

[0898] In some embodiments, a last dose of a primary regimen and a first dose of a booster regimen are given at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, or more apart. In some embodiments, a primary regimen may comprises two doses. In some embodiments, a primary regimen may comprises three doses.

[0899] In some embodiments, a first dose and a second dose (and/or other subsequent dose) may be administered by intramuscular injection. In some embodiments, a first dose and a second dose (and/or other subsequent dose) may be administered in the deltoid muscle. In some embodiments, a first dose and a second dose (and/or other subsequent dose) may be administered in the same arm.

[0900] In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular injection) as a series of two doses (e.g., 0.3 mL each) 21 days apart. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular injection) as a series of two doses (e.g., 0.2 mL each) 21 days apart. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular injection) as a series of three doses (e.g., 0.3 mL or lower including, e.g., 0.2 mL), wherein doses are given at least 3 weeks apart. In some embodiments, the first and second doses may be administered 3 weeks apart, while the second and third doses may be administered at a longer time interval than that between the first and the second doses, e.g., at least 4 weeks apart or longer (including, at least 5 weeks,

at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, or longer). In some embodiments, each dose is about 60 ug. In some embodiments, each dose is about 50 ug. In some embodiments, each dose is about 30 ug. In some embodiments, each dose is about 25 ug. In some embodiments, each dose is about 20 ug. In some embodiments, each dose is about 15 ug. In some embodiments, each dose is about 10 ug. In some embodiments, each dose is about 3 ug.

[0901] In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 60 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 50 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 30 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 25 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 20 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 15 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 10 ug. In some embodiments, at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 3 ug.

[0902] In one embodiment, an amount of the RNA described herein of about 60 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 50 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 30 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 25 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 20 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 15 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 10 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 5 μg is administered per dose. In one embodiment, an amount of the RNA described herein of about 3 μg is administered per dose. In one embodiment, at least two of such doses are administered. For example, a second dose may be administered about 21 days following administration of the first dose.

[0903] In some embodiments, the efficacy of the RNA vaccine described herein (e.g., administered in two doses, wherein a second dose may be administered about 21 days following administration of the first dose, and administered, for example, in an amount of about 30 μg per dose) is at least 70%, at least 80%, at least 90, or at least 95% beginning 7 days after administration of the second dose (e.g., beginning 28 days after administration of the first dose if a second dose is administered 21 days following administration of the first dose). In some embodiments, such efficacy is observed in populations of age of at least 50, at least 55, at least 60, at least 65, at least 70, or older. In some embodiments, the efficacy of the RNA vaccine described herein (e.g., administered in two doses, wherein a second dose may be administered about 21 days following administration of the first dose, and administered, for example, in an amount of about 30 μg per dose) beginning 7 days after administration of the second dose (e.g., beginning 28 days after administration of the first dose if a second dose is administered 21 days following administration of the first dose) in populations of age of at least 65, such as 65 to 80, 65 to 75, or 65 to 70, is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, or at least 95%. Such efficacy may be observed over time periods of up to 1 month, 2 months, 3 months, 6 months or even longer.

[0904] In one embodiment, vaccine efficacy is defined as the percent reduction in the number of subjects with evidence of infection (vaccinated subjects vs. non-vaccinated subjects).

[0905] In one embodiment, efficacy is assessed through surveillance for potential cases of COVID-19. If, at any time, a patient develops acute respiratory illness, for the purposes herein, the patient can be considered to

potentially have COVID-19 illness. The assessments can include a nasal (midturbinate) swab, which may be tested using a reverse transcription-polymerase chain reaction (RT-PCR) test to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests can be assessed.

[0906] In some embodiments, efficacy assessments may utilize a definition of SARS-CoV-2-related cases wherein:

[0907] • Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT (nucleic acid amplification-based test) positive during, or within 4 days before or after, the symptomatic period: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting.

[0908] Alternatively or additionally, in some embodiments, efficacy assessments may utilize a definition of SARS-CoV-2-related cases wherein one or more of the following additional symptoms defined by the CDC can be considered: fatigue; headache; nasal congestion or runny nose; nausea.

[0909] In some embodiments, efficacy assessments may utilize a definition of SARS-CoV-2-related severe cases

[0910] • Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following: clinical signs at rest indicative of severe systemic illness (e.g., RR ≥30 breaths per minute, HR ≥125 beats per minute, $SpO_2 \leq 93\%$ on room air at sea level, or $PaO_2/FiO_2 < 300$mm Hg); respiratory failure (which can be defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); evidence of shock (e.g., SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors); significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; death.

[0911] Alternatively or additionally, in some embodiments a serological definition can be used for patients without clinical presentation of COVID-19: e.g., confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: e.g., positive N-binding antibody result in a patient with a prior negative N-binding antibody result.

[0912] In some embodiments, any or all of the following assays can be performed on serum samples: SARS-CoV-2 neutralization assay; S1-binding IgG level assay; RBD-binding IgG level assay; N-binding antibody assay.

[0913] In one embodiment, methods and agents described herein are administered to a paediatric population. In various embodiments, the paediatric population comprises or consists of subjects under 18 years, e.g., 5 to less than 18 years of age, 12 to less than 18 years of age, 16 to less than 18 years of age, 12 to less than 16 years of age, 5 to less than 12 years of age, or 6 months to less than 12 years of age. In various embodiments, the paediatric population comprises or consists of subjects under 5 years, e.g., 2 to less than 5 years of age, 12 to less than 24 months of age, 7 to less than 12 months of age, or less than 6 months of age. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of less than 2 years old, for example, 6 months to less than 2 years old. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of less than 6 months old, for example, 1 month to less than 4 months old. In some embodiments, a dosing regimen (e.g., doses and/or dosing schedule) for a paediatric population may vary for different age groups. For example, in some embodiments, a subject 6 months through 4 years of age may be administered according to a primary regimen comprising at least three doses, in which the initial two doses are administered at least 3 weeks (including, e.g., at least 4 weeks, at least 5 weeks, at least 6 weeks, or longer) apart followed by a third dose administered at least 8 weeks (including, e.g., at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, or longer) after the second dose. In some such embodiments, at least one dose administered is 3 ug RNA described herein. In some embodiments, a subject 5 years of age and older may be administered according to a primary regimen comprising at least two doses, in which the two doses are administered at least 3 weeks (including, e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, or longer) apart. In some such embodiments, at least one dose administered is 10 ug RNA described herein. In some

embodiments, a subject 5 years of age and older who are immunocompromised (e.g., in some embodiments subjects who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent of immunocompromise) may be administered according to a primary regimen comprising at least three doses, in which the initial two doses are administered at least 3 weeks (including, e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, or longer) apart, followed by a third dose administered at least 4 weeks (including, e.g., at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, or longer) after the second dose.

[0914] In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and each dose is about 30 ug. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older (including, e.g., age 18 or older) and each dose is higher than 30 ug, including, e.g., 35 ug, 40 ug, 45 ug, 50 ug, 55 ug, 60 ug, 65 ug , 70 ug, or higher. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and each dose is about 60 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and each dose is about 50 ug. In one embodiment, the paediatric population comprises or consists of subjects 12 to less than 18 years of age including subjects 16 to less than 18 years of age and/or subjects 12 to less than 16 years of age. In this embodiment, treatments may comprise 2 vaccinations 21 days apart, wherein, in one embodiment, the vaccine is administered in an amount of 30 µg RNA per dose, e.g., by intramuscular administration. In some embodiments, higher doses are administered to older pediatric patients and adults, e.g., to patients 12 years or older, compared to younger children or infants, e.g. 2 to less than 5 years old, 6 months to less than 2 years old, or less than 6 months old. In some embodiments, higher doses are administered to children who are 2 to less than 5 years old, as compared to toddlers and/or infants, e.g., who are 6 months to less than 2 years old, or less than 6 months old.

[0915] In one embodiment, the paediatric population comprises or consists of subjects 5 to less than 18 years of age including subjects 12 to less than 18 years of age and/or subjects 5 to less than 12 years of age. In this embodiment, treatments may comprise 2 vaccinations 21 days apart, wherein, in various embodiments, the vaccine is administered in an amount of 10 µg, 20µg, or 30 µg RNA per dose, e.g., by intramuscular administration. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 5 to 11 and each dose is about 10 ug

[0916] In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a first variant and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a second variant. In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and about 5 ug of RNA encoding a SARS-CoV-2 S protein of an Omicron variant. In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a BA.1 Omicron variant (e.g., RNA comprising SEQ ID NO: 51). In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20)and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a BA.4/5 Omicron variant (e.g., RNA comprising SEQ ID NO: 72).

[0917] In one embodiment, the paediatric population comprises or consists of subjects less than 5 years of age including subjects 2 to less than 5 years of age, subjects 12 to less than 24 months of age, subjects 7 to less than 12 months of age, subjects 6 to less than 12 months of age and/or subjects less than 6 months of age. In this embodiment, treatments may comprise 2 vaccinations, e.g., 21 to 42 days apart, e.g., 21 days apart, wherein, in various embodiments, the vaccine is administered in an amount of 3 µg, 6 µg, 10 µg, 20 µg, or 30 µg RNA per dose, e.g., by intramuscular administration. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 2 to less than 5 and each dose is about 3 ug. In some such

embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of about 6 months to less than about 5 years and each dose is about 3 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 2 to less than 5 and each dose is about 6 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of about 6 months to less than about 5 years and each dose is about 6 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 2 to less than 5 and each dose is about 10 ug. In some such embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of about 6 months to less than about 5 years and each dose is about 10 ug.

[0918] In some embodiments, each dose comprises about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of a first variant and about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of a second variant. In some embodiments, each dose comprises about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of an Omicron variant. In some embodiments, each dose comprises about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 1.5 ug of RNA encoding a SARS-CoV-2 S protein of a BA.4/5 Omicron variant (e.g., RNA comprising SEQ ID NO: 72).

[0919] In some embodiments, each dose comprises about 3 ug of RNA encoding a SARS-CoV-2 S protein of a first variant and about 3 ug of RNA encoding a SARS-CoV-2 S protein of a second variant. In some embodiments, each dose comprises about 3 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and about 3 ug of RNA encoding a SARS-CoV-2 S protein of an Omicron variant. In some embodiments, each dose comprises about 3 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 3 ug of RNA encoding a SARS-CoV-2 S protein of a BA.1 Omicron variant (e.g., RNA comprising SEQ ID NO: 51). In some embodiments, each dose comprises about 3 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 6 ug of RNA encoding a SARS-CoV-2 S protein of a BA.4/5 Omicron variant (e.g., RNA comprising SEQ ID NO: 72). In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a first variant and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a second variant. In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and about 5 ug of RNA encoding a SARS-CoV-2 S protein of an Omicron variant. In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a BA.1 Omicron variant (e.g., RNA comprising SEQ ID NO: 51). In some embodiments, each dose comprises about 5 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., RNA comprising SEQ ID NO: 20) and about 5 ug of RNA encoding a SARS-CoV-2 S protein of a BA.4/5 Omicron variant (e.g., RNA comprising SEQ ID NO: 72).

[0920] In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 60 ug. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 30 ug. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 12 or older and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 15 ug. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 5 to less than 12 years of age and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 10 ug. In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of age 2 to less than 5 and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 3 ug. In

some embodiments, an RNA (e.g., mRNA) composition described herein is administered to subjects of 6 months to less than age 2 and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 3 ug or lower, including, e.g., 2 ug, 1 ug, or lower). In some embodiments, an RNA (e.g., mRNA) composition described herein is administered to infants of less than 6 months and at least one dose given in a vaccination regimen (e.g., a primary vaccination regimen and/or a booster vaccination regimen) is about 3 ug or lower, including, e.g., 2 ug, 1 ug, 0.5 ug, or lower).

[0921] In some embodiments, an RNA (e.g., mRNA) composition described herein is administered (e.g., by intramuscular injection) as a single dose. In some embodiments, a single dose comprise a single RNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof (e.g., an RBD domain). In some embodiments, a single dose comprise at least two RNAs described herein, for example, each RNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof (e.g., an RBD domain) from different strains. In some embodiments, such at least two RNAs described herein can be administered as a single mixture. For example, in some such embodiments, two separate RNA compositions described herein can be mixed to generate a single mixture prior to injection. In some embodiments, such at least two RNAs described herein can be administered as two separate compositions, which, for example, can be administered at different injection sites (e.g., on different arms, or different sites on the same arm).

[0922] In some embodiments, a dose administered to subjects in need thereof may comprise administration of a single RNA (e.g., mRNA) composition described herein.

[0923] In some embodiments, a dose administered to subjects in need thereof may comprise administration of at least two or more (including, e.g., at least three or more) different drug products/formulations. For example, in some embodiments, at least two or more different drug products/formulations may comprise at least two different RNA (e.g., mRNA) compositions described herein (e.g., in some embodiments each comprising a different RNA construct).

[0924] In some embodiments, an RNA (e.g., mRNA) composition disclosed herein may be administered in conjunction with a vaccine targeting a different infectious agent. In some embodiments, the different infectious agent is one that increases the likelihood of a subject experiencing deleterious symptoms when coinfected with SARS-CoV-2 and the infectious agent. In some embodiments, the infectious agent is one that increases the infectivity of SARS-CoV-2 when a subject is coinfected with SARS-CoV-2 and the infectious agent. In some embodiments, at least one RNA (e.g., mRNA) composition described herein may be administered in combination with a vaccine that targets influenza. In some embodiments, at least two or more different drug products/formulations may comprise at least one RNA (e.g., mRNA) composition described herein and a vaccine targeting a different infectious agent (e.g., an influenza vaccine). In some embodiments, different drug products/ formulations are separately administered. In some embodiments, such different drug product/formulations are separately administered at the same time (e.g., at the same vaccination session) at different sites of a subject (e.g., at different arms of the subject).

[0925] In one embodiment, at least two doses are administered. For example, a second dose may be administered about 21 days following administration of the first dose.

[0926] In some embodiments, at least one single dose is administered. In some embodiments, such single dose is administered to subjects, for example, who may have previously received one or more doses of, or a complete regimen of, a SARS-CoV-2 vaccine (e.g., of a BNT162b2 vaccine [including, e.g., as described herein], an mRNA-1273 vaccine, an Ad26.CoV2.S vaccine, a ChAdxOx1 vaccine, an NVX-CoV2373 vaccine, a CvnCoV vaccine, a GAM-COVID0Vac vaccine, a CoronaVac vaccine, a BBIBP-CorV vaccine, an Ad5-nCoV vaccine, a zf2001 vaccine, a SCB-2019 vaccine, or other approved RNA (e.g., mRNA) or adenovector vaccines, etc. Alternatively or additionally, in some embodiments, a single dose is administered to subjects who have been exposed to and/or infected by

SARS-CoV-2. In some embodiments, at least one single dose is administered to subjects who have received one or more doses of, or a complete regimen of, a SARS-CoV-2 vaccine and have been exposed to and/or infected with SARS-CoV-2.

[0927] In some particular embodiments where at least one single dose is administered to subjects who have received one or more doses of a prior SARS-CoV-2 vaccine, such prior SARS-CoV-2 vaccine is a different vaccine, or a different form (e.g., formulation) and/or dose of a vaccine with the same active (e.g., BNT162b2); in some such embodiments, such subjects have not received a complete regimen of such prior vaccine and/or have experienced one or more undesirable reactions to or effects of one or more received doses of such prior vaccine. In some particular embodiments, such prior vaccine is or comprises higher dose(s) of the same active (e.g., BNT162b2). Alternatively or additionally, in some such embodiments, such subjects were exposed to and/or infected by SARS-CoV-2 prior to completion (but, in some embodiments, after initiation) of a full regimen of such prior vaccine.

[0928] In some embodiments, an RNA described herein is administered to a subject who has previously been administered at least two doses of BNT162b2 (e.g., two doses of BNT162b2 administered about 21 days apart).

[0929] In some embodiment, an RNA described herein is administered to a subject who has previously been administered a vaccine that delivers an antigen of a SARS-CoV-2 variant (e.g., an Omicron BA.4/5 variant (e.g., a vaccine described herein)).

[0930] In one embodiment, at least two doses are administered. For example, a second dose may be administered about 21 days following administration of the first dose.

[0931] In one embodiment, at least three doses are administered. In some embodiments, such third dose is administered a period of time after the second dose that is comparable to (e.g., the same as) the period of time between the first and second doses. For example, in some embodiments, a third dose may be administered about 21 days following administration of the second dose. In some embodiments, a third dose is administered after a longer period of time relative to the second dose than the second dose was relative to the first dose. In some embodiments, a three-dose regimen is administered to an immunocompromised patient, e.g., a cancer patient, an HIV patient, a patient who has received and/or is receiving immunosuppressant therapy (e.g., an organ transplant patient). In some embodiments, the length of time between the second and third dose (e.g., a second and third dose administered to an immunocompromised patient) is at least about 21 days (e.g., at least about 28 days).

[0932] In some embodiments, a vaccination regimen comprises administering the same amount of RNA in different doses (e.g., in first and/or second and/or third and/or subsequent doses). In some embodiments, a vaccination regimen comprises administering different amounts of RNA in different doses. In some embodiments, one or more later doses is larger than one or more earlier doses (e.g., in situations where waning of vaccine efficacy from one or more earlier doses is observed and/or immune escape by a variant (e.g., one described herein) that is prevalent or rapidly spreading is observed in a relevant jurisdiction at the time of administration is observed). In some embodiments, one or more later doses may be larger than one or more earlier doses by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or higher, provided that safety and/or tolerability of such a dose is clinically acceptable. In some embodiments, one or more later doses may be larger than one or more earlier doses by at least 1.1-fold, at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, or higher provided that safety and/or tolerability of such a dose is clinically acceptable. In some embodiments, one or more later doses is smaller than one or more earlier doses (e.g., in a negative reaction was experienced after one or more earlier doses and/or if exposure to and/or infection by SARS-CoV-2 between an earlier dose and a subsequent dose). In some embodiments, one or more later doses may be smaller than one or more earlier doses by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, or higher.

In some embodiments, where different doses are utilized, they are related to one another by identity with and/or dilution of a common stock as described herein.

[0933] In some embodiments, where at least two or more doses are administered (e.g., at least two doses administered in a primary regimen, at least two doses administered in a booster regimen, or at least one dose administered in a primary regimen and at least one dose in a booster regimen), the same RNA compositions described herein may be administered in such doses and each of such doses can be the same or different (as described herein). In some embodiments, where at least two or more doses are administered (e.g., at least two doses administered in a primary regimen, at least two doses administered in a booster regimen, or at least one dose administered in a primary regimen and at least one dose in a booster regimen), different RNA compositions described herein (e.g., different encoded viral polypeptides, e.g., from different coronavirus clades, or from different strains of the same coronavirus clade; different construct elements such as 5' cap, 3' UTR, 5' UTR, etc.; different formulations, e.g., different excipients and/or buffers (e.g., PBS vs. Tris); different LNP compositions; or combinations thereof) may be administered in such doses and each of such doses can be the same or different (e.g., as described herein).

[0934] In some embodiments, a subject is administered two or more RNAs (e.g., as part of either a primary regimen or a booster regimen), wherein the two or more RNAs are administered on the same day or same visit. In some embodiments, the two or more RNAs are administered in separate compositions, e.g., by administering each RNA to a separate part of the subject (e.g., by intramuscular administration to different arms of the subject or to different sites of the same arm of the subject). In some embodiments, the two or more RNAs are mixed prior to administration (e.g., mixed immediately prior to administration, e.g., by the administering practitioner). In some embodiments, the two or more RNAs are formulated together (e.g., by (a) mixing separate populations of LNPs, each population comprising a different RNA; or (b) by mixing two or more RNAs prior to LNP formulation, so that each LNP comprises two or more RNAs). In some embodiments, the two or more RNAs comprise an RNA that encode a coronavirus S protein or immunogenic fragment thereof (e.g., RBD or other relevant domains) from one strain (e.g., Wuhan strain) and a variant that is prevalent or rapidly spreading in a relevant jurisdiction at the time of administration (e.g., a variant described herein). In some embodiments, such a variant is an Omicron variant (e.g., a BA.1, BA.2, or BA.3 variant). In some embodiments, the two or more RNAs comprise a first RNA and a second RNA that have been shown to elicit a broad immune response in subject. In some embodiments the two or more RNAs comprise an RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and an RNA encoding a SARS-CoV-2 S protein from a BA.4 or BA.5 Omicron variant.

[0935] In some embodiments, a subject may be administered any one of combinations 1 to 66, listed in the below table. In some embodiments, such combinations can be administered using an LNP formulation, where the first RNA and the second RNA are encapsulated in the same LNP or in separate LNPs. In some embodiments, such combinations can be administered as separate LNP formulations (e.g., by administering at separate sites to a subject).

Combination	SARS-CoV-2 S protein encoded by a first RNA[1]	SARS-CoV-2 S protein encoded by a second RNA[1]
1	Wuhan	Alpha
2	Wuhan	Beta
3	Wuhan	Delta
4	Wuhan	BA.1
5	Wuhan	BA.2

6	Wuhan	BA.2.12.1
7	Wuhan	BA.3
8	Wuhan	BA.4/5
9	Wuhan	XBB
10	Wuhan	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
11	Wuhan	BQ.1.1
12	Alpha	Beta
13	Alpha	Delta
14	Alpha	BA.1
15	Alpha	BA.2
16	Alpha	BA.2.12.1
17	Alpha	BA.3
18	Alpha	BA.4/5
19	Alpha	XBB
20	Alpha	XBB variant (e.g.,XBB.1, XBB.2, XBB.1.3)
21	Alpha	BQ.1.1
22	Beta	Delta
23	Beta	BA.1
24	Beta	BA.2
25	Beta	BA.2.12.1
26	Beta	BA.3
27	Beta	BA.4/5
28	Beta	XBB
29	Beta	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
30	Beta	BQ.1.1
31	Delta	BA.1
32	Delta	BA.2
33	Delta	BA.2.12.1
34	Delta	BA.3
35	Delta	BA.4/5
36	Delta	XBB
37	Delta	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
38	Delta	BQ.1.1
39	BA.1	BA.2
40	BA.1	BA.2.12.1
41	BA.1	BA.3
42	BA.1	BA.4/5

43	BA.1	XBB
44	BA.1	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
45	BA.1	BQ.1.1
46	BA.2	BA.2.12.1
47	BA.2	BA.3
48	BA.2	BA.4/5
49	BA.2	XBB
50	BA.2	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
51	BA.2	BQ.1.1
52	BA.2.12.1	BA.3
53	BA.2.12.1	BA.4/5
54	BA.2.12.1	XBB
55	BA.2.12.1	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
56	BA.2.12.1	BQ.1.1
57	BA.3	BA.4/5
58	BA.3	XBB
59	BA.3	XBB variant (e.g., XBB.1, XBB.2, XBB.3)
60	BA.3	BQ.1.1
61	BA.4/5	XBB
62	BA.4/5	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
63	BA.4/5	BQ.1.1
64	XBB	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)
65	XBB	BQ.1.1
66	XBB variant (e.g., XBB.1, XBB.2, XBB.1.3)	BQ.1.1

[1]Listed RNAs encode a SARS-CoV-2 S protein having mutations characteristic of the indicated SARS-CoV-2 variant.

[0936] In some embodiments, synergistic categories of coronavirus strain and/or variant sequences (e.g., SARS-CoV-2 strain and/or variant sequences) can be defined, for example, based on shared amino acid alterations in S glycoprotein of coronavirus strain and/or variant sequences. For example, while many of the amino acid changes in the RBD of S protein are shared between Omicron variants (e.g., BA.1, BA.2, BA.2.12.1, and BA.4/5), alterations within the NTD of BA.2 and BA.2-derived sub-lineages including BA.4/5 are mostly distinct from those found in BA.1. Therefore, in some embodiments, synergistic categories of coronavirus strain and/or variant sequences (e.g., SARS-CoV-2 strain and/or variant sequences) can be defined based on the degree of shared amino acid mutations present with the NTD of a S protein. For example, in some embodiments where two SARS-CoV-2 strain and/or variant sequences share at least 50% (including, e.g., at least 60%, at least 70%, at least 80%, at least 90%, or more) of the amino acid mutations present in the NTD of a S protein, both SARS-CoV-2 strain and variant sequences can be grouped into the same category. In some embodiments where two SARS-CoV-2 strain and/or variant

sequences share no more 50% (including, e.g., no more than 45%, no more than 40%, no more than 30%, or lower) of the amino acid mutations present in the NTD of a S protein, both SARS-CoV-2 strain and variant sequences can be grouped into different categories. Among other things, the present findings provide insights that exposing subjects (e.g., via infection and/or vaccination) to at least two antigens that are of different synergistic categories (e.g., as shown in the table below) can produce a more robust immune response (e.g., broadening the spectrum of cross-neutralization against different variants and/or producing an immune response that is less prone to immune escape).

Category I	**Category II**
Wuhan strain	Omicron BA.2
Alpha variant	Omicron BA.2.11.2
Beta variant	Omicron BA.4
Delta variant	Omicron BA.5
Omicron BA.1	XBB.1.5
Sublineages derived from any one of the above	BA.2.75.2
	BQ.1.1
	Sublineages derived from any one of the above

[0937] For example, in some embodiments, vaccine-naïve subjects without prior infection may be administered a combination of vaccines, at least two of which are each adapted to a SARS-CoV-2 strain of different synergistic categories (e.g., as described herein). In some embodiments, such vaccines in a combination may be administered at different times, for example, in some embodiments as a first dose and a second dose administered apart by a pre-determined period of time (e.g., according to certain dosing regimens as described herein). In some embodiments, such vaccines in a combination may be administered as a multivalent vaccine. In some embodiments, a subject infected or vaccinated with a SARS-CoV-2 strain of one category may be administered a vaccine adapted to a SARS-CoV-2 strain of a different category (e.g., as described herein). In some embodiments, such a vaccine may be a polypeptide-based or RNA-based vaccine.

[0938] In some embodiments, a dose comprising one or more vaccines of Category II is administered to a subject previously administered one or more vaccines of Category I. In some embodiments, a dose comprising one or more vaccines of Category I and one or more vaccines of Category II is administered to a subject to whom one or more vaccines of Category I was previously administered (e.g., in some embodiments, the dose comprises at least one vaccine that was previously administered to the subject).

[0939] In some embodiments, a combination of vaccines comprising a vaccine from Category I and a BA.4/5 vaccine may provide a particularly superior immune response (e.g., an immune response with particularly strong cross-neutralization effects).

[0940] Due to the large number of differences between XBB and its variants and other SARS-CoV-2 variants of concern, in some embodiments, a particularly improved synergistic effect can be produced by a combination comprising a vaccine of Category I and an XBB vaccine. In some embodiments, a particularly improved synergistic effect can be produced by a combination comprising a BA.4/5 vaccine and an XBB vaccine (e.g., a combination comprising an RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and an RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 Omicron variant).

[0941] In some embodiments, a vaccine can comprise a polypeptide (e.g., a non-natural polypeptide, e.g., a chimeric polypeptide) comprising one or more mutations that are characteristic of one or more different SARS-CoV-2 variants, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments,

a vaccine can comprise a polypeptide (e.g., a non-natural polypeptide, e.g., a chimeric polypeptide) comprising one or more mutations that are characteristic of a first SARS-CoV-2 variant and one or more mutations that are characteristic of a second SARS-CoV-2 variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a first SARS-CoV-2 variant can be a SARS-CoV-2 strain/variant from Category I of the table above, while a second SARS-CoV-2 variant can be a SARS-CoV-2 strain/variant from Category II of the table above. For example, in some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations that are characteristic of a first SARS-CoV-2 variant and an NTD comprising one or more mutations that are characteristic of a second SARS-CoV-2 variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide.

[0942] In some embodiments, (i) one or more doses of a composition (e.g., an RNA composition) that delivers an S protein of a Wuhan strain, an alpha variant, a beta variant, a delta variant, or an omicron BA.1 variant (or a sublineage derived from one of these) is administered to a subject (e.g., as a priming dose regimen and/or one or more booster dose regimens), and (ii) one or more doses of a composition (e.g., an RNA composition) that delivers an S protein of an omicron BA.2, omicron BA.2.11.2, omicron BA.4, omicron BA.5, XBB.1.5, BA.2.75.2, or BQ.1.1 (or a sublineage derived from one of these) is administered to the subject (e.g., as one or more booster dose regimens). In some embodiments, (i) one or more doses of a composition (e.g., a composition comprising two or more RNA compositions) that delivers a combination of S proteins of 2, 3, or 4 of: a Wuhan strain, an alpha variant, a beta variant, a delta variant, and an omicron BA.1 variant (or a sublineage derived from one of these) is administered to a subject (e.g., as a priming dose regimen and/or one or more booster dose regimens), and (ii) one or more doses of a composition (e.g., a composition comprising two or more RNA compositions) that delivers a combination of S proteins of 2, 3, or 4 of: an omicron BA.2, omicron BA.2.11.2, omicron BA.4, omicron BA.5, XBB.1.5, BA.2.75.2, and BQ.1.1 (or a sublineage derived from one of these) is administered to the subject (e.g., as one or more booster dose regimens).

[0943] In some embodiments, a composition (e.g., an RNA composition) delivers an S protein, or an immunogenic fragment thereof, of a SARS-CoV-2 strain or variant or a combination of SARS-CoV-2 strains/variants listed in the below Table D.

Table D: Exemplary monovalent, bivalent, and trivalent compositions comprising at least one RNA encoding an S protein of a SARS-CoV-2 variant

	Variant or Strain Combination of Variants/Strains
1	Wuhan + Omicron BA.4/5
2	Wuhan + XBB.1.5
3	Wuhan + BQ.1.1
4	Wuhan + BA.2.75.2
5	XBB.1.5
6	XBB.1.5 + BA.4/5
7	XBB.1.5 + BA.2.75.2
8	XBB.1.5 + BQ.1.1
9	BA.2.75.2
10	BA.2.75.2 + BQ.1.1
11	BQ.1.1
12	Wuhan + BA.4/5 + XBB.1.5

13	Wuhan + BA.4/5 + BQ.1.1
14	Wuhan + BA.4/5 + BA.2.75.2
15	BA.4/5 + BA.2.75.2
16	BA.4/5 + BQ.1.1
17	XBB.1.16
18	XBB.1.16 + BA.4/5
19	XBB.2.3
20	XBB.2.3 + BA.4/5
21	XBB.2.3 + Wuhan
22	XBB.2.3.2
23	XBB.2.3.2 + BA.4/5
24	XBB.2.3.2 + Wuhan

[0944] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain or variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D can produce an improved immune response (e.g., an immune response with improved cross-neutralization and/or higher neutralization titers against one or more variants of concern), e.g., relative to a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain.

[0945] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain or variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a first dose and/or as part of a priming vaccination regimen to a subject (e.g., a vaccine-naïve subject is administered (i) two doses of such a composition, approximately 21 days apart, or (ii) three doses of such a composition, where the first and the second doses are administered approximately 21 days apart and the second and the third dose are administered about 28 days apart).

[0946] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain or variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered to a subject who has previously been exposed to SARS-CoV-2 (e.g., a subject who has previously received at least one dose (e.g., a complete dosing regimen) of a SARS-CoV-2 vaccine and/or previously been infected one or more times with SARS-CoV-2). In some embodiments, a composition that delivers one or more S protein(s) of a variant or combination of strain/variants listed in Table D is administered as a booster dose. In some embodiments, a composition that delivers one or more S protein(s) of a variant or combination of strain/variants listed in Table D is administered as a booster dose to a subject who has previously received one or more doses (e.g., a complete primary dosing regimen and/or one or more booster doses) of a vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a composition comprising an RNA that comprises SEQ ID NO: 20, a commercially available vaccine (e.g., a commercially available vaccine described herein, (e.g., BND162b2)) or any combination thereof).

[0947] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered to a subject previously administered one or more doses of a composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain. In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a booster dose to a subject previously administered a priming dosing regimen of a composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a subject

previously administered (i) two doses of an RNA vaccine that encodes a SARS-CoV-2 S protein of a Wuhan strain, where the first and the second doses were administered about 21 days apart, or (ii) three doses of an RNA vaccine that encodes a SARS-CoV-2 S protein of a Wuhan strain, where the first and the second dose were administered about 21 days apart and the third dose was administered about 28 days after the second dose).

[0948] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a further booster dose to a subject previously administered a priming dosing regimen and one or more booster doses of a composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a subject previously administered (i) three doses of an RNA vaccine that encodes a SARS-CoV-2 S protein of a Wuhan strain, where the first and the second doses were administered about 21 days apart, and the third dose was administered at least about 2 months after the second dose, (ii) four doses of an RNA vaccine that encodes a SARS-CoV-2 S protein of a Wuhan strain, where the first and the second dose were administered about 21 days apart, the third dose was administered about 28 days after the second dose, and the fourth dose was administered at least about three months after the second dose, or (iii) four doses of an RNA vaccine that encodes a SARS-CoV-2 S protein of a Wuhan strain, where the first and the second dose were administered about 21 days apart, the third dose was administered at least about 2 months after the second dose, and the fourth dose was administered at least about two months after the second dose).

[0949] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered to a subject previously administered one or more doses of a bivalent composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain and a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. In some embodiments, a composition that delivers one or more SARS-CoV-2 S protein(s) of a strain/variant or combination of strain/variants listed in Table D is administered as a booster dose to a subject previously administered a priming dosing regimen of a bivalent composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain and a SARS-CoV-2 S protein of an Omicron BA.4/5 variant (e.g., a subject previously administered (i) two doses of a bivalent RNA vaccine, where the first and the second doses were administered about 21 days apart, or (ii) three doses of a bivalent RNA vaccine, where the first and the second dose were administered about 21 days apart and the third dose was administered about 28 days after the second dose). In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a further booster dose to a subject previously administered a priming dosing regimen and one or more booster doses of a bivalent composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain and a SARS-CoV-2 S protein of an Omicron BA.4/5 variant (e.g., a subject previously administered (i) three doses of a bivalent RNA vaccine, where the first and the second doses were administered about 21 days apart, and the third dose was administered at least about 2 months after the second dose, (ii) four doses of a bivalent RNA vaccine, where the first and the second dose were administered about 21 days apart, the third dose was administered about 28 days after the second dose, and the fourth dose was administered at least about three months after the second dose, or (iii) four doses of a bivalent RNA vaccine, where the first and the second dose were administered about 21 days apart, the third dose was administered at least about 2 months after the second dose, and the fourth was administered at least about two months after the second dose).

[0950] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered to a subject previously administered (i) one or more doses of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain and (ii) one or more doses of a bivalent composition (e.g., an RNA composition) that delivers a SARS-

CoV-2 S protein of a Wuhan strain and a SARS-CoV-2 S protein of an Omicron BA.4/5 variant. In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a booster dose to a subject previously administered a priming dosing regimen of a composition (e.g., an RNA composition) that delivers a SARS-CoV-2 S protein of a Wuhan strain and at least one booster dose of a bivalent composition that delivers a SARS-CoV-2 S protein of a Wuhan strain and a SARS-CoV-2 S protein of an Omicron BA.4/5 variant.

[0951] In some embodiments, a composition that delivers a SARS-CoV-2 S protein of a strain/variant listed in Table D, or a SARS-CoV-2 S protein of each strain/variant in a combination listed in Table D is administered as a booster dose to a subject previously administered:

(i) a first dose of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain, and a second dose of a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered about 21 days after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain;

(ii) two doses (administered about 21 days apart) of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain, and a dose of a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered at least about two months after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain;

(iii) three doses of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (where the first and the second dose were administered about 21 days apart and the third dose was administered about 28 days after the second dose) and at least one dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered at least about 2 months after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain;

(iv) three doses of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (where the first and the second dose were administered about 21 days apart and the third dose was administered at least about 2 months after the second dose) and at least one dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered at least about 2 months after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain.

(v) four doses of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (where the first and the second dose are administered about 21 days apart, the third dose was administered about 28 days after the second dose, and the fourth dose was administered at least about 2 months after the third dose) and at least one dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered at least about 2 months after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain; or four doses of an RNA vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (where the first and the second dose were administered about 21 days apart, the third dose was administered at least about 2 months after the second dose, and the fourth dose was administered at least about 4 months after the third dose) and at least one dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, where the bivalent composition was administered at least about 2 months after the most recent dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain

[0952] In some embodiments, a subject is administered a dosing regimen as summarized in the below Table E.

Table E: Exemplary Dosing Regimens comprising 3 doses

1st Dose	2nd Dose	3rd dose
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BNT162b2 + BA.4/5 (bivalent)
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	XBB.1.5
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.2.75.2
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BQ.1.1
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BNT162b2 + BA.4/5+XBB.1.5 (trivalent)
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BNT162b2 + BA.4/5+BA.2.75.2 (trivalent)
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5+XBB.1.5 (bivalent)
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5 + BA.2.75.2 (bivalent)
BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5 + BQ.1.1 (bivalent)
BNT162b2 + BA.4/5 (bivalent)	BNT162b2 + BA.4/5 (bivalent)	XBB.1.5
BNT162b2 + BA.4/5 (bivalent)	BNT162b2 + BA.4/5 (bivalent)	XBB.1.5

In some embodiments, a subject is administered a dosing regimen as summarized in the below Table F.

Table F: Exemplary Dosing Regimens comprising 4 doses

1st Dose	2nd Dose	3rd Dose	4th dose
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	XBB.1.5
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.2.75.2
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BQ.1.1
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5+XBB.1.5
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5 + BA.2.75.2
BNT162b2	BNT162b2	BNT162b2 + BA.4/5 (bivalent)	BA.4/5 + BQ.1.1

[0953] In some embodiments, a dosing regimen listed in Table E or F is administered to a vaccine naïve subject. In some embodiments, a first dose and a second dose listed in Table E or F are administered about 21 days apart. In some embodiments, a third dose listed in Table E or F is administered at least about 2 months after a second dose. In some embodiments, a fourth dose listed in Table F is administered at least about two months after a third dose.

[0954] In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.1 Omicron variant and an NTD comprising one or more mutations characteristic of a second SARS-CoV-2 variant that is not a BA.1 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise or encode a

polypeptide comprising an NTD comprising one or more mutations characteristic of a BA.1 Omicron variant and an RBD comprising one or more mutations characteristic of a second SARS-CoV-2 variant that is not a BA.1 Omicron variant. In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.1 Omicron variant and an NTD comprising one or more mutations characteristic of a BA.2 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.1 Omicron variant and an NTD comprising one or more mutations characteristic of a BA.4/5 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide.

[0955] In some embodiments, a vaccine can comprise a polypeptide that comprises an NTD comprising one or more mutations characteristic of a BA.1 Omicron variant and an RBD comprising one or more mutations characteristic of a second SARS-CoV-2 variant that is not a BA.1 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.1 Omicron variant and an NTD comprising one or more mutations characteristic of a second SARS-CoV-2 variant that is not a BA.1 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an NTD comprising one or more mutations characteristic of a BA.1 Omicron variant and an RBD comprising one or more mutations characteristic of a BA.2 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises one or more mutations characteristic of an NTD of a BA.1 Omicron variant and an RBD comprising one or more mutations characteristic of a BA.4/5 Omicron variant, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide.

[0956] In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.1 Omicron variant and an NTD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.2 Omicron variant and an NTD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an RBD comprising one or more mutations characteristic of a BA.4/5 Omicron variant and an NTD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide.

[0957] In some embodiments, a vaccine can comprise a polypeptide that comprises an NTD comprising one or more mutations characteristic of a BA.1 Omicron variant and an RBD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an NTD comprising one or more mutations characteristic of a BA.2 Omicron variant and an RBD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide. In some embodiments, a vaccine can comprise a polypeptide that comprises an NTD comprising one or more mutations characteristic of a BA.4/5 Omicron variant and an RBD of a Wuhan S protein, or a nucleic acid (e.g., in some embodiments an RNA) encoding the polypeptide.

[0958] In some embodiments, a subject is administered a first RNA and a second RNA, each in the same amount (i.e., at a 1:1 ratio).

[0959] In some embodiments, a subject is administered a first RNA and a second RNA, each in a different amount. For example, in some embodiments, a subject is administered a first RNA in an amount that is 0.01 to 100 times that of a second RNA (e.g., wherein the amount of a first RNA is 0.01 to 50, 0.01 to 4, 0.01 to 30, 0.01 to 25, 0.01 to 20, 0.01 to 15, 0.01 to 10, 0.01 to 9, 0.01 to 8, 0.01 to 7, 0.01 to 6, 0.01 to 5, 0.01 to 4, 0.01 to 3,

0.01 to 2, 0.01 to 1.5, 1 to 50, 1 to 4, 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, or 1 to 1.5 times that of a second RNA). In some embodiments, a subject is administered a first RNA and a second RNA, wherein the concentration of the first RNA is 1 to 10 times that of the second RNA. In some embodiments, a subject is administered a first RNA and a second RNA, wherein the amount of the first RNA is 1 to 5 times that of the second RNA. In some embodiments, a subject is administered a first RNA and a second RNA, wherein the concentration of the first RNA is 1 to 3 times that of the second RNA. In some embodiments, a subject is administered a first RNA and a second RNA, wherein the amount of the first RNA is 2 times that of the second RNA. In some embodiments, a subject is administered a first RNA and a second RNA, wherein the concentration of the first RNA is 3 times that of the second RNA.

[0960] In some embodiments, a subject is administered three RNAs, each encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a different SARS-CoV-2 variant, and each in the same amount (i.e., at a 1:1:1 ratio).

[0961] In some embodiments, a subject is administered three RNAs, each encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a different SARS-CoV-2 variant, wherein the amount of each RNA is not the same (e.g., one RNA is present in an amount that is different than the other two RNA, or all three RNAs are present in different amounts). For example, in some embodiments, the ratio of first RNA:second RNA:third RNA is 1: 0.01-100: 0.01-100 (e.g., 1: 0.01-50: 0.01-50; 1: 0.01-40: 0.01-40; 1: 0.01-30: 0.01-25; 1: 0.01-25: 0.01-25; 1: 0.01-20: 0.01-20; 1: 0.01-15: 0.01-15; 1: 0.01-10: 0.01-9; 1: 0.01-9: 0.01-9; 1: 0.01-8: 0.01-8; 1: 0.01-7: 0.01-7; 1: 0.01-6: 0.01-6; 1: 0.01-5: 0.01-5; 1: 0.01-4: 0.01-4; 1: 0.01-3: 0.01-3; 1: 0.01-2: 0.01-2; or 1: 0.01-1.5: 0.01-1.5). In some embodiments, a subject is administered three RNAs at a ratio of 1:1:3. In some embodiments, a subject is administered three RNAs at a ratio of 1:3:3.

[0962] In some embodiments, a vaccination regimen comprises a first vaccination regimen (e.g., a primary regimen) that includes at least two doses of an RNA composition as described herein, e.g., wherein the second dose may be administered about 21 days following administration of the first dose, and a second vaccination (e.g., a booster regimen) that comprises a single dose or multiple doses, e.g., two doses, of an RNA composition as described herein. In some embodiments, doses of a booster regimen are related to those of a primary regimen by identity with or dilution from a common stock as described herein. In various embodiments, a booster regimen is administered (e.g., is initiated) at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, or at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, or longer, after administration of a primary regimen, e.g., after completion of a primary regimen comprising at least two doses. In various embodiments, a booster regimen is administered (e.g., is initiated) 1-12 months, 2-12 months, 3-12 months, 4-12 months, 6-12 months, 1-6 months, 1-5 months, 1-4 months, 1-3 months, or 2-3 months after administration of a primary regimen, e.g., after completion of a primary regimen comprising at least two doses. In various embodiments, a booster regimen is administered (e.g., is initiated) 1 to 60 months, 2 to 48 months, 2 to 24 months, 3 to 24 months, 6 to 18 months, 6 to 12 months, or 5 to 7 months after administration of a primary regimen, e.g., after completion of a two-dose primary regimen. In some embodiments, each dose of a primary regimen is about 60 μg per dose. In some embodiments, each dose of a primary regimen is about 50 μg per dose. In some embodiments, each dose of a primary regimen is about 30 μg per dose. In some embodiments, each dose of a primary regimen is about 25 μg per dose. In some embodiments, each dose of a primary regimen is about 20 μg per dose. In some embodiments, each dose of a primary regimen is about 15 μg per dose. In some embodiments, each dose of a primary regimen is about 10 μg per dose. In some embodiments, each dose of a primary regimen is about 3 μg per dose. In some embodiments, each dose of a booster regimen is the same as that of the primary regimen. In some embodiments, each dose of a booster regimen comprises the same amount of RNA as a dose

administered in a primary regimen. In some embodiments, at least one dose of a booster regimen is the same as that of the primary regimen. In some embodiments, at least one dose of a booster regimen comprises the same amount of RNA as at least one dose of a primary regimen. In some embodiments, at least one dose of a booster regimen is lower than that of the primary regimen. In some embodiments, at least one dose of a booster regimen comprises an amount of RNA that is lower than that of a primary regimen. In some embodiments, at least one dose of a booster regimen is higher than that of the primary regimen. In some embodiments, at least one dose of a booster regimen comprises an amount of RNA that is higher than that of a primary regimen.

[0963] In some embodiments, a booster regimen (e.g., as described herein) is administered to a pediatric patient (e.g., a patient aged 2 through 5 years old, a patient aged 5 through 11 years old, or a patient aged 12 through 15 years old). In some embodiments, a booster regimen is administered to a pediatric patient who is 6 months old to less than 2 years old. In some embodiments, a booster regimen is administered to a pediatric patient who is less than 6 months old. In some embodiments, a booster regimen is administered to a pediatric patient who is 6 months old to less than 5 years old. In some embodiments, a booster regimen is administered to a pediatric patient who is 2 years old to less than 5 years old. In some embodiments, a booster regimen is administered to a pediatric patient who is 5 years old to less than 12 years old. In some embodiments, a booster regimen is administered to a pediatric patient who is 12 years old to less than 16 years old. In some embodiments, each dose of a pediatric booster regimen comprises about 3 μg of RNA. In some embodiments, each dose of a pediatric booster regimen comprises about 10 μg of RNA. In some embodiments, each dose of a pediatric booster regimen comprises about 15 μg of RNA. In some embodiments, each dose of a pediatric booster regimen comprises about 20 μg of RNA. In some embodiments, each dose of a pediatric booster regimen comprises about 25 μg of RNA. In some embodiments, each dose of a pediatric booster regimen comprises about 30 μg of RNA. In some embodiments, a booster regimen is administered to a non-pediatric patient (e.g., a patient 16 years or older, a patient aged 18 through 64 years old, and/or a patient 65 years and older). In some embodiments, each dose of a non-pediatric booster regimen comprises about 3 ug of RNA, about 10 ug of RNA, about 25 μg or RNA, about 30 μg of RNA, about 40 μg of RNA, about 45 μg of RNA, about 50 μg of RNA, about 55 μg of RNA, or about 60 μg of RNA . In some embodiments, the same booster regimen may be administered to both pediatric and non-pediatric patients (e.g., to a patient 12 years or older). In some embodiments, a booster regimen that is administered to a non-pediatric patient is administered in a formulation and dose that is related to that of a primary regimen previously received by the patient by identity with or by dilution as described herein. In some embodiments, a non-pediatric patient who receives a booster regimen at a lower dose than a primary regimen may have experienced an adverse reaction to one or more doses of such primary regimen and/or may have been exposed to and/or infected by SARS-CoV-2 between such primary regimen and such booster regimen, or between doses of such primary regimen and/or of such booster regimen. In some embodiments, pediatric and non-pediatric patients may receive a booster regimen at a higher dose than a primary regimen when waning of vaccine efficacy at lower doses is observed, and/or when immune escape of a variant that is prevalent and/or spreading rapidly at a relevant jurisdiction at the time of administration is observed.

[0964] In some embodiments one or more doses of a booster regimen differs from that of a primary regimen. For example, in some embodiments, an administered dose may correspond to a subject's age and a patient may age out of one treatment age group and into a next. Alternatively or additionally, in some embodiments, an administered dose may correspond to a patient's condition (e.g., immunocompromised state) and a different dose may be selected for one or more doses of a booster regimen than for a primary regimen (e.g., due to intervening cancer treatment, infection with HIV, receipt of immunosuppressive therapy, for example associated with an organ transplant. In some embodiments, at least one dose of a booster regimen may comprise an amount of RNA that is higher than at least one dose administered in a primary regimen (e.g., in situations where waning of vaccine efficacy

from one or more earlier doses is observed and/or immune escape by a variant (e.g., one described herein) that is prevalent or rapidly spreading is observed in a relevant jurisdiction at the time of administration).

[0965] In some embodiments, a primary regimen may involve one or more 3 ug doses and a booster regimen may involve one or more 10 ug doses, and/or one or more 20 ug doses, or one or more 30 ug doses. In some embodiments, a primary regimen may involve one or more 3 ug doses and a booster regimen may involve one or more 3 ug doses. In some embodiments, a primary regimen may involve two or more 3 ug doses (e.g., at least two doses, each comprising 3 ug of RNA, and administered about 21 days after one another) and a booster regimen may involve one or more 3 ug doses. In some embodiments, a primary regimen may involve one or more 10 ug doses and a booster regimen may involve one or more 20 ug doses, and/or one or more 30 ug doses. In some embodiments, a primary regimen may involve one or more 10 ug doses and a booster regimen may involve one or more 10 ug doses. In some embodiments, a primary regimen may involve two or more 10 ug doses (e.g., two doses, each comprising 10 ug of RNA, administered about 21 days apart) and a booster regimen may involve one or more 10 ug doses. In some embodiments, a primary regimen may involve one or more 20 ug doses and a booster regimen may involve one or more 30 ug doses. In some embodiments, a primary regimen may involve one or more 20 ug doses and a booster regimen may involve one or more 20 ug doses. In some embodiments, a primary regimen may involve one or more 30 ug doses, and a booster regimen may also involve one or more 30 ug doses. In some embodiments, a primary regimen may involve two or more 30 ug doses (e.g., two doses, each comprising 30 ug of RNA, administered about 21 days apart), and a booster regimen may also involve one or more 30 ug doses. In some embodiments, a primary regimen may involve two or more 30 ug doses (e.g., two doses, each comprising 30 ug of RNA, administered about 21 days apart), and a booster regimen may involve one or more 50 ug doses. In some embodiments, a primary regimen may involve two or more 30 ug doses (e.g., two doses, each comprising 30 ug of RNA, administered about 21 days apart), and a booster regimen may involve one or more 60 ug doses.

[0966] In some embodiments, a subject is administered a booster regimen comprising at least one 30 ug dose of RNA. In some embodiments, a subject is administered a booster regimen comprising at least one 30 ug dose of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain of SARS-CoV-2 (e.g., BNT162b2). In some embodiments, a subject is administered a booster regimen comprising at least one dose of 30 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a SARS-CoV-2 variant (e.g., a variant described herein). In some embodiments, a subject is administered a booster regimen comprising at least one dose of 30 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant (e.g., a BA.1, BA.2, BA.3, or BA.4 or BA.5 Omicron variant). In some embodiments, a subject is administered a booster regimen comprising at least one dose of 30 ug of RNA, wherein the 30 ug of RNA comprises RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and RNA encoding a SARS-CoV-2 S protein comprising mutations that are characteristic of a SARS-CoV-2 variant (e.g., in some embodiments, a subject is administered a booster regimen comprising at least one dose comprising 15 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 15 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant). In some embodiments, a subject is administered a booster regimen comprising at least one dose comprising 15 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 15 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a BA.4 or BA.5 Omicron variant. In some embodiments, a subject is administered a booster regimen comprising at least one dose comprising 10 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 20 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a BA.4 or BA.5 Omicron variant. In some embodiments, a subject is administered a booster regimen comprising at least one dose comprising 7.5 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 22.5 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a BA.4 or BA.5 Omicron variant.

[0967] In some embodiments, a subject is administered a booster regimen comprising two or more doses of 30 ug of RNA, administered at least two months apart from each other. For example, in some embodiments, subjects are administered a booster regimen comprising two doses of 30 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant (e.g., a BA.1, BA.2, or BA.4 or BA.5 Omicron variant).

[0968] In some embodiments, a subject is administered (i) a primary regimen comprising at least two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered at least approximately 21 days apart, and (ii) a booster regimen comprising a dose of 30 ug of RNA encoding a SARS-CoV-2 S protein having one or mutations that are characteristic of an Omicron variant of SARS-CoV-2 (e.g., a BA.1, BA.2, BA.3, BA.4, or BA.5 Omicron variant), wherein the booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of the primary regimen. In some embodiments, a subject is administered (i) a primary regimen comprising at least two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered at least approximately 21 days apart, and (ii) a booster regimen comprising a 30 ug dose of RNA comprising 15 ug RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 15 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant.

[0969] In some embodiments, a subject is administered (i) a primary regimen comprising two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered at least approximately 21 days apart, and (ii) a booster regimen comprising at least two 30 ug doses of RNA encoding a SARS-CoV-2 S protein having one or more mutations characteristic of an Omicron variant, wherein the booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of the primary regimen, and the two booster doses are administered at least two months apart from each other.

[0970] In some embodiments, a subject is administered a booster regimen comprising at least one 50 ug dose of RNA. In some embodiments, a subject is administered a booster regimen comprising at least one dose of 50 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a SARS-CoV-2 variant (e.g., a variant described herein). In some embodiments, a subject is administered a booster regimen comprising at least one dose of 50 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant. In some embodiments, a subject is administered a booster regimen comprising at least one 50 ug dose of RNA, wherein the 50 ug of RNA comprises RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and RNA encoding a SARS-CoV-2 S protein comprising mutations that are characteristic of a SARS-CoV-2 variant (e.g., in some embodiments, a subject is administered a booster regimen comprising a 50 ug dose of RNA comprising 25 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 25 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant).

[0971] In some embodiments, a subject is administered (i) a primary regimen comprising two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered approximately 21 days apart, and (ii) a booster regimen comprising at least one 50 ug dose of RNA encoding a SARS-CoV-2 S protein having one or mutations that are characteristic of an Omicron variant of SARS-CoV-2 (e.g., a BA.1, BA.2, BA.4 or BA.5 Omicron variant), wherein the booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of the primary regimen. In some embodiments, a subject is administered (i) a primary regimen comprising two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered approximately 21 days apart, and (ii) a booster regimen comprising at least one 50 ug dose of RNA, wherein the 50 ug of RNA comprises 25 ug of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and

25 ug of RNA encoding a SARS-CoV-2 S protein having one or mutations that are characteristic of an Omicron variant (e.g., a BA.1, BA.2, BA.4, or BA.5 variant), wherein the booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of a first booster regimen.

[0972] In some embodiments, a subject is administered a booster regimen comprising at least one 60 ug dose of RNA. In some embodiments, a subject is administered 60 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of a SARS-CoV-2 variant (e.g., a variant described herein). In some embodiments, a subject is administered a booster regimen comprising 60 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant (e.g., an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant). In some embodiments, a subject is administered a booster regimen comprising 60 ug of RNA, wherein the RNA comprises a first RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, and at least one additional RNA encoding a SARS-CoV-2 S protein comprising mutations that are characteristic of a SARS-CoV-2 variant (e.g., in some embodiments, a subject is administered a booster regimen comprising 30 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 30 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant (e.g., an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 variant).

[0973] In some embodiments, a subject is administered (i) a primary regimen comprising two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered approximately 21 days apart, and (ii) a booster regimen comprising at least one 60 ug dose of RNA encoding a SARS-CoV-2 S protein having one or mutations that are characteristic of an Omicron variant of SARS-CoV-2 (e.g., an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant), wherein the booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of the primary regimen. In some embodiments, a subject is administered (i) a primary regimen comprising two 30 ug doses of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein the two doses are administered approximately 21 days apart, and (iii) a booster regimen comprising at least one 60 ug dose of RNA comprising 30 ug of RNA encoding a SARS-CoV-2 S protein having one or mutations that are characteristic of an Omicron variant of SARS-CoV-2 and 30 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, wherein a second booster regimen is administered at least two months (including, e.g., at least three months, at least four months, at least five months, at least six months, or more) after completion of a first booster regimen.

[0974] In some embodiments, a patient is administered a primary regimen comprising two 30 ug doses, administered approximately 21 days apart, and a booster regimen comprising at least one 60 ug dose of RNA (e.g., 60 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, 60 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant (e.g., an XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2 Omicron variant), or 30 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 30 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant). In some embodiments, a patient is administered a primary regimen comprising two 30 ug doses, administered approximately 21 days apart, and a booster regimen comprising at least one 50 ug dose of RNA (e.g., 50 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, 50 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant, or 25 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 25 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant). In some embodiments, a patient is administered a primary regimen comprising two 30 ug doses, administered approximately 21 days apart, and a booster regimen comprising at least one 30 ug dose of RNA (e.g., 30 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain, 30 ug

of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant, or 15 ug of RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and 15 ug of RNA encoding a SARS-CoV-2 S protein having one or more mutations that are characteristic of an Omicron variant).

[0975] In some embodiments, a primary regimen may involve one or more 30 ug doses and a booster regimen may involve one or more 20 ug doses, one or more 10 ug doses, and/or one or more 3 ug doses. In some embodiments, a primary regimen may involve one or more 20 ug doses and a booster regimen may involve one or more 10 ug doses, and/or one or more 3 ug doses. In some embodiments, a primary regimen may involve one or more 10 ug doses and a booster regimen may involve one or more 3 ug doses. In some embodiments, a primary regimen may involve one or more 3 ug doses, and a booster regimen may also involve one or more 3 ug doses.

[0976] In some embodiments, a booster regimen comprises a single dose, e.g., for patients who experienced an adverse reaction while receiving the primary regimen.

[0977] In some embodiments, the same RNA as used in a primary regimen is used in a booster regimen. In some embodiment, an RNA used in primary and booster regimens is BNT162b2.

[0978] In some embodiments, a different RNA is used in a booster regimen relative to that used in a primary regimen administered to the same subject. In some embodiments, BNT162b2 is used in a primary regimen but not in a booster regimen. In some embodiments, BNT162b2 is used in a booster regimen but not in a primary regimen. In some embodiments, a similar BNT162b2 construct can be used in a primary regimen and in a booster regimen, except that the RNA constructs used in the primary and booster regimens encode a SARS-CoV-2 S protein (or an immunogenic portion thereof) of different SARS-CoV-2 strains (e.g., as described herein).

[0979] In some embodiments, where BNT162b2 is used for a primary regimen or a booster regimen but not both, and a different RNA is used in the other, such different RNA may be an RNA encoding the same SARS-CoV-2 S protein but with different codon optimization or other different RNA sequence. In some embodiments, such different RNA may encode a SARS-CoV-2 S protein (or an immunogenic portion thereof) of a different SARS-CoV-2 strain, e.g., of a variant strain discussed herein. In some such embodiments, such variant strain that is prevalent or rapidly spreading in a relevant jurisdiction. In some embodiments, such different RNA may be an RNA encoding a SARS-CoV-2 S protein or variant thereof (or immunogenic portion of either) comprising one or more mutations described herein for S protein variants such as SARS-CoV-2 S protein variants, in particular naturally occurring S protein variants; in some such embodiments, a SARS-CoV-2 variant may be selected from the group consisting of VOC-202012/01, 501.V2, Cluster 5 and B.1.1.248. In some embodiments, a SARS-CoV-2 variant may be selected from the group consisting of VOC-202012/01, 501.V2, Cluster 5 and B.1.1.248, B.1.1.7, B.1.617.2, and B.1.1.529. In some embodiments, a booster regimen comprises at least one dose of RNA that encodes a SARS-CoV-2 S protein (or an immunogenic fragment thereof) of a variant that is spreading rapidly in a relevant jurisdiction at the time of administration. In some such embodiments, a variant that is encoded by RNA administered in a booster regimen may be different from that encoded by RNA administered in a primary regimen.

[0980] In some embodiments, a booster regimen comprises administering (i) a dose of RNA encoding the same SARS-CoV-2 S protein (or an immunogenic fragment thereof) as the RNA administered in the primary regimen (e.g., an RNA encoding a SARS-CoV-2the S protein (or an immunogenic fragment thereof) from the SARS-CoV-2 Wuhan strain) and (ii) a dose of RNA encoding a SARS-CoV-2 S protein (or an immunogenic fragment thereof) of a variant that is spreading rapidly in a relevant jurisdiction at the time of administration (e.g., a SARS-CoV-2 S protein (or an immunogenic fragment thereof) from one of the SARS-CoV-2 variants discussed herein).

[0981] In some embodiments, a booster regimen comprises multiple doses (e.g., at least two doses, at least three doses, or more). For example, in some embodiments, a first dose of a booster regimen may comprise an RNA encoding the same SARS-CoV-2 S protein (or an immunogenic fragment thereof) administered in the primary regimen and a second dose of a booster regimen may comprise the RNA encoding a SARS-CoV-2 S protein of a

variant that is spreading rapidly in a relevant jurisdiction at the time of administration. In some embodiments, a first dose of a booster regimen may comprise RNA encoding a SARS-CoV-2 S protein (or an immunogenic fragment thereof) of a variant that is spreading rapidly in a relevant jurisdiction at the time of administration and a second dose of a booster regimen may comprise RNA encoding the same SARS-CoV-2 S protein (or an immunogenic fragment thereof) administered in the primary regimen. In some embodiments, the booster regimen comprises multiple doses, and the RNA encoding the S protein of a variant that is spreading rapidly in a relevant jurisdiction is administered in a first dose and the RNA encoding the S protein administered in the primary regimen is administered in a second dose.

[0982] In some embodiments, doses (e.g., a first and a second dose or any two consecutive doses) in a booster regimen are administered at least 2 weeks apart, including, e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 week, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks, at least 16 weeks, or longer, apart. In some embodiments, doses (e.g., a first and a second dose or any two consecutive doses) in a booster regimen are administered approximately 2 to 168 weeks apart. In some embodiments, doses (e.g., a first and a second dose or any two consecutive doses) in a booster regimen are administered approximately 3 to 12 weeks apart. In some embodiments, doses (e.g., a first and a second dose or any two consecutive doses) in a booster regimen are administered approximately 4 to 10 weeks apart. In some embodiments, doses (e.g., a first and a second dose or any two consecutive doses) in a booster regimen are administered approximately 6 to 8 weeks apart. (e.g., about 21 days apart, or about 6 to 8 weeks apart). In some embodiments, the first and second dose are administered on the same day (e.g., by intramuscular injection at different sites on the subject).

[0983] In such embodiments, the booster regimen can optionally further comprise a third and fourth dose, administered approximately 2 to 8 weeks after the first and second dose (e.g., about 21 days after the first and second dose, or about 6 weeks to about 8 weeks after the first and second dose), where the third and fourth dose are also administered on the same day (e.g., by intramuscular injection at different sites on the subject), and comprise the same RNAs administered in the first and second doses of the booster regimen.

[0984] In some embodiments, multiple booster regimens may be administered. In some embodiments, a booster regimen is administered to a patient who has previously been administered a booster regimen.

[0985] In some embodiments, a second booster regimen is administered to a patient who has previously received a first booster regimen, and the amount of RNA administered in at least one dose of a second booster regimen is higher than the amount of RNA administered in at least one dose of a first booster regimen.

[0986] In some embodiments, a second booster regimen comprises administering at least one dose of 3 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 5 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 10 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 15 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 20 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 25 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 30 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 50 ug of RNA. In some embodiments, a second booster regimen comprises administering at least one dose of 60 ug of RNA.

[0987] In some embodiments, a subject is administered a primary regimen that comprises two doses of 30 ug of RNA, administered approximately 21 days apart, and a booster regimen comprising at least one dose of approximately 30 ug of RNA. In some embodiments, a subject is administered a primary regimen that comprises two doses of 30 ug of RNA, administered approximately 21 days apart, and a booster regimen comprising at least one dose of approximately 50 ug of RNA. In some embodiments, a subject is administered a primary regimen that

comprises two doses of 30 ug of RNA, administered approximately 21 days apart, and a booster regimen comprising at least one dose of approximately 60 ug of RNA.

[0988] In some embodiments, a subject is administered a primary regimen that comprises two doses of 30 ug of RNA, administered approximately 21 days apart, a first booster regimen comprising at least one dose of approximately 30 ug of RNA, and a second booster regimen comprising at least one dose of approximately 30 ug of RNA. In some embodiments, a subject is administered a primary regimen that comprises two doses of 30 ug of RNA, administered approximately 21 days apart, a first booster regimen comprising at least one dose of approximately 30 ug of RNA, and a second booster regimen comprising at least one dose of approximately 50 ug of RNA. In some embodiments, a subject is administered a primary regimen that comprises two doses of 30 ug of RNA, administered approximately 21 days apart, a first booster regimen comprising at least one dose of approximately 30 ug of RNA, and a second booster regimen comprising at least one dose of approximately 60 ug of RNA. In some embodiments, a first booster regimen comprises two doses of RNA, wherein each dose comprises an RNA encoding a Spike protein from a different SARS-CoV-2 variant. In some embodiments, a first booster regimen comprises two doses of RNA, wherein each dose comprises an RNA encoding a Spike protein from a different SARS-CoV-2 variant, and wherein the two doses of RNA are administered on the same day. In some embodiments, the two doses of RNA are administered in a single composition (e.g., by mixing a first composition comprising an RNA encoding a Spike protein from a first SARS-CoV-2 variant with a second composition comprising an RNA encoding a Spike protein from a second SARS-CoV-2 variant).

[0989] In some embodiments, a subject is administered a booster regimen comprising a first dose comprising an RNA that encodes a Spike protein from a Wuhan strain of SARS-CoV-2 and a second dose comprising an RNA that encodes a Spike protein comprising mutations from a variant that is prevalent and/or rapidly spreading in a relevant jurisdiction at the time of administering the booster regimen, wherein the first dose and the second dose of RNA may be administered on the same day. In some embodiments, a subject is administered a booster regimen comprising a first dose comprising an RNA that encodes a Spike protein from a Wuhan strain of SARS-CoV-2 and a second dose comprising an RNA that encodes a Spike protein comprising mutations from an alpha variant of SARS-CoV-2, wherein the first dose and the second dose may be administered on the same day. In some embodiments, a subject is administered a booster regimen comprising a first dose comprising an RNA that encodes a Spike protein from a Wuhan strain of SARS-CoV-2 and a second dose comprising an RNA that encodes a Spike protein comprising mutations from a beta variant of SARS-CoV-2, wherein the first dose and the second dose may be administered on the same day. In some embodiments, a subject is administered a booster regimen comprising a first dose comprising an RNA that encodes a Spike protein from a Wuhan strain of SARS-CoV-2 and a second dose comprising an RNA that encodes a Spike protein comprising mutations from a delta variant of SARS-CoV-2, wherein the first dose and the second dose may be administered on the same day. In some embodiments, a subject is administered a booster regimen comprising a first dose comprising an RNA that encodes a Spike protein from a Wuhan strain of SARS-CoV-2 and a second dose comprising an RNA that encodes a Spike protein comprising mutations from an Omicron variant of SARS-CoV-2, wherein the first dose and the second dose may be administered on the same day. Such booster regimens may be administered, e.g., to a subject previously administered a primary dosing regimen and/or to a subject previously administered a primary dosing regimen and a booster regimen.

[0990] In some embodiments, a subject is administered a first booster regimen comprising a first dose of 15 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 15 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2, where the first and the second dose are administered on the same day (e.g., wherein compositions comprising the RNA are mixed prior to administration, and the mixture is then administered to a patient). In some embodiments, a subject is administered a first booster regimen comprising a first dose of 25 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 25 ug of RNA

encoding a Spike protein from an Omicron variant of SARS-CoV-2. In some embodiments, the first and the second doses are optionally administered on the same day. In some embodiments, a subject is administered a first booster regimen comprising a first dose of 25 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 25 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2. In some embodiments, the first and the second doses are administered on the same day. In some embodiments, a subject is administered a first booster regimen comprising a first dose of 30 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 30 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2, wherein the first and the second dose are optionally administered on the same day (e.g., in separate administrations or as administration of a multivalent vaccine). In some embodiments, such a first booster regimen is administered to a subject previously administered a primary regimen comprising two doses of 30 ug of RNA, administered about 21 days apart wherein the first booster regimen is administered at least 3 months (e.g., at least 4, at least 5, or at least 6 months) after administration of a primary regimen.

[0991] In some embodiments, a subject is administered a second booster regimen comprising a first dose of 15 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 15 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2, where the first and the second dose are administered on the same day (e.g., wherein compositions comprising the RNA are mixed prior to administration to form a multivalent vaccine, and the mixture is then administered to a patient). In some embodiments, a subject is administered a second booster regimen comprising a first dose of 25 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 25 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2, wherein the first dose and the second dose are optionally administered on the same day (e.g., via administration of a multivalent vaccine or via administration of separate compositions). In some embodiments, a subject is administered a second booster regimen comprising a first dose of 25 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 25 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2. In some embodiments, a subject is administered a second booster regimen comprising a first dose of 30 ug of RNA encoding a Spike protein from a Wuhan variant and a second dose of 30 ug of RNA encoding a Spike protein from an Omicron variant of SARS-CoV-2, wherein the first dose and the second dose are optionally administered on the same day (e.g., via administration of a multivalent vaccine or via administration of separate compositions). In some embodiments, such a second booster regimen is administered to a subject previously administered a primary regimen comprising two doses of 30 ug of RNA, administered about 21 days apart. In some embodiments, such a second booster regimen is administered to a subject previously administered a primary regimen comprising two doses of 30 ug of RNA, administered about 21 days apart, and a first booster regimen comprising a dose of 30 ug of RNA, wherein the second booster regimen is administered at least 3 months (e.g., at least 4, at least 5, or at least 6 months) after administration of a first booster regimen.

[0992] In some embodiments, patients receiving dose(s) of RNA compositions as described herein are monitored for one or more particular conditions, e.g., following administration of one or more doses. In some embodiments, such condition(s) may be or comprise allergic reaction(s) (particularly in subject(s) with a history of relevant allergies or allergic reactions), myocarditis (inflammation of the heart muscle, particularly where the subject is a young male and/or may have experienced prior such inflammation), pericarditis (inflammation of the lining outside the heart, particularly where the subject is a young males and/or may have experienced prior such inflammation), fever, bleeding (particularly where the subject is known to have a bleeding disorder or to be receiving therapy with a blood thinner). Alternatively or additionally, patients who may receive closer monitoring may be or include patients who are immunocompromised or are receiving therapy with a medicine that affects the immune system, are pregnant or planning to become pregnant, are breastfeeding, have received another COVID-19 vaccine, and/or have ever fainted in association with an injection. In some embodiments, patients are monitored for

myocarditis following administration of one of the compositions disclosed herein. In some embodiments, patients are monitored for pericarditis following administration of one of the compositions disclosed herein. Patients may be monitored and/or treated for the condition using current standards of care.

[0993] In some embodiments, efficacy for RNA (e.g., mRNA) compositions described in pediatric populations (e.g., described herein) may be assessed by various metrics described herein (including, e.g., but not limited to COVID-19 incidence per 1000 person-years in subjects with no serological or virological evidence of past SARS-CoV-2 infection; geometric mean ratio (GMR) of SARS CoV-2 neutralizing titers measured, e.g., 7 days after a second dose; etc.)

[0994] In some embodiments, pediatric populations described herein (e.g., from 12 to less than 16 years of age) may be monitored for occurrence of multisystem inflammatory syndrome (MIS) (e.g., inflammation in different body parts such as, e.g., heart, lung, kidneys, brain, skin ,eyes, and/or gastrointestinal organs), after administration of an RNA composition (e.g., mRNA) described herein. Exemplary symptoms of MIS in children may include, but are not limited to fever, abdominal pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes, feeling extra tried, and combinations thereof.

[0995] In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) described herein as BNT162b1 (RBP020.3), BNT162b2 (RBP020.1 or RBP020.2), or BNT162b3 (e.g., BNT162b3c). In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) described herein as RBP020.2. In one embodiment, RNA encoding a vaccine antigen is nucleoside modified messenger RNA (modRNA) described herein as BNT162b3 (e.g., BNT162b3c).

[0996] In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) and (i) comprises the nucleotide sequence of SEQ ID NO: 19, or 20, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19, or 20, and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 7. In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) and (i) comprises the nucleotide sequence of SEQ ID NO: 19, or 20; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 7.

[0997] In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) and (i) comprises the nucleotide sequence of SEQ ID NO: 20, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 20, and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 7, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 7. In one embodiment, RNA administered as described above is nucleoside modified messenger RNA (modRNA) and (i) comprises the nucleotide sequence of SEQ ID NO: 20; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 7.

[0998] In one embodiment, RNA administered is nucleoside modified messenger RNA (modRNA), (i) comprises the nucleotide sequence of SEQ ID NO: 20; and/or (ii) encodes an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 7, and is administered in an amount of about 30 µg per dose. In one embodiment, at least two of such doses are administered. For example, a second dose may be administered about 21 days following administration of the first dose.

[0999] In some embodiments, populations to be treated with RNA described herein comprise, essentially consist of, or consist of subjects of age of at least 50, at least 55, at least 60, or at least 65. In some embodiments, populations to be treated with RNA described herein comprise, essentially consist of, or consist of subjects of age of between 55 to 90, 60 to 85, or 65 to 85.

[1000] In some embodiments, the period of time between the doses administered is at least 7 days, at least 14 days, or at least 21 days. In some embodiments, the period of time between the doses administered is between 7 days and 28 days such as between 14 days and 23 days.

[1001] In some embodiments, no more than 5 doses, no more than 4 doses, or no more than 3 doses of the RNA described herein may be administered to a subject.

[1002] In some embodiments, the methods and agents described herein are administered (in a regimen, e.g., at a dose, frequency of doses and/or number of doses) such that adverse events (AE), i.e., any unwanted medical occurrence in a patient, e.g., any unfavourable and unintended sign, symptom, or disease associated with the use of a medicinal product, whether or not related to the medicinal product, are mild or moderate in intensity. In some embodiments, the methods and agents described herein are administered such that adverse events (AE) can be managed with interventions such as treatment with, e.g., paracetamol or other drugs that provide analgesic, antipyretic (fever-reducing) and/or anti-inflammatory effects, e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., aspirin, ibuprofen, and naproxen. Paracetamol or "acetaminophen" which is not classified as a NSAID exerts weak anti-inflammatory effects and can be administered as analgesic according to the present disclosure.

[1003] In some embodiments, the methods and agents described herein provide a neutralizing effect in a subject to coronavirus, coronavirus infection, or to a disease or disorder associated with coronavirus.

[1004] In some embodiments, the methods and agents described herein following administration to a subject induce an immune response that blocks or neutralizes coronavirus in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce the generation of antibodies such as IgG antibodies that block or neutralize coronavirus in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce an immune response that blocks or neutralizes coronavirus S protein binding to ACE2 in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce the generation of antibodies that block or neutralize coronavirus S protein binding to ACE2 in the subject.

[1005] In some embodiments, the methods and agents described herein following administration to a subject induce geometric mean concentrations (GMCs) of RBD domain-binding antibodies such as IgG antibodies of at least 500 U/ml, 1000 U/ml, 2000 U/ml, 3000 U/ml, 4000 U/ml, 5000 U/ml, 10000 U/ml, 15000 U/ml, 20000 U/ml, 25000 U/ml, 30000 U/ml or even higher. In some embodiments, the elevated GMCs of RBD domain-binding antibodies persist for at least 14 days, 21 days, 28 days, 1 month, 3 months, 6 months, 12 months or even longer.

[1006] In some embodiments, the methods and agents described herein following administration to a subject induce geometric mean titers (GMTs) of neutralizing antibodies such as IgG antibodies of at least 100 U/ml, 200 U/ml, 300 U/ml, 400 U/ml, 500 U/ml, 1000 U/ml, 1500 U/ml, or even higher. In some embodiments, the elevated GMTs of neutralizing antibodies persist for at least 14 days, 21 days, 28 days, 1 month, 3 months, 6 months, 12 months or even longer.

[1007] As used herein, the term "neutralization" refers to an event in which binding agents such as antibodies bind to a biological active site of a virus such as a receptor binding protein, thereby inhibiting the viral infection of cells. As used herein, the term "neutralization" with respect to coronavirus, in particular coronavirus S protein, refers to an event in which binding agents such as antibodies bind to the RBD domain of the S protein, thereby inhibiting the viral infection of cells. In particular, the term "neutralization" refers to an event in which binding agents eliminate or significantly reduce virulence (e.g. ability of infecting cells) of viruses of interest.

[1008] The type of immune response generated in response to an antigenic challenge can generally be distinguished by the subset of T helper (Th) cells involved in the response. Immune responses can be broadly divided into two types: Th1 and Th2. Th1 immune activation is optimized for intracellular infections such as viruses, whereas Th2 immune responses are optimized for humoral (antibody) responses. Th1 cells produce interleukin 2

(IL-2), tumor necrosis factor (TNFα) and interferon gamma (IFNγ). Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. Th1 immune activation is the most highly desired in many clinical situations. Vaccine compositions specialized in eliciting Th2 or humoral immune responses are generally not effective against most viral diseases.

[1009] In some embodiments, the methods and agents described herein following administration to a subject induce or promote a Th1-mediated immune response in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce or promote a cytokine profile that is typical for a Th1-mediated immune response in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce or promote the production of interleukin 2 (IL-2), tumor necrosis factor (TNFα) and/or interferon gamma (IFNγ) in the subject. In some embodiments, the methods and agents described herein following administration to a subject induce or promote the production of interleukin 2 (IL-2) and interferon gamma (IFNγ) in the subject. In some embodiments, the methods and agents described herein following administration to a subject do not induce or promote a Th2-mediated immune response in the subject, or induce or promote a Th2-mediated immune response in the subject to a significant lower extent compared to the induction or promotion of a Th1-mediated immune response. In some embodiments, the methods and agents described herein following administration to a subject do not induce or promote a cytokine profile that is typical for a Th2-mediated immune response in the subject, or induce or promote a cytokine profile that is typical for a Th2-mediated immune response in the subject to a significant lower extent compared to the induction or promotion of a cytokine profile that is typical for a Th1-mediated immune response. In some embodiments, the methods and agents described herein following administration to a subject do not induce or promote the production of IL-4, IL-5, IL-6, IL-9, IL-10 and/or IL-13, or induce or promote the production of IL-4, IL-5, IL-6, IL-9, IL-10 and/or IL-13 in the subject to a significant lower extent compared to the induction or promotion of interleukin 2 (IL-2), tumor necrosis factor (TNFα) and/or interferon gamma (IFNγ) in the subject. In some embodiments, the methods and agents described herein following administration to a subject do not induce or promote the production of IL-4, or induce or promote the production of IL-4 in the subject to a significant lower extent compared to the induction or promotion of interleukin 2 (IL-2) and interferon gamma (IFNγ) in the subject.

[1010] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a panel of different S protein variants such as SARS-CoV-2 S protein variants, in particular naturally occurring S protein variants. In some embodiments, the panel of different S protein variants comprises at least 5, at least 10, at least 15, or even more S protein variants. In some embodiments, such S protein variants comprise variants having amino acid modifications in the RBD domain and/or variants having amino acid modifications outside the RBD domain .

[1011] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets VOC-202012/01.

[1012] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1013] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets VOC-202012/01.

[1014] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "Cluster 5".

[1015] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a

mutation at a position corresponding to position 614 (D) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 614 (D) in SEQ ID NO: 1 is G.

[1016] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets VOC-202012/01.

[1017] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets VOC-202012/01.

[1018] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a mutation at a position corresponding to position 484 (E) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 484 (E) in SEQ ID NO: 1 is K.

[1019] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1020] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "B.1.1.28".

[1021] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "B.1.1.248".

[1022] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a mutation at positions corresponding to positions 501 (N) and 484 (E) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 501 (N) in SEQ ID NO: 1 is Y and the amino acid corresponding to position 484 (E) in SEQ ID NO: 1 is K.

[1023] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1024] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "B.1.1.248".

[1025] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a mutation at positions corresponding to positions 501 (N), 484 (E) and 614 (D) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 501 (N) in SEQ ID NO: 1 is Y, the amino acid corresponding to position 484 (E) in SEQ ID NO: 1 is K and the amino acid corresponding to position 614 (D) in SEQ ID NO: 1 is G.

[1026] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a deletion at a position corresponding to positions 242 (L), 243 (A) and 244 (L) in SEQ ID NO: 1.

[1027] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1028] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a

mutation at a position corresponding to position 417 (K) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 417 (K) in SEQ ID NO: 1 is N. In one embodiment, the amino acid corresponding to position 417 (K) in SEQ ID NO: 1 is T.

[1029] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1030] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "B.1.1.248".

[1031] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets a S protein variant such as SARS-CoV-2 S protein variant, in particular naturally occurring S protein variant comprising a mutation at positions corresponding to positions 417 (K) and 484 (E) and/or 501 (N) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 417 (K) in SEQ ID NO: 1 is N, and the amino acid corresponding to position 484 (E) in SEQ ID NO: 1 is K and/or the amino acid corresponding to position 501 (N) in SEQ ID NO: 1 is Y. In one embodiment, the amino acid corresponding to position 417 (K) in SEQ ID NO: 1 is T, and the amino acid corresponding to position 484 (E) in SEQ ID NO: 1 is K and/or the amino acid corresponding to position 501 (N) in SEQ ID NO: 1 is Y.

[1032] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets 501.V2.

[1033] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets "B.1.1.248".

[1034] In some embodiments, the methods and agents described herein following administration to a subject induce an antibody response, in particular a neutralizing antibody response, in the subject that targets the Omicron (B.1.1.529) variant.

[1035] In some embodiments, the methods and agents described herein following administration to a subject induce an immune response (cellular and/or antibody response, in particular neutralizing antibody response) in the subject that targets the Omicron (B.1.1.529) variant.

[1036] The term "amino acid corresponding to position..." as used herein refers to an amino acid position number corresponding to an amino acid position number in SARS-CoV-2 S protein, in particular the amino acid sequence shown in SEQ ID NO: 1. The phrase "as compared to SEQ ID NO: 1" is equivalent to "at positions corresponding to the following positions in SEQ ID NO: 1". Corresponding amino acid positions in other coronavirus S protein variants such as SARS-CoV-2 S protein variants may be found by alignment with SARS-CoV-2 S protein, in particular the amino acid sequence shown in SEQ ID NO: 1. It is considered well-known in the art how to align a sequence or segment in a sequence and thereby determine the corresponding position in a sequence to an amino acid position according to the present disclosure. Standard sequence alignment programs such as ALIGN, ClustalW or similar, typically at default settings may be used.

[1037] In some embodiments, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described herein, comprises one or more of the mutations described herein for S protein variants such as SARS-CoV-2 S protein variants, in particular naturally occurring S protein variants. In one embodiment, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described herein, comprises a mutation at a position corresponding to position 501 (N) in SEQ ID NO: 1. In one embodiment, the amino acid corresponding to position 501 (N) in SEQ ID NO: 1 is Y. In some embodiments, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described

herein, comprises one or more mutations, such as all mutations, of a SARS-CoV-2 S protein of a SARS-CoV-2 variant selected from the group consisting of VOC-202012/01, 501.V2, Cluster 5 and B.1.1.248. In some embodiments, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described herein, comprises an amino acid sequence with alanine substitution at position 80, glycine substitution at position 215, lysine substitution at position 484, tyrosine substitution at position 501, valine substitution at position 701, phenylalanine substitution at position 18, isoleucine substitution at position 246, asparagine substitution at position 417, glycine substitution at position 614, deletions at positions 242 to 244, and proline substitutions at positions 986 and 987 of SEQ ID NO:1.

[1038] In some embodiments, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described herein, comprising said mutations comprises K986P and V987P, as compared to SEQ ID NO: 1.

[1039] In some embodiments, a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, e.g., as encoded by the RNA described herein, comprising said mutations comprises K986P and V987P, as compared to SEQ ID NO: 1.

[1040] In some embodiments, administration of a variant specific vaccine (e.g., a variant specific vaccine disclosed herein) may result in an improved immune response in a patient as compared to administration of vaccine encoding or comprising a SARS-CoV-2 S protein from a Wuhan strain, or an immunogenic fragment thereof. In some embodiments, administration of a variant-specific vaccine may result in induction of a broader immune response in a subject as compared to a patient administered a vaccine comprising or encoding a SARS-CoV-2 S protein from a Wuhan strain (or an immunogenic fragment thereof) (e.g., induce a stronger neutralization response against a greater number of SARS-CoV-2 variants and/or a neutralization response that recognizes epitopes in a greater number of SARS-CoV-2 variants). In particular embodiments, a broader immune response may be induced when a variant specific vaccine is administered in combination with a vaccine comprising or encoding a SARS-CoV-2 S protein from a different variant or from a Wuhan strain (e.g., in some embodiments, a broader immune response may be induced when a variant specific vaccine is administered in combination with a vaccine comprising or encoding a SARS-CoV-2 S protein from a Wuhan strain or a vaccine comprising or encoding a SARS-CoV-2 S protein comprising mutations characteristic of a different SARS-CoV-2 variant). For example, a broader immune response may be induced when an RNA vaccine encoding a SARS-CoV-2 S protein from a Wuhan strain is administered in combination with an RNA vaccine encoding a SARS-CoV-2 S protein having mutations characteristic of an Omicron variant. In another embodiment, a broader immune response may be induced when an RNA vaccine encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a delta variant is administered in combination with an RNA vaccine encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an Omicron variant. In such embodiments, a "broader" immune response may be defined relative to a patient administered a vaccine comprising or encoding a SARS-CoV-2 S protein from a single variant (e.g., an RNA vaccine encoding a SARS-CoV-2 S protein from a Wuhan strain). Vaccines comprising or encoding S proteins from different SARS-CoV-2 variants, or immunogenic fragments thereof, may be administered in combination by administering at different time points (e.g., administering a vaccine encoding a SARS-CoV-2 S protein from a Wuhan strain and a vaccine encoding a SARS-CoV-2 S protein having one or more mutations characteristic of a variant strain at different time points, e.g., both administered as part of a primary regimen or part of a booster regimen; or one is administered as part of a primary regimen while another is administered as part of a booster regimen). In some embodiments, vaccines comprising or encoding S proteins from different SARS-CoV-2 variants, or immunogenic fragments thereof, may be administered in combination by administering a multivalent vaccine (e.g., a composition comprising RNA encoding a SARS-CoV-2 S protein from a Wuhan strain and RNA encoding a SARS-CoV-2 S protein having mutations characteristic of an Omicron variant). In some embodiments, a variant specific vaccine may induce

a superior immune response (e.g., inducing higher concentrations of neutralizing antibodies) against a variant against which the vaccine is specifically designed to immunize, and an immune response against one or more other variants. In some such embodiments, an immune response against other variant(s) may be comparable to or higher than that as observed with a vaccine that encodes or comprises a SARS-CoV-2 S protein from a Wuhan strain.

[1041] In some embodiments, the geometric mean ratio (GMR) or geometric mean fold rise (GMFR) of neutralization antibodies induced by a variant specific vaccine is at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0 (e.g., 1.1 to 4, 1.1 to 3.5, 1.1 to 3, 1.5 to 3, or 1.1 to 1.5) fold higher than that induced by a non-variant specific vaccine (e.g., as measured 1 day to 3 months after immunization, 7 days to 2 months after administration, about 7 days, or about 1 month after administration).

[1042] In some embodiments, the methods and agents, e.g., RNA (e.g., mRNA) compositions, described herein following administration to a subject induce a cell-mediated immune response (e.g., CD4+ and/or CD8+ T cell response). In some embodiments, T cells are induced that recognize one or more epitopes (e.g., MHC class I-restricted epitopes) selected from the group consisting of LPFNDGVYF, GVYFASTEK, YLQPRTFLL, QPTESIVRF, CVADYSVLY, KCYGVSPTK, NYNYLYRLF, FQPTNGVGY, IPFAMQMAY, RLQSLQTYV, GTHWFVTQR, VYDPLQPEL, QYIKWPWYI, and KWPWYIWLGF. In one embodiment, T cells are induced that recognize the epitope YLQPRTFLL. In one embodiment, T cells are induced that recognize the epitope NYNYLYRLF. In one embodiment, T cells are induced that recognize the epitope QYIKWPWYI. In one embodiment, T cells are induced that recognize the epitope KCYGVSPTK. In one embodiment, T cells are induced that recognize the epitope RLQSLQTYV. In some embodiments, the methods and agents, e.g., RNA (e.g., mRNA) compositions, described herein are administered according to a regimen which achieves such induction of T cells.

[1043] In some embodiments, the methods and agents, e.g., RNA (e.g., mRNA) compositions, described herein following administration to a subject induce a cell-mediated immune response (e.g., CD4+ and/or CD8+ T cell response) that is detectable 15 weeks or later, 16 weeks or later, 17 weeks or later, 18 weeks or later, 19 weeks or later, 20 weeks or later, 21 weeks or later, 22 weeks or later, 23 weeks or later, 24 weeks or later or 25 weeks or later after administration, e.g., using two doses of the RNA described herein (wherein the second dose may be administered about 21 days following administration of the first dose). In some embodiments, the methods and agents, e.g., RNA (e.g., mRNA) compositions, described herein are administered according to a regimen which achieves such induction of a cell-mediated immune response.

[1044] In one embodiment, vaccination against Coronavirus described herein, e.g., using RNA described herein which may be administered in the amounts and regimens described herein, e.g., at two doses of 30 µg per dose e.g. administered 21 days apart, may be repeated after a certain period of time, e.g., once it is observed that protection against Coronavirus infection diminishes, using the same or a different vaccine as used for the first vaccination. Such certain period of time may be at least 6 months, 1 year, two years etc. In one embodiment, the same RNA as used for the first vaccination is used for the second or further vaccination, however, at a lower dose or a lower frequency of administration. For example, the first vaccination may comprise vaccination using a dose of about 30 µg per dose, wherein in one embodiment, at least two of such doses are administered, (for example, a second dose may be administered about 21 days following administration of the first dose) and the second or further vaccination may comprise vaccination using a dose of less than about 30 µg per dose, wherein in one embodiment, only one of such doses is administered. In one embodiment, a different RNA as used for the first vaccination is used for the second or further vaccination, e.g., BNT162b2 is used for the first vaccination and BNT162B1 or BNT162b3 is used for the second or further vaccination.

[1045] In one embodiment, the vaccination regimen comprises a first vaccination using at least two doses of the RNA described herein, e.g., two doses of the RNA described herein (wherein the second dose may be administered about 21 days following administration of the first dose), and a second vaccination using a single dose

or multiple doses, e.g., two doses, of the RNA described herein. In various embodiments, the second vaccination is administered 3 to 24 months, 6 to 18 months, 6 to 12 months, or 5 to 7 months after administration of the first vaccination, e.g., after the initial two-dose regimen. The amount of RNA used in each dose of the second vaccination may be equal or different to the amount of RNA used in each dose of the first vaccination. In one embodiment, the amount of RNA used in each dose of the second vaccination is equal to the amount of RNA used in each dose of the first vaccination. In one embodiment, the amount of RNA used in each dose of the second vaccination and the amount of RNA used in each dose of the first vaccination is about 30 µg per dose. In one embodiment, the same RNA as used for the first vaccination is used for the second vaccination.

[1046] In one embodiment, the RNA used for the first vaccination and for the second vaccination is BNT162b2.

[1047] In some embodiments, when the RNA used for the first vaccination and for the second vaccination is BNT162b2, the aim is to induce an immune response that targets SARS-CoV-2 variants including, but not limited to, an Omicron (B.1.1.529) variant. Accordingly, in some embodiments, when the RNA used for the first vaccination and for the second vaccination is BNT162b2, the aim is to protect a subject from infection with SARS-CoV-2 variants including, but not limited to, the Omicron (B.1.1.529) variant.

[1048] In one embodiment, a different RNA as used for the first vaccination is used for the second vaccination. In one embodiment, the RNA used for the first vaccination is BNT162b2 and the RNA used for the second vaccination is RNA encoding a SARS-CoV-2 S protein of a SARS-CoV-2 variant strain, e.g., a strain discussed herein. In one embodiment, the RNA used for the first vaccination is BNT162b2 and the RNA used for the second vaccination is RNA encoding a SARS-CoV-2 S protein of a SARS-CoV-2 variant strain that is prevalent or rapidly spreading at the time of the second vaccination. In one embodiment, the RNA used for the first vaccination is BNT162b2 and the RNA used for the second vaccination is RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprising one or more of the mutations described herein for S protein variants such as SARS-CoV-2 S protein variants, in particular naturally occurring S protein variants. In one embodiment, the RNA used for the first vaccination is BNT162b2 and the RNA used for the second vaccination is RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprising one or more mutations, such as all mutations, of a SARS-CoV-2 S protein of a SARS-CoV-2 variant selected from the group consisting of VOC-202012/01, 501.V2, Cluster 5, B.1.1.248, and Omicron (B.1.1.529).

[1049] In one embodiment, the vaccination regimen comprises a first vaccination using two doses of RNA encoding a polypeptide comprising an amino acid sequence with proline residue substitutions at positions 986 and 987 of SEQ ID NO:1 administered about 21 days apart and a second vaccination using a single dose or multiple doses of RNA encoding a polypeptide comprising an amino acid sequence with proline residue substitutions at positions 986 and 987 of SEQ ID NO:1 administered about 4 to 12 months, 5 to 12 months, or 6 to 12 months after administration of the first vaccination, i.e., after the initial two-dose regimen. In one embodiment, each RNA dose comprises 30 µg RNA. In this embodiment, the aim in one embodiment is to induce an immune response that targets SARS-CoV-2 variants including, but not limited to, an Omicron (B.1.1.529) variant. Accordingly, in this embodiment, the aim in one embodiment is to protect a subject from infection with SARS-CoV-2 variants including, but not limited to, an Omicron (B.1.1.529) variant.

[1050] In one embodiment, the second vaccination results in a boosting of the immune response.

[1051] In one embodiment, RNA described herein is co-administered with other vaccines. In some embodiments, RNA described herein is co-administered with a composition comprising one or more T-cell epitopes of SARS-CoV-2 or RNA encoding the same. In some embodiments, RNA described herein is co-administered one or

more T-cell epitopes, or RNA encoding the same, derived from an M protein, an N protein, and/or an ORF1ab protein of SARS-CoV-2, e.g., a composition disclosed in WO2021188969, the contents of which is incorporated by reference herein in its entirety. In some embodiments, RNA described herein (e.g., RNA encoding a SARS-CoV-2 S protein comprising mutations characteristic of a BA.1, BA.2, or BA.4/5 Omicron variant, optionally administered with RNA encoding a SARS-CoV-2 S protein of a Wuhan variant) is co-administered with a T-string construct described in WO2021188969 (e.g., an RNA encoding SEQ ID NO: RS C7p2full of WO2021/188969). In some embodiments, RNA described herein and a T-string construct described in WO2021188969 are administered in a combination of up to about 100 ug RNA total. In some embodiments, subjects are administered with at least 2 doses of RNA described herein (e.g., in some embodiments at 30 ug each) in combination with a T-string construct (e.g., an RNA encoding SEQ ID NO: RS C7p2full of WO2021/188969), e.g., each dose of a combination of RNA described herein and an RNA encoding SEQ ID NO: RS C7p2full of up to about 100 ug RNA total, wherein the two doses are administered, for example, at least 4 weeks or longer (including, e.g., at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, or at least 12 weeks, or longer) apart from one another. In some embodiments, subjects are administered at least 3 doses of RNA described herein (e.g., in some embodiments at 30 ug each) in combination with a T-string construct (e.g., an RNA encoding SEQ ID NO: RS C7p2full of WO2021/188969), e.g., each dose of a combination of RNA described herein and an RNA encoding SEQ ID NO: RS C7p2full of up to about 100 ug RNA total, wherein the first and the second doses and the second and third doses are each independently administered at least 4 weeks or longer (including, e.g., at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, or at least 12 weeks, or longer) apart from one another. In some embodiments, the RNA described herein and the T-string construct may be co-administered as separate formulations (e.g., formulations administered on the same day to separate injection sites). In some embodiments, the RNA described herein and the T-string construct may be co-administered as a co-formulation (e.g., a formulation comprising RNA described herein and the T-string construct as separate LNP formulations or as LNP formulations comprising both a T-string construct and RNA described herein).

[1052] In some embodiments, an RNA composition described herein is co-administered with one or more vaccines against a non-SARS-CoV-2 disease. In some embodiments, an RNA composition described herein is co-administered with one or more vaccines against a non-SARS-COV-2 viral disease. In some embodiments, an RNA composition described herein is co-administered with one or more vaccines against a non-SARS-CoV-2 respiratory disease. In some embodiments, the non-SARS-CoV-2 respiratory disease is a non-SARS-CoV-2 Coronavirus, an Influenza virus, a Pneumoviridae virus, or a Paramyxoviridae virus. In some embodiments, the Pneumoviridae virus is a Respiratory syncytial virus or a Metapneumovirus. In some embodiments, the Metapneumovirus is a human metapneumovirus (hMPV). In some embodiments, the Paramyxoviridae virus is a Parainfluenza virus or a Henipavirus. In some embodiments the parainfluenzavirus is PIV3. In some embodiments, the non-SARS-CoV-2 coronavirus is a betacoronavirus (e.g., SARS-CoV-1). In come embodiments the non-SARS-CoV-2 coronavirus is a Merbecovirus (e.g., a MERS-CoV virus).

[1053] In some embodiments, an RNA composition described herein is co-administered with an RSV vaccine (e.g., an RSV A or RSV B vaccine). In some embodiments, the RSV vaccine comprises an RSV fusion protein (F), an RSV attachment protein (G), an RSV small hydrophobic protein (SH), an RSV matrix protein (M), an RSV nucleoprotein (N), an RSV M2-1 protein, an RSV Large polymerase (L), and/or an RSV phosphoprotein (P), or an immunogenic fragment of immunogenic variant thereof, or a nucleic acid (e.g., RNA), encoding any one of the same.

[1054] Numerous RSV vaccines are known in the art, any one of which can be co-administered with an RNA composition described herein. See, for example, the list of RSV vaccines provided on the website of PATH, a global

health organization (see https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/), as well as in Mazur, Natalie I., et al, "The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates," The Lancet Infectious Diseases 18.10 (2018): e295-e311, the contents of each of which is incorporated by reference herein. In some embodiments, an RNA composition described herein is co-administered with an RSV vaccine that has been previously published on (e.g., an RSV vaccine described on the PATH website page linked to above, or in Mazur et al.). In some embodiments, an RNA composition described herein is co-administered with a live-attenuated or chimeric vaccine (e.g., rBCG-N-hRSV (developed by Ponteificia Uinersidad Catolica de Chile), RSV D46 cp ΔM202 (developed by Sanofi Pasteur/LID/NIAD/NIH), RSV LID ΔM2-2 1030s (developed by Sanofi Pasteur/LID/NIAD/NIH), RSV ΔNS2 Δ1313/I1314L (developed by Sanofi Pasteur/LID/NIAD/NIH), RSV D46 ΔNS2 N ΔM2-2 HindIII (developed by Sanofi Pasteur/LID/NIAD/NIH) or RSV LID ΔM2-2 1030s (developed by Sanofi Pasteur/LID/NIAD/NIH), MV-012-968 (developed by Meissa Vaccines), SP0125 (developed by Sanofi), blb201 (developed by Blue lake), CodaVax™-RSV (developed by Cadagenix), RSVDeltaG (developed by Intravacc), or SeVRSV (developed by SIHPL and St. Jude hospital), a particle based vaccine (e.g., RSV F nanoparticle (developed by Novavax) or SynGEM (developed by Mucosis), Icosavzx (developed by IVX-121), or V-306 (developed by Virometix)), a subunit vaccine (e.g., GSK RSV F (developed by GSK), Arexvy (developed by GSK), DPX-RSV (developed by Dalousie Univeristy, Immunovaccine, and VIB), RSV F DS-Cav1 (developed by NIH/NIAID/VRC), MEDI-7510 (developed by MedImmune), RSVpreF (developed by Pfizer), ADV110 (developed by Advaccine), VN-0200 (developed by Daiichi Sankyo, Inc.)), a vector vaccine (e.g., MVA-BN RSV (developed by Banarian Nordic), VXA-RSVf oral (developed by Vaxart), Ad26.RSV.pref (developed by Janssen), ChAd155-RSV (developed by GSK) Immunovaccine, DPX-RSV (developed by VIB), or DS-Cav1 (developed by NIH/NIAID/VRC) or a nucleic acid vaccine (e.g., an mRNA vaccine being developed by CureVac (currently unnamed) or mRNA-1345 (developed by Moderna), or SP0274 (developed by Sanofi)).

[1055] In some embodiments, an RNA composition described herein is co-administered with an influenza vaccine. In some embodiments, the influenza vaccine is an alphainfluenza virus, a betainfluenza virus, a gammainfluenza virus or a deltainfluenza virus vaccine. In some embodiments the vaccine is an Influenza A virus, an Influenza B virus, an Influenza C virus, or an Influenza D virus vaccine. In some embodiments, the influenza A virus vaccine comprises a hemagglutinin selected from H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17, and H18, or an immunogenic fragment or variant of the same, or a nucleic acid (e.g., RNA) encoding any one of the same. In some embodiments the influenza A vaccine comprises or encodes a neuraminidase (NA) selected from N1, N2, N3, N4, N5, N6, N7, N8, N9, N10, and N11, or an immunogenic fragment or variant of the same, or a nucleic acid (e.g., RNA) encoding any one of the same. In some embodiments, the influenza vaccine comprises at least one Influenza virus hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), matrix protein 1 (M1), matrix protein 2 (M2), non-structural protein 1 (NS1), non-structural protein 2 (NS2), nuclear export protein (NEP), polymerase acidic protein (PA), polymerase basic protein PB1, PB1-F2, and/or polymerase basic protein 2 (PB2), or an immunogenic fragment or variant thereof, or a nucleic acid (e.g., RNA) encoding any of one of the same.

[1056] In some embodiments, an RNA composition described herein can be co-administered with a commercially approved influenza vaccine. In some embodiments, an RNA composition described herein can be co-administered with an inactivated influenza virus (e.g., Fluzone®, Fluzone high-dose quadrivalent®, Fluzone quadrivalent®, Fluzone intradermal quardivalent®, Fluzone quadrivalent southern hemisphere®, Fluad®, Fluad quadrivalent®, Afluria Quardivalent®, Fluarix Quadrivalent®, FluLaval Quadrivalent®, or Flucelvax Quadrivalent®), a recombinant influenza vaccine (e.g., Flublok quadrivalent®), a live attenuated influenza vaccine (e.g., FluMist Quadrivalent®), a non-adjuvanted influenza vaccine, an adjuvanted influenza vaccine, or a subunit or split vaccine.

[1057] In some embodiments, an RNA composition described herein is co-administered with an influenza vaccine and/or an RSV vaccine.

[1058] In some embodiments, an RNA composition provided herein and other injectable vaccine(s) are administered at different times. In some embodiments, an RNA composition provided herein is administered at the same time as other injectable vaccine(s). In some such embodiments, an RNA composition provided herein and at least one another injectable vaccine(s) are administered at different injection sites. In some embodiments, an RNA composition provided herein is not mixed with any other vaccine in the same syringe. In some embodiments, an RNA composition provided herein is not combined with other coronavirus vaccines as part of vaccination against coronavirus, e.g., SARS-CoV-2.

[1059] The term "disease" refers to an abnormal condition that affects the body of an individual. A disease is often construed as a medical condition associated with specific symptoms and signs. A disease may be caused by factors originally from an external source, such as infectious disease, or it may be caused by internal dysfunctions, such as autoimmune diseases. In humans, "disease" is often used more broadly to refer to any condition that causes pain, dysfunction, distress, social problems, or death to the individual afflicted, or similar problems for those in contact with the individual. In this broader sense, it sometimes includes injuries, disabilities, disorders, syndromes, infections, isolated symptoms, deviant behaviors, and atypical variations of structure and function, while in other contexts and for other purposes these may be considered distinguishable categories. Diseases usually affect individuals not only physically, but also emotionally, as contracting and living with many diseases can alter one's perspective on life, and one's personality.

[1060] In the present context, the term "treatment", "treating" or "therapeutic intervention" relates to the management and care of a subject for the purpose of combating a condition such as a disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the subject is suffering, such as administration of the therapeutically effective compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of an individual for the purpose of combating the disease, condition or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

[1061] The term "therapeutic treatment" relates to any treatment which improves the health status and/or prolongs (increases) the lifespan of an individual. Said treatment may eliminate the disease in an individual, arrest or slow the development of a disease in an individual, inhibit or slow the development of a disease in an individual, decrease the frequency or severity of symptoms in an individual, and/or decrease the recurrence in an individual who currently has or who previously has had a disease.

[1062] The terms "prophylactic treatment" or "preventive treatment" relate to any treatment that is intended to prevent a disease from occurring in an individual. The terms "prophylactic treatment" or "preventive treatment" are used herein interchangeably.

[1063] The terms "individual" and "subject" are used herein interchangeably. They refer to a human or another mammal (e.g. mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate) that can be afflicted with or is susceptible to a disease or disorder but may or may not have the disease or disorder. In many embodiments, the individual is a human being. Unless otherwise stated, the terms "individual" and "subject" do not denote a particular age, and thus encompass adults, elderlies, children, and newborns. In some embodiments, the term "subject" includes humans of age of at least 50, at least 55, at least 60, at least 65, at least 70, or older. In some embodiments, the term "subject" includes humans of age of at least 65, such as 65 to 80, 65 to 75, or 65 to 70. In embodiments of the present disclosure, the "individual" or "subject" is a "patient".

[1064] The term "patient" means an individual or subject for treatment, in particular a diseased individual or subject.

[1065] In one embodiment of the present disclosure, the aim is to provide an immune response against coronavirus, and to prevent or treat coronavirus infection.

[1066] A pharmaceutical composition comprising RNA encoding a peptide or protein comprising an epitope may be administered to a subject to elicit an immune response against an antigen comprising said epitope in the subject which may be therapeutic or partially or fully protective. A person skilled in the art will know that one of the principles of immunotherapy and vaccination is based on the fact that an immunoprotective reaction to a disease is produced by immunizing a subject with an antigen or an epitope, which is immunologically relevant with respect to the disease to be treated. Accordingly, pharmaceutical compositions described herein are applicable for inducing or enhancing an immune response. Pharmaceutical compositions described herein are thus useful in a prophylactic and/or therapeutic treatment of a disease involving an antigen or epitope.

[1067] As used herein, "immune response" refers to an integrated bodily response to an antigen or a cell expressing an antigen and refers to a cellular immune response and/or a humoral immune response. The immune system is divided into a more primitive innate immune system, and acquired or adaptive immune system of vertebrates, each of which contains humoral and cellular components.

[1068] "Cell-mediated immunity", "cellular immunity", "cellular immune response", or similar terms are meant to include a cellular response directed to cells characterized by expression of an antigen, in particular characterized by presentation of an antigen with class I or class II MHC. The cellular response relates to immune effector cells, in particular to cells called T cells or T lymphocytes which act as either "helpers" or "killers". The helper T cells (also termed $CD4^+$ T cells) play a central role by regulating the immune response and the killer cells (also termed cytotoxic T cells, cytolytic T cells, $CD8^+$ T cells or CTLs) kill diseased cells such as virus-infected cells, preventing the production of more diseased cells.

[1069] An immune effector cell includes any cell which is responsive to vaccine antigen. Such responsiveness includes activation, differentiation, proliferation, survival and/or indication of one or more immune effector functions. The cells include, in particular, cells with lytic potential, in particular lymphoid cells, and are preferably T cells, in particular cytotoxic lymphocytes, preferably selected from cytotoxic T cells, natural killer (NK) cells, and lymphokine-activated killer (LAK) cells. Upon activation, each of these cytotoxic lymphocytes triggers the destruction of target cells. For example, cytotoxic T cells trigger the destruction of target cells by either or both of the following means. First, upon activation T cells release cytotoxins such as perforin, granzymes, and granulysin. Perforin and granulysin create pores in the target cell, and granzymes enter the cell and trigger a caspase cascade in the cytoplasm that induces apoptosis (programmed cell death) of the cell. Second, apoptosis can be induced via Fas-Fas ligand interaction between the T cells and target cells.

[1070] The term "effector functions" in the context of the present disclosure includes any functions mediated by components of the immune system that result, for example, in the neutralization of a pathogenic agent such as a virus and/or in the killing of diseased cells such as virus-infected cells. In one embodiment, the effector functions in the context of the present disclosure are T cell mediated effector functions. Such functions comprise in the case of a helper T cell ($CD4^+$ T cell) the release of cytokines and/or the activation of $CD8^+$ lymphocytes (CTLs) and/or B cells, and in the case of CTL the elimination of cells, i.e., cells characterized by expression of an antigen, for example, via apoptosis or perforin-mediated cell lysis, production of cytokines such as IFN-γ and TNF-α, and specific cytolytic killing of antigen expressing target cells.

[1071] The term "immune effector cell" or "immunoreactive cell" in the context of the present disclosure relates to a cell which exerts effector functions during an immune reaction. An "immune effector cell" in one embodiment is capable of binding an antigen such as an antigen presented in the context of MHC on a cell or

expressed on the surface of a cell and mediating an immune response. For example, immune effector cells comprise T cells (cytotoxic T cells, helper T cells, tumor infiltrating T cells), B cells, natural killer cells, neutrophils, macrophages, and dendritic cells. Preferably, in the context of the present disclosure, "immune effector cells" are T cells, preferably $CD4^+$ and/or $CD8^+$ T cells, most preferably $CD8^+$ T cells. According to the present disclosure, the term "immune effector cell" also includes a cell which can mature into an immune cell (such as T cell, in particular T helper cell, or cytolytic T cell) with suitable stimulation. Immune effector cells comprise $CD34^+$ hematopoietic stem cells, immature and mature T cells and immature and mature B cells. The differentiation of T cell precursors into a cytolytic T cell, when exposed to an antigen, is similar to clonal selection of the immune system.

[1072] A "lymphoid cell" is a cell which is capable of producing an immune response such as a cellular immune response, or a precursor cell of such cell, and includes lymphocytes, preferably T lymphocytes, lymphoblasts, and plasma cells. A lymphoid cell may be an immune effector cell as described herein. A preferred lymphoid cell is a T cell.

[1073] The terms "T cell" and "T lymphocyte" are used interchangeably herein and include T helper cells (CD4+ T cells) and cytotoxic T cells (CTLs, CD8+ T cells) which comprise cytolytic T cells. The term "antigen-specific T cell" or similar terms relate to a T cell which recognizes the antigen to which the T cell is targeted and preferably exerts effector functions of T cells.

[1074] T cells belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity. They can be distinguished from other lymphocyte types, such as B cells and natural killer cells by the presence of a special receptor on their cell surface called T cell receptor (TCR). The thymus is the principal organ responsible for the maturation of T cells. Several different subsets of T cells have been discovered, each with a distinct function.

[1075] T helper cells assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and activation of cytotoxic T cells and macrophages, among other functions. These cells are also known as CD4+ T cells because they express the CD4 glycoprotein on their surface. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules that are expressed on the surface of antigen presenting cells (APCs). Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response.

[1076] Cytotoxic T cells destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T cells since they express the CD8 glycoprotein on their surface. These cells recognize their targets by binding to antigen associated with MHC class I, which is present on the surface of nearly every cell of the body.

[1077] A majority of T cells have a T cell receptor (TCR) existing as a complex of several proteins. The TCR of a T cell is able to interact with immunogenic peptides (epitopes) bound to major histocompatibility complex (MHC) molecules and presented on the surface of target cells. Specific binding of the TCR triggers a signal cascade inside the T cell leading to proliferation and differentiation into a maturated effector T cell. The actual T cell receptor is composed of two separate peptide chains, which are produced from the independent T cell receptor alpha and beta (TCRα and TCRβ) genes and are called α- and β-TCR chains. γδ T cells (gamma delta T cells) represent a small subset of T cells that possess a distinct T cell receptor (TCR) on their surface. However, in γδ T cells, the TCR is made up of one γ-chain and one δ-chain. This group of T cells is much less common (2% of total T cells) than the αβ T cells.

[1078] "Humoral immunity" or "humoral immune response" is the aspect of immunity that is mediated by macromolecules found in extracellular fluids such as secreted antibodies, complement proteins, and certain antimicrobial peptides. It contrasts with cell-mediated immunity. Its aspects involving antibodies are often called antibody-mediated immunity.

[1079] Humoral immunity refers to antibody production and the accessory processes that accompany it, including: Th2 activation and cytokine production, germinal center formation and isotype switching, affinity maturation and memory cell generation. It also refers to the effector functions of antibodies, which include pathogen neutralization, classical complement activation, and opsonin promotion of phagocytosis and pathogen elimination.

[1080] In humoral immune response, first the B cells mature in the bone marrow and gain B-cell receptors (BCR's) which are displayed in large number on the cell surface. These membrane-bound protein complexes have antibodies which are specific for antigen detection. Each B cell has a unique antibody that binds with an antigen. The mature B cells migrate from the bone marrow to the lymph nodes or other lymphatic organs, where they begin to encounter pathogens. When a B cell encounters an antigen, the antigen is bound to the receptor and taken inside the B cell by endocytosis. The antigen is processed and presented on the B cell's surface again by MHC-II proteins. The B cell waits for a helper T cell (TH) to bind to the complex. This binding will activate the TH cell, which then releases cytokines that induce B cells to divide rapidly, making thousands of identical clones of the B cell. These daughter cells either become plasma cells or memory cells. The memory B cells remain inactive here; later when these memory B cells encounter the same antigen due to reinfection, they divide and form plasma cells. On the other hand, the plasma cells produce a large number of antibodies which are released free into the circulatory system. These antibodies will encounter antigens and bind with them. This will either interfere with the chemical interaction between host and foreign cells, or they may form bridges between their antigenic sites hindering their proper functioning, or their presence will attract macrophages or killer cells to attack and phagocytose them.

[1081] The term "antibody" includes an immunoglobulin comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system. An antibody binds, preferably specifically binds with an antigen.

[1082] Antibodies expressed by B cells are sometimes referred to as the BCR (B cell receptor) or antigen receptor. The five members included in this class of proteins are IgA, IgG, IgM, IgD, and IgE. IgA is the primary antibody that is present in body secretions, such as saliva, tears, breast milk, gastrointestinal secretions and mucus secretions of the respiratory and genitourinary tracts. IgG is the most common circulating antibody. IgM is the main immunoglobulin produced in the primary immune response in most subjects. It is the most efficient immunoglobulin in agglutination, complement fixation, and other antibody responses, and is important in defense against bacteria and viruses. IgD is the immunoglobulin that has no known antibody function, but may serve as an antigen receptor. IgE is the immunoglobulin that mediates immediate hypersensitivity by causing release of mediators from mast cells and basophils upon exposure to allergen.

[1083] An "antibody heavy chain", as used herein, refers to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations.

[1084] An "antibody light chain", as used herein, refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, κ and λ light chains refer to the two major antibody light chain isotypes.

[1085] The present disclosure contemplates an immune response that may be protective, preventive, prophylactic and/or therapeutic. As used herein, "induces [or inducing] an immune response" may indicate that no immune response against a particular antigen was present before induction or it may indicate that there was a basal level of immune response against a particular antigen before induction, which was enhanced after induction. Therefore, "induces [or inducing] an immune response" includes "enhances [or enhancing] an immune response".

[1086] The term "immunotherapy" relates to the treatment of a disease or condition by inducing, or enhancing an immune response. The term "immunotherapy" includes antigen immunization or antigen vaccination.

[1087] The terms "immunization" or "vaccination" describe the process of administering an antigen to an individual with the purpose of inducing an immune response, for example, for therapeutic or prophylactic reasons.

[1088] The term "macrophage" refers to a subgroup of phagocytic cells produced by the differentiation of monocytes. Macrophages which are activated by inflammation, immune cytokines or microbial products nonspecifically engulf and kill foreign pathogens within the macrophage by hydrolytic and oxidative attack resulting in degradation of the pathogen. Peptides from degraded proteins are displayed on the macrophage cell surface where they can be recognized by T cells, and they can directly interact with antibodies on the B cell surface, resulting in T and B cell activation and further stimulation of the immune response. Macrophages belong to the class of antigen presenting cells. In one embodiment, the macrophages are splenic macrophages.

[1089] The term "dendritic cell" (DC) refers to another subtype of phagocytic cells belonging to the class of antigen presenting cells. In one embodiment, dendritic cells are derived from hematopoietic bone marrow progenitor cells. These progenitor cells initially transform into immature dendritic cells. These immature cells are characterized by high phagocytic activity and low T cell activation potential. Immature dendritic cells constantly sample the surrounding environment for pathogens such as viruses and bacteria. Once they have come into contact with a presentable antigen, they become activated into mature dendritic cells and begin to migrate to the spleen or to the lymph node. Immature dendritic cells phagocytose pathogens and degrade their proteins into small pieces and upon maturation present those fragments at their cell surface using MHC molecules. Simultaneously, they upregulate cell-surface receptors that act as co-receptors in T cell activation such as CD80, CD86, and CD40 greatly enhancing their ability to activate T cells. They also upregulate CCR7, a chemotactic receptor that induces the dendritic cell to travel through the blood stream to the spleen or through the lymphatic system to a lymph node. Here they act as antigen-presenting cells and activate helper T cells and killer T cells as well as B cells by presenting them antigens, alongside non-antigen specific co-stimulatory signals. Thus, dendritic cells can actively induce a T cell- or B cell-related immune response. In one embodiment, the dendritic cells are splenic dendritic cells.

[1090] The term "antigen presenting cell" (APC) is a cell of a variety of cells capable of displaying, acquiring, and/or presenting at least one antigen or antigenic fragment on (or at) its cell surface. Antigen-presenting cells can be distinguished in professional antigen presenting cells and non-professional antigen presenting cells.

[1091] The term "professional antigen presenting cells" relates to antigen presenting cells which constitutively express the Major Histocompatibility Complex class II (MHC class II) molecules required for interaction with naive T cells. If a T cell interacts with the MHC class II molecule complex on the membrane of the antigen presenting cell, the antigen presenting cell produces a co-stimulatory molecule inducing activation of the T cell. Professional antigen presenting cells comprise dendritic cells and macrophages.

[1092] The term "non-professional antigen presenting cells" relates to antigen presenting cells which do not constitutively express MHC class II molecules, but upon stimulation by certain cytokines such as interferon-gamma. Exemplary, non-professional antigen presenting cells include fibroblasts, thymic epithelial cells, thyroid epithelial cells, glial cells, pancreatic beta cells or vascular endothelial cells.

[1093] "Antigen processing" refers to the degradation of an antigen into procession products, which are fragments of said antigen (e.g., the degradation of a protein into peptides) and the association of one or more of

these fragments (e.g., via binding) with MHC molecules for presentation by cells, such as antigen presenting cells to specific T cells.

[1094] The term "disease involving an antigen" refers to any disease which implicates an antigen, e.g. a disease which is characterized by the presence of an antigen. The disease involving an antigen can be an infectious disease. As mentioned above, the antigen may be a disease-associated antigen, such as a viral antigen. In one embodiment, a disease involving an antigen is a disease involving cells expressing an antigen, preferably on the cell surface.

[1095] The term "infectious disease" refers to any disease which can be transmitted from individual to individual or from organism to organism, and is caused by a microbial agent (e.g. common cold). Infectious diseases are known in the art and include, for example, a viral disease, a bacterial disease, or a parasitic disease, which diseases are caused by a virus, a bacterium, and a parasite, respectively. In this regard, the infectious disease can be, for example, hepatitis, sexually transmitted diseases (e.g. chlamydia or gonorrhea), tuberculosis, HIV/acquired immune deficiency syndrome (AIDS), diphtheria, hepatitis B, hepatitis C, cholera, severe acute respiratory syndrome (SARS), the bird flu, and influenza.

Exemplary Dosing Regimens

[1096] In some embodiments, compositions and methods disclosed herein can be used in accordance with an exemplary vaccination regimen as illustrated in Figure 6.

Primary Dosing Regimens

[1097] In some embodiments, subjects are administered a primary dosing regimen. A primary dosing regimen can comprise one or more doses. For example, in some embodiments, a primary dosing regimen comprises a single dose (PD_1). In some embodiments a primary dosing regimen comprises a first dose (PD_1) and a second dose (PD_2). In some embodiments, a primary dosing regimen comprises a first dose, a second dose, and a third dose (PD_3). In some embodiments, a primary dosing regimen comprises a first dose, a second dose, a third dose, and one or more additional doses (PD_n) of any one of the pharmaceutical compositions described herein.

[1098] In some embodiments, PD_1 comprises administering 1 to 100 ug of RNA. In some embodiments, PD_1 comprises administering 1 to 60 ug of RNA. In some embodiments, PD_1 comprises administering 1 to 50 ug of RNA. In some embodiments, PD_1 comprises administering 1 to 30 ug of RNA. In some embodiments, PD_1 comprises administering about 3 ug of RNA. In some embodiments, PD_1 comprises administering about 5 ug of RNA. In some embodiments, PD_1 comprises administering about 10 ug of RNA. In some embodiments, PD_1 comprises administering about 15 ug of RNA. In some embodiments, PD_1 comprises administering about 20 ug of RNA. In some embodiments, PD_1 comprises administering about 30 ug of RNA. In some embodiments, PD_1 comprises administering about 50 ug of RNA. In some embodiments, PD_1 comprises administering about 60 ug of RNA.

[1099] In some embodiments, PD_2 comprises administering 1 to 100 ug of RNA. In some embodiments, PD_2 comprises administering 1 to 60 ug of RNA. In some embodiments, PD_2 comprises administering 1 to 50 ug of RNA. In some embodiments, PD_2 comprises administering 1 to 30 ug of RNA. In some embodiments, PD_2 comprises administering about 3 ug. In some embodiments, PD_2 comprises administering about 5 ug of RNA. In some embodiments, PD_2 comprises administering about 10 ug of RNA. In some embodiments, PD_2 comprises administering about 15 ug of RNA. In some embodiments, PD_2 comprises administering about 20 ug RNA. In some embodiments, PD_2 comprises administering about 30 ug of RNA. In some embodiments, PD_2 comprises administering about 50 ug of RNA. In some embodiments, PD_2 comprises administering about 60 ug of RNA.

[1100] In some embodiments, PD_3 comprises administering 1 to 100 ug of RNA. In some embodiments, PD_3 comprises administering 1 to 60 ug of RNA. In some embodiments, PD_3 comprises administering 1 to 50 ug of RNA. In some embodiments, PD_3 comprises administering 1 to 30 ug of RNA. In some embodiments, PD_3 comprises administering about 3 ug of RNA. In some embodiments, PD_3 comprises administering about 5 ug of RNA. In some

embodiments, PD_3 comprises administering about 10 ug of RNA. In some embodiments, PD_3 comprises administering about 15 ug of RNA. In some embodiments, PD_3 comprises administering about 20 ug of RNA. In some embodiments, PD_3 comprises administering about 30 ug of RNA. In some embodiments, PD_3 comprises administering about 50 ug of RNA. In some embodiments, PD_3 comprises administering about 60 ug of RNA.

[1101] In some embodiments, PD_n comprises administering 1 to 100 ug of RNA. In some embodiments, PD_n comprises administering 1 to 60 ug of RNA. In some embodiments, PD_n comprises administering 1 to 50 ug of RNA. In some embodiments, PD_n comprises administering 1 to 30 ug of RNA. In some embodiments, PD_n comprises administering about 3 ug of RNA. In some embodiments, PD_n comprises administering about 5 ug of RNA. In some embodiments, PD_n comprises administering about 10 ug of RNA. In some embodiments, PD_n comprises administering about 15 ug of RNA. In some embodiments, PD_n comprises administering about 20 ug of RNA. In some embodiments, PD_n comprises administering about 30 ug of RNA. In some embodiments, PD_n comprises administering about 50 ug of RNA. In some embodiments, PD_n comprises administering about 60 ug of RNA.

[1102] In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, PD_1 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more additional RNAs encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1103] In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, PD_2 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_2 comprises an RNA encoding a

SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more additional RNAs encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1104] In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, PD_3 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more additional RNAs encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, or XBB.2.3.2, or BQ.1 Omicron variant).

[1105] In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, PD_n comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more additional RNAs encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, PD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1106] In some embodiments, PD_1, PD_2, PD_3, and PD_n can each independently comprise a plurality of (e.g., at least two) mRNA compositions described herein. In some embodiments PD_1, PD_2, PD_3, and PD_n can each independently comprise a first and a second mRNA composition. In some embodiments, at least one of a plurality of mRNA compositions comprises BNT162b2 (e.g., as described herein). In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a different SARS-CoV-2 variant. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a Wuhan strain of SARS-CoV-2. In some embodiments, at least one of a plurarity of mRNA compositions comprises an RNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1107] In some embodiments, a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can each independently comprise at least two different mRNA constructs (e.g., differing in at protein-encoding sequences).

For example, in some embodiments a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a Wuhan strain of SARS-CoV-2 and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof derived from a Wuhan strain of SARS-CoV-2 and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some such embodiments, a variant can be an alpha variant. In some such embodiments, a variant can be a delta variant. In some such embodiments a variant can be an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1108] In some embodiments, each of a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can independently comprise at least two mRNAs, each encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a distinct variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, each of a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from an alpha variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, each of a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from an alpha variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments, each of a plurality of mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a delta variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1109] In some embodiments, PD_1, PD_2, PD_3, and/or PD_n each comprise a plurality of mRNA compositions, wherein each mRNA composition is separately administered to a subject. For example, in some embodiments each mRNA composition is administered via intramuscular injection at different injection sites. For example, in some embodiments, a first and second mRNA composition given in PD_1, PD_2, PD_3, and/or PD_n are separately administered to different arms of a subject via intramuscular injection.

[1110] In some embodiments, PD_1, PD_2, PD_3, and/or PD_n comprise administering a plurality of RNA molecules, wherein each RNA molecule encodes a Spike protein comprising mutations from a different SARS-CoV-2 variant, and wherein the plurality of RNA molecules are administered to the subject in a single formulation. In some embodiments, the single formulation comprises an RNA encoding a Spike protein or an immunogenic variant thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, the single formulation comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, the single formulation comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, the single formulation comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic

fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1111] In some embodiments, the length of time between PD_1 and PD_2 (PI_1) is at least about 1 week, at least about 2 weeks, at least about 3 weeks, or at least about 4 weeks. In some embodiments, PI_1 is about 1 week to about 12 weeks. In some embodiments, PI_1 is about 1 week to about 10 weeks. In some embodiments, PI_1 is about 2 weeks to about 10 weeks. In some embodiments, PI_1 is about 2 weeks to about 8 weeks. In some embodiments, PI_1 is about 3 weeks to about 8 weeks. In some embodiments, PI_1 is about 4 weeks to about 8 weeks. In some embodiments, PI_1 is about 6 weeks to about 8 weeks. In some embodiments PI_1 is about 3 to about 4 weeks. In some embodiments, PI_1 is about 1 week. In some embodiments, PI_1 is about 2 weeks. In some embodiments, PI_1 is about 3 weeks. In some embodiments, PI_1 is about 4 weeks. In some embodiments, PI_1 is about 5 weeks. In some embodiments, PI_1 is about 6 weeks. In some embodiments, PI_1 is about 7 weeks. In some embodiments, PI_1 is about 8 weeks. In some embodiments, PI_1 is about 9 weeks. In some embodiments, PI_1 is about 10 weeks. In some embodiments, PI_1 is about 11 weeks. In some embodiments, PI_1 is about 12 weeks.

[1112] In some embodiments, the length of time between PD_2 and PD_3 (PI_2) is at least about 1 week, at least about 2 weeks, or at least about 3 weeks. In some embodiments, PI_2 is about 1 week to about 12 weeks. In some embodiments, PI_2 is about 1 week to about 10 weeks. In some embodiments, PI_2 is about 2 weeks to about 10 weeks. In some embodiments, PI_2 is about 2 weeks to about 8 weeks. In some embodiments, PI_2 is about 3 weeks to about 8 weeks. In some embodiments, PI_2 is about 4 weeks to about 8 weeks. In some embodiments, PI_2 is about 6 weeks to about 8 weeks. In some embodiments PI_2 is about 3 to about 4 weeks. In some embodiments, PI_2 is about 1 week. In some embodiments, PI_2 is about 2 weeks. In some embodiments, PI_2 is about 3 weeks. In some embodiments, PI_2 is about 4 weeks. In some embodiments, PI_2 is about 5 weeks. In some embodiments, PI_2 is about 6 weeks. In some embodiments, PI_2 is about 7 weeks. In some embodiments, PI_2 is about 8 weeks. In some embodiments, PI_2 is about 9 weeks. In some embodiments, PI_2 is about 10 weeks. In some embodiments, PI_2 is about 11 weeks. In some embodiments, PI_2 is about 12 weeks.

[1113] In some embodiments, the length of time between PD_3 and a subsequent dose that is part of the Primary Dosing Regimen, or between doses for any dose beyond PD_3 (PI_n) is each separately and independently selected from: about 1 week or more, about 2 weeks or more, or about 3 weeks or more. In some embodiments, PI_n is about 1 week to about 12 weeks. In some embodiments, PI_n is about 1 week to about 10 weeks. In some embodiments, PI_n is about 2 weeks to about 10 weeks. In some embodiments, PI_n is about 2 weeks to about 8 weeks. In some embodiments, PI_n is about 3 weeks to about 8 weeks. In some embodiments, PI_n is about 4 weeks to about 8 weeks. In some embodiments, PI_n is about 6 weeks to about 8 weeks. In some embodiments PI_n is about 3 to about 4 weeks. In some embodiments, PI_2 is about 1 week. In some embodiments, PI_n is about 2 weeks. In some embodiments, PI_n is about 3 weeks. In some embodiments, PI_n is about 4 weeks. In some embodiments, PI_n is about 5 weeks. In some embodiments, $PI_n$is about 6 weeks. In some embodiments, PI_n is about 7 weeks. In some embodiments, $PI_n$is about 8 weeks. In some embodiments, PI_n is about 9 weeks. In some embodiments, PI_n is about 10 weeks. In some embodiments, PI_n is about 11 weeks. In some embodiments, PI_n is about 12 weeks.

[1114] In some embodiments, one or more compositions administered in PD_1 are formulated in a Tris buffer. In some embodiments, one or more compositions administered in PD_2 are formulated in a Tris buffer. In some embodiments, one or more compositions administering in PD_3 are formulated in a Tris buffer. In some embodiments, one or more compositions adminsitered in PD_n are formulated in a Tris buffer.

[1115] In some embodiments, the primary dosing regimen comprises administering two or more mRNA compositions described herein, and at least two of the mRNA compositions have different formulations. In some embodiments, the primary dosing regimen comprises PD_1 and PD_2, where PD_1 comprises administering an mRNA formulated in a Tris buffer and PD_2 comprises administering an mRNA formulated in a PBS buffer. In some

embodiments, the primary dosing regimen comprises PD_1 and PD_2, where PD_1 comprises administering an mRNA formulated in a PBS buffer and PD_2 comprises administering an mRNA formulated in a Tris buffer.

[1116] In some embodiments, one or more mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n can be administered in combination with another vaccine. In some embodiments, another vaccine is for a disease that is not COVID-19. In some embodiments, the disease is one that increases deleterious effects of SARS-CoV-2 when a subject is coinfected with the disease and SARS-CoV-2. In some embodiments, the disease is one that increases the transmission rate of SARS-CoV-2 when a subject is coinfected with the disease and SARS-CoV-2. In some embodiments, another vaccine is a different commercially available vaccine. In some embodiments, the different commercially available vaccine is an RNA vaccine. In some embodiments, the different commercially available vaccine is a polypeptide-based vaccine. In some embodiments, another vaccine (e.g., as described herein) and one or more mRNA compositions given in PD_1, PD_2, PD_3, and/or PD_n are separately administered, for example, in some embodiments via intramuscular injection, at different injection sites. For example, in some embodiments, an influenza vaccine and one or more SARS-CoV-2 mRNA compositions described herein given in PD_1, PD_2, PD_3, and/or PD_n are separately administered to different arms of a subject via intramuscular injection.

Booster Dosing Regimens

[1117] In some embodiments, methods of vaccination disclosed herein comprise one or more Booster Dosing Regimens. The Booster Dosing Regimens disclosed herein comprise one or more doses. In some embodiments, a Booster Dosing Regimen is administered to patients who have been administered a Primary Dosing Regimen (e.g., as described herein). In some embodiments a Booster Dosing Regimen is administered to patients who have not received a pharmaceutical composition disclosed herein. In some embodiments a Booster Dosing Regimen is administered to patients who have been previously vaccinated with a COVID-19 vaccine that is different from the vaccine administered in a Primary Dosing Regimen.

[1118] In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months or longer. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is about 1 month. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least about 2 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least about 3 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least about 4 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least about 5 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is at least about 6 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 1 month to about 48 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 1 month to about 36 months. In some embodiments, the length of time between the primary dosing regimen and the Booster Dosing Regimen is from about 1 month to about 24 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 2 months to about 24 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 3 months to about 24 months. In some embodiments, the length of time between the primary dosing regimen and the Booster Dosing Regimen is from about 3 months to about 18 months. In some embodiments, the length of time between the primary dosing regimen and the Booster Dosing Regimen is from

about 3 months to about 12 months. In some embodiments, the length of time between the primary dosing regimen and the Booster Dosing Regimen is from about 6 months to about 12 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 3 months to about 9 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is from about 5 months to about 7 months. In some embodiments, the length of time between the Primary Dosing Regimen and the Booster Dosing Regimen is about 6 months.

[1119] In some embodiments, subjects are administered a Booster Dosing Regimen. A Booster dosing regimen can comprise one or more doses. For example, in some embodiments, a Booster Dosing Regimen comprises a single dose (BD_1). In some embodiments a Booster Dosing Regimen comprises a first dose (BD_1) and a second dose (BD_2). In some embodiments, a Booster Dosing Regimen comprises a first dose, a second dose, and a third dose (BD_3). In some embodiments, a Booster Dosing Regimen comprises a first dose, a second dose, a third dose, and one or more additional doses (BD_n) of any one of the pharmaceutical compositions described herein.

[1120] In some embodiments, BD_1 comprises administering 1 to 100 ug of RNA. In some embodiments, BD_1 comprises administering 1 to 60 ug of RNA. In some embodiments, BD_1 comprises administering 1 to 50 ug of RNA. In some embodiments, BD_1 comprises administering 1 to 30 ug of RNA. In some embodiments, BD_1 comprises administering about 3 ug of RNA. In some embodiments, BD_1 comprises administering about 5 ug of RNA. In some embodiments, BD_1 comprises administering about 10 ug of RNA. In some embodiments, BD_1 comprises administering about 15 ug of RNA. In some embodiments, BD_1 comprises administering about 20 ug of RNA. In some embodiments, BD_1 comprises administering about 30 ug of RNA. In some embodiments, BD_1 comprises administering about 50 ug of RNA. In some embodiments, BD_1 comprises administering about 60 ug of RNA.

[1121] In some embodiments, BD_2 comprises administering 1 to 100 ug of RNA. In some embodiments, BD_2 comprises administering 1 to 60 ug of RNA. In some embodiments, BD_2 comprises administering 1 to 50 ug of RNA. In some embodiments, BD_2 comprises administering 1 to 30 ug of RNA. In some embodiments, BD_2 comprises administering about 3 ug. In some embodiments, BD_2 comprises administering about 5 ug of RNA. In some embodiments, BD_2 comprises administering about 10 ug of RNA. In some embodiments, BD_2 comprises administering about 15 ug of RNA. In some embodiments, BD_2 comprises administering about 20 ug RNA. In some embodiments, BD_2 comprises administering about 30 ug of RNA. In some embodiments, BD_2 comprises administering about 50 ug of RNA. In some embodiments, BD_2 comprises administering about 60 ug of RNA.

[1122] In some embodiments, BD_3 comprises administering 1 to 100 ug of RNA. In some embodiments, BD_3 comprises administering 1 to 60 ug of RNA. In some embodiments, BD_3 comprises administering 1 to 50 ug of RNA. In some embodiments, BD_3 comprises administering 1 to 30 ug of RNA. In some embodiments, BD_3 comprises administering about 3 ug of RNA. In some embodiments, BD_3 comprises administering about 5 ug of RNA. In some embodiments, BD_3 comprises administering about 10 ug of RNA. In some embodiments, BD_3 comprises administering about 15 ug of RNA. In some embodiments, BD_3 comprises administering about 20 ug of RNA. In some embodiments, BD_3 comprises administering about 30 ug of RNA. In some embodiments, BD_3 comprises administering about 50 ug of RNA. In some embodiments, BD_3 comprises administering about 60 ug of RNA.

[1123] In some embodiments, BD_n comprises administering 1 to 100 ug of RNA. In some embodiments, BD_n comprises administering 1 to 60 ug of RNA. In some embodiments, BD_n comprises administering 1 to 50 ug of RNA. In some embodiments, BD_n comprises administering 1 to 30 ug of RNA. In some embodiments, BD_n comprises administering about 3 ug of RNA. In some embodiments, BD_n comprises administering about 5 ug of RNA. In some embodiments, BD_n comprises administering about 10 ug of RNA. In some embodiments, BD_n comprises administering about 15 ug of RNA. In some embodiments, BD_n comprises administering about 20 ug of RNA. In some embodiments, BD_n comprises administering about 30 ug of RNA. In some embodiments, BD_n comprises administering about 60 ug of RNA. In some embodiments, BD_n comprises administering about 50 ug of RNA.

[1124] In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, BD_1 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, or BQ.1 Omicron variant).

[1125] In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_1 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, or BQ.1 Omicron variant).

[1126] In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, BD_2 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, or BQ.1 Omicron variant). In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike

protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_2 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1127] In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, BD_3 comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1128] In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_3 comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1129] In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain. In some embodiments, BD_n comprises an RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant(e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1130] In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and one or more RNA encoding a Spike protein or an immunogenic fragment thereof from a SARS-CoV-2 strain that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from a beta variant. In some embodiments, BD_n comprises an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof from the Wuhan strain and an RNA encoding a SARS-CoV-2 Spike protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1131] In some embodiments, BD_1, BD_2, BD_3, and BD_n can each independently comprise a plurality of (e.g., at least two) mRNA compositions described herein. In some embodiments BD_1, BD_2, BD_3, and BD_n can each independently comprise a first and a second mRNA composition. In some embodiments, BD_1, BD_2, BD_3, and BD_n can each independently comprise a plurality of (e.g., at least two) mRNA compositions, wherein , at least one of the plurality of mRNA compositions comprises BNT162b2 (e.g., as described herein). In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a different SARS-CoV-2 variant (e.g., a variant that is prevalent or rapidly spreading in a relevant jurisdiction, e.g., a variant disclosed herein). In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a Wuhan strain of SARS-CoV-2. In some embodiments, at least one of a plurality of mRNA compositions comprises an RNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an alpha variant. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments, at least one of a plurality of mRNA compositions comprises an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1132] In some embodiments, a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise at least two different mRNA constructs (e.g., mRNA constructs having differing protein-encoding sequences). For example, in some embodiments a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a Wuhan strain of SARS-CoV-2 and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof derived from a Wuhan strain of SARS-CoV-2 and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a variant that is prevalent and/or

spreading rapidly in a relevant jurisdiction. In some such embodiments, a variant can be an alpha variant. In some such embodiments, a variant can be a delta variant. In some such embodiments a variant can be an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1133] In some embodiments, a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise at least two mRNAs each encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a distinct variant that is prevalent and/or spreading rapidly in a relevant jurisdiction. In some embodiments a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from an alpha variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from a delta variant. In some embodiments a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from an alpha variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant). In some embodiments a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can each independently comprise an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof from a delta variant and an mRNA encoding a SARS-CoV-2 S protein or an immunogenic fragment thereof comprising one or more mutations from an Omicron variant (e.g., a BA.4/5, BA.1, BA.2, XBB, XBB.1, XBB.1.5, XBB.1.16, XBB.2.3, XBB.2.3.2, or BQ.1 Omicron variant).

[1134] In some embodiments, a plurality of mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n are separately administered to a subject, for example, in some embodiments via intramuscular injection, at different injection sites. For example, in some embodiments, a first and second mRNA composition given in BD_1, BD_2, BD_3, and/or BD_n are separately administered to different arms of a subject via intramuscular injection.

[1135] In some embodiments, the length of time between BD_1 and BD_2 (BI_1) is at least about 1 week, at least about 2 weeks, at least about 3 weeks, or at least about 4 weeks. In some embodiments, BI_1 is about 1 week to about 12 weeks. In some embodiments, BI_1 is about 1 week to about 10 weeks. In some embodiments, BI_1 is about 2 weeks to about 10 weeks. In some embodiments, BI_1 is about 2 weeks to about 8 weeks. In some embodiments, BI_1 is about 3 weeks to about 8 weeks. In some embodiments, BI_1 is about 4 weeks to about 8 weeks. In some embodiments, BI_1 is about 6 weeks to about 8 weeks. In some embodiments BI_1 is about 3 to about 4 weeks. In some embodiments, BI_1 is about 1 week. In some embodiments, BI_1 is about 2 weeks. In some embodiments, BI_1 is about 3 weeks. In some embodiments, BI_1 is about 4 weeks. In some embodiments, BI_1 is about 5 weeks. In some embodiments, BI_1 is about 6 weeks. In some embodiments, BI_1 is about 7 weeks. In some embodiments, BI_1 is about 8 weeks. In some embodiments, BI_1 is about 9 weeks. In some embodiments, BI_1 is about 10 weeks.

[1136] In some embodiments, the length of time between BD_2 and BD_3 (BI_2) is at least about 1 week, at least about 2 weeks, or at least about 3 weeks. In some embodiments, BI_2 is about 1 week to about 12 weeks. In some embodiments, BI_2 is about 1 week to about 10 weeks. In some embodiments, BI_2 is about 2 weeks to about 10 weeks. In some embodiments, BI_2 is about 2 weeks to about 8 weeks. In some embodiments, BI_2 is about 3 weeks to about 8 weeks. In some embodiments, BI_2 is about 4 weeks to about 8 weeks. In some embodiments, BI_2 is about 6 weeks to about 8 weeks. In some embodiments BI_2 is about 3 to about 4 weeks. In some embodiments, BI_2 is about 1 week. In some embodiments, BI_2 is about 2 weeks. In some embodiments, BI_2 is about 3 weeks. In some embodiments, BI_2 is about 4 weeks. In some embodiments, BI_2 is about 5 weeks. In some embodiments, BI_2 is about 6 weeks. In some embodiments, BI_2 is about 7 weeks. In some embodiments, BI_2 is about 8 weeks. In some embodiments, BI_2 is about 9 weeks. In some embodiments, BI_2 is about 10 weeks.

[1137] In some embodiments, the length of time between BD_3 and a subsequent dose that is part of the Booster Dosing Regimen, or between doses for any dose beyond BD_3 (BI_n) is each separately and independently selected from: about 1 week or more, about 2 weeks or more, or about 3 weeks or more. In some embodiments, BI_n is about 1 week to about 12 weeks. In some embodiments, BI_n is about 1 week to about 10 weeks. In some embodiments, BI_n is about 2 weeks to about 10 weeks. In some embodiments, BI_n is about 2 weeks to about 8 weeks. In some embodiments, BI_n is about 3 weeks to about 8 weeks. In some embodiments, BI_n is about 4 weeks to about 8 weeks. In some embodiments, BI_n is about 6 weeks to about 8 weeks. In some embodiments BI_n is about 3 to about 4 weeks. In some embodiments, BI_n is about 1 week. In some embodiments, BI_n is about 2 weeks. In some embodiments, BI_n is about 3 weeks. In some embodiments, BI_n is about 4 weeks. In some embodiments, BI_n is about 5 weeks. In some embodiments, BI_n is about 6 weeks. In some embodiments, BI_n is about 7 weeks. In some embodiments, BI_n is about 8 weeks. In some embodiments, BI_n is about 9 weeks. In some embodiments, BI_n is about 10 weeks.

[1138] In some embodiments, one or more compositions adminstered in BD_1 are formulated in a Tris buffer. In some embodiments, one or more compositions administered in BD_2 are formulated in a Tris buffer. In some embodiments, one or more compositions administering in BD_3 are formulated in a Tris buffer. In some embodiments, one or more compositions adminsitered in BD_3 are formulated in a Tris buffer.

[1139] In some embodiments, the Booster dosing regimen comprises administering two or more mRNA compositions described herein, and at least two of the mRNA compositions have different formulations. In some embodiments, the Booster dosing regimen comprises BD_1 and BD_2, where BD_1 comprises administering an mRNA formulated in a Tris buffer and BD_2 comprises administering an mRNA formulated in a PBS buffer. In some embodiments, the Booster dosing regimen comprises BD_1 and BD_2, where BD_1 comprises administering an mRNA formulated in a PBS buffer and BD_2 comprises administering an mRNA formulated in a Tris buffer.

[1140] In some embodiments, one or more mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n can be administered in combination with another vaccine. In some embodiments, another vaccine is for a disease that is not COVID-19. In some embodiments, the disease is one that increases deleterious effects of SARS-CoV-2 when a subject is coinfected with the disease and SARS-CoV-2. In some embodiments, the disease is one that increases the transmission rate of SARS-CoV-2 when a subject is coinfected with the disease and SARS-CoV-2. In some embodiments, another vaccine is a different commercially available vaccine. In some embodiments, the different commercially available vaccine is an RNA vaccine. In some embodiments, the different commercially available vaccine is a polypeptide-based vaccine. In some embodiments, another vaccine (e.g., as described herein) and one or more mRNA compositions given in BD_1, BD_2, BD_3, and/or BD_n are separately administered, for example, in some embodiments via intramuscular injection, at different injection sites. For example, in some embodiments, an influenza vaccine and one or more SARS-CoV-2 mRNA compositions described herein given in BD_1, BD_2, BD_3, and/or BD_n are separately administered to different arms of a subject via intramuscular injection.

Additional Booster Regimens

[1141] In some embodiments, methods of vaccination disclosed herein comprise administering more than one Booster Dosing Regimen. In some embodiments, more than one Booster Dosing Regimen may need to be administered to increase neutralizing antibody response. In some embodiments, more than one booster dosing regimen may be needed to counteract a SARS-CoV-2 strain that has been shown to have a high likelihood of evading immune response elicited by vaccines that a patient has previously received. In some embodiments, an additional Booster Dosing Regimen is administered to a patient who has been determined to produce low concentrations of neutralizing antibodies. In some embodiments, an additional booster dosing regimen is administered to a patient who has been determined to have a high likelihood of being susceptible to SARS-CoV-2 infection, despite previous vaccination (e.g., an immunocompromised patient, a cancer patient, and/or an organ transplant patient).

[1142] The description provided above for the first Booster Dosing Regimen also describes the one or more additional Booster Dosing Regimens. The interval of time between the first Booster Dosing Regimen and a second Booster Dosing Regimen, or between subsequent Booster Dosing Regimens can be any of the acceptable intervals of time described above between the Primary Dosing Regimen and the First Booster Dosing Regimen.

[1143] In some embodiments, a dosing regimen comprises a primary regimen and a booster regimen, wherein at least one dose given in the primary regimen and/or the booster regimen comprises a composition comprising an RNA that encodes a S protein or immunogenic fragment thereof from a variant that is prevalent or is spreading rapidly in a relevant jurisdiction (e.g., Omicron variant as described herein). For example, in some embodiments, a primary regimen comprises at least 2 doses of BNT162b2 (e.g., encoding a Wuhan strain), for example, given at least 3 weeks apart, and a booster regimen comprises at least 1 dose of a composition comprising RNA that encodes a S protein or immunogenic fragment thereof from a variant that is prevalent or is spreading rapidly in a relevant jurisdiction (e.g., Omicron variant as described herein). In some such embodiments, such a dose of a booster regimen may further comprise an RNA that encodes a S protein or immunogenic fragment thereof from a Wuhan strain, which can be administered with an RNA that encodes a S protein or immunogenic fragment thereof from a variant that is prevalent or is spreading rapidly in a relevant jurisdiction (e.g., Omicron variant as described herein), as a single mixture, or as two separate compositions, for example, in 1:1 weight ratio. In some embodiments, a booster regimen can also comprise at least 1 dose of BNT162b2, which can be administered as a first booster dose or a subsequent booster dose.

[1144] In some embodiments, an RNA composition described herein is given as a booster at a dose that is higher than the doses given during a primary regimen (primary doses) and/or the dose given for a first booster, if any. For example, in some embodiments, such a dose may be 60 ug; or in some embodiments such a dose may be higher than 30 ug and lower than 60 ug (e.g., 55 ug, 50 ug, or lower). In some embodiments, an RNA composition described herein is given as a booster at least 3-12 months or 4-12 months, or 5-12 months, or 6-12 months after the last dose (e.g., the last dose of a primary regimen or a first dose of a booster regimen). In some embodiments, the primary doses and/or the first booster dose (if any) may comprise BNT162b2, for example at 30 ug per dose.

[1145] In some embodiments, an RNA composition described herein comprises an RNA encoding a polypeptide as set forth in SEQ ID NO: 158 or an immunogenic fragment thereof, or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 158). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 159 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 159). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 161 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 161).

[1146] In some embodiments, an RNA composition comprises an RNA comprising (a) a nucleotide sequence of SEQ ID NO: 161 or a sequence that is at least 70% identical to SEQ ID NO: 161 (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher, identity to SEQ ID NO: 108), and/or (b) a nucleotide sequence that encodes a SARS-CoV-2 S protein having an amino acid sequence of SEQ ID NO: 158, or an amino acid sequence that is at least 70% identical to SEQ ID NO: 158 (e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or higher, identity to SEQ ID NO: 158), and (c) wherein the SARS-CoV-2 S protein optionally comprises one or more mutations that stabilize a prefusion confirmation (e.g., proline mutations at positions 982 and 983 of SEQ ID NO: 158). In some embodiments, such a composition comprises one or more additional RNAs, each encoding an S protein of a non-

XBB.1.5 SARS-CoV strain or variant (e.g., a Wuhan strain, an Omicron BA.4/5 variant, and/or an Omicron BA.2.75.2 variant (e.g., such RNAs described herein)).

[1147] In some embodiments, an RNA composition described herein (e.g., a monovalent, bivalent, trivalent, or quadrivalent composition) comprises an RNA encoding a polypeptide as set forth in SEQ ID NO: 163 or an immunogenic fragment thereof, or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 163). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 164 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 164). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 166 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 166).

[1148] In some embodiments, an RNA composition described herein (e.g., a monovalent, bivalent, trivalent, or quadrivalent composition) comprises an RNA encoding a polypeptide as set forth in SEQ ID NO: 168 or an immunogenic fragment thereof, or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 168). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 169 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 169). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 171 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 171).

[1149] In some embodiments, an RNA composition described herein (e.g., a monovalent, bivalent, trivalent, or quadrivalent composition) comprises an RNA encoding a polypeptide as set forth in SEQ ID NO: 173 or an immunogenic fragment thereof, or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 173). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 174 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 174). In some embodiments, an RNA composition comprises an RNA that includes the sequence of SEQ ID NO: 176 or a variant thereof (e.g., having at least 70% or more, including, e.g., at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or higher, identity to SEQ ID NO: 176).

[1150] In some embodiments, the formulations disclosed herein can be used to carry out any of the dosing regimens described in Table C (below).

Table C: Exemplary Dosing Regimens:

	Primary Regimen				Time between the last dose of a Primary regimen and a first dose of Booster Regimen	Booster Regimen			
#	Dose 1 (µg RNA)	Dose 2 (µg RNA)	Time Between Doses 1 and 2	Dose 1 and Dose 2 Formulation		Dose 1 (µg RNA)	Dose 2 (µg RNA)	Time Between Doses 1 and 2	Dose 1 and Dose 2 Formulation
1	30	30	2 to 8 weeks	PBS	At least 2 months	30	N/A[1]	N/A	PBS
2	30	30	2 to 8 weeks	PBS	At least 3 months	30	N/A[1]	N/A	PBS
3	30	30	2 to 8 weeks	PBS	6 to 12 months	30	N/A[1]	N/A	PBS
4	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	15	N/A[1]	N/A	PBS or Tris
5	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	10	N/A[1]	N/A	PBS or Tris
6	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	30	4 to 12 months	PBS or Tris
7	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	15	4 to 12 months	PBS or Tris
8	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	10	4 to 12 months	PBS or Tris
9	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	60	4 to 12 months	PBS or Tris
10	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	>30 to < 60	4 to 12 months	PBS or Tris
11	30	30	2 to 8 weeks	PBS or Tris	4 to 12 months	30	50	4 to 12 months	PBS or Tris
12	30	30	2 to 8 weeks	PBS	At least 6 months	30	N/A[1]	N/A	PBS
13	30	30	~21 days	PBS	At least 2 months	30	N/A[1]	N/A	PBS
14	30	30	~21 days	PBS	At least 3 months	30	N/A[1]	N/A	PBS
15	30	30	~21 days	PBS	6 to 12 months	30	N/A[1]	N/A	PBS
16	30	30	~21 days	PBS	At least 6 months	30	N/A[1]	N/A	PBS
17	30	30	21 days	PBS	At least 6 months	15	15	~21 days	PBS
18	30	30	21 days	PBS	At least 6 months	15	15	~21 days	PBS
19	30	30	2 to 8 weeks	PBS	At least 2 months	30	N/A[1]	N/A	Tris

20	30	30	2 to 8 weeks	PBS	At least 3 months	30	N/A[1]	N/A	Tris
21	30	30	2 to 8 weeks	PBS	6 to 12 months	30	N/A[1]	N/A	Tris
22	30	30	2 to 8 weeks	PBS	At least 6 months	30	N/A[1]	N/A	Tris
23	30	30	~21 days	PBS	At least 2 months	30	N/A[1]	N/A	Tris
24	30	30	~21 days	PBS	At least 3 months	30	N/A[1]	N/A	Tris
25	30	30	~21 days	PBS	6 to 12 months	30	N/A[1]	N/A	Tris
26	30	30	~21 days	PBS	At least 6 months	30	N/A[1]	N/A	Tris
27	30	30	21 days	PBS	At least 6 months	15	15	~21 days	Tris
28	30	30	21 days	PBS	At least 6 months	15	15	~21 days	Tris
29	30	30	2 to 8 weeks	Tris	At least 2 months	30	N/A[1]	N/A	Tris
30	30	30	2 to 8 weeks	Tris	At least 3 months	30	N/A[1]	N/A	Tris
31	30	30	2 to 8 weeks	Tris	6 to 12 months	30	N/A[1]	N/A	Tris
32	30	30	2 to 8 weeks	Tris	At least 6 months	30	N/A[1]	N/A	Tris
33	30	30	~21 days	Tris	At least 2 months	30	N/A[1]	N/A	Tris
34	30	30	~21 days	Tris	At least 3 months	30	N/A[1]	N/A	Tris
35	30	30	~21 days	Tris	6 to 12 months	30	N/A[1]	N/A	Tris
36	30	30	~21 days	Tris	At least 6 months	30	N/A[1]	N/A	Tris
37	30	30	21 days	Tris	At least 6 months	15	15	~21 days	Tris
38	30	30	21 days	Tris	At least 6 months	15	15	~21 days	Tris
39	10	10	2 to 8 weeks	Tris	At least 2 months	10	N/A[1]	N/A	Tris
40	10	10	2 to 8 weeks	Tris	At least 3 months	10	N/A[1]	N/A	Tris
41	10	10	2 to 8 weeks	Tris	6 to 12 months	10	N/A[1]	N/A	Tris
42	10	10	2 to 8 weeks	Tris	At least 6 months	10	N/A[1]	N/A	Tris
43	10	10	~21 days	Tris	At least 2 months	10	N/A[1]	N/A	Tris
44	10	10	~21 days	Tris	At least 3 months	10	N/A[1]	N/A	Tris

45	10	10	~21 days	Tris	6 to 12 months	10	N/A[1]	N/A	Tris
46	10	10	~21 days	Tris	At least 6 months	10	N/A[1]	N/A	Tris
47	3	3	2 to 8 weeks	Tris	At least 2 months	3	N/A[1]	N/A	Tris
48	3	3	2 to 8 weeks	Tris	At least 3 months	3	N/A[1]	N/A	Tris
49	3	3	2 to 8 weeks	Tris	6 to 12 months	3	N/A[1]	N/A	Tris
50	3	3	2 to 8 weeks	Tris	At least 6 months	3	N/A[1]	N/A	Tris
51	3	3	~21 days	Tris	At least 2 months	3	N/A[1]	N/A	Tris
52	3	3	~21 days	Tris	At least 3 months	3	N/A[1]	N/A	Tris
53	3	3	~21 days	Tris	6 to 12 months	3	N/A[1]	N/A	Tris
54	3	3	~21 days	Tris	At least 6 months	3	N/A[1]	N/A	Tris

[1]N/A refers to no dose necessary.

[1151] In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a first dose of a primary regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a second dose of a primary regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a first dose and a second dose of a primary regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a first dose of a booster regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a second dose of a booster regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a first dose and a second dose of a booster regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a first dose and a second dose of a primary regimen and also in at least one dose of a booster regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in at least one dose (including, e.g., at least two doses) of a booster regimen and BNT162b2 is given in a primary regimen. In some embodiments of certain exemplary dosing regimens as described in Table C above, an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) is given in a second dose of a booster regimen and BNT162b2 is given in a primary regimen and in a first dose of a booster regimen.

[1152] In some embodiments, such an RNA composition described herein (e.g., comprising RNA encoding a variant described herein) can further comprise RNA encoding a S protein or an immunogenic fragment thereof of a different strain (e.g., a Wuhan strain). By way of example, in some embodiments, a second dose of a booster regimen of Regimens #9-11 as described in Table C above can comprise an RNA composition described herein (e.g., comprising RNA encoding a variant described herein such as Omicron, for example, in one embodiment RNA as described in this Example) and a BNT162b2 construct, for example, in 1: 1 weight ratio.

[1153] In some embodiments of Regimen #6 as described in Table C above, a first dose and a second dose of a primary regimen and a first dose and a second dose of a booster regimen each comprise an RNA composition described herein (e.g., comprising RNA encoding a variant described herein such as Omicron, for example, in one embodiment RNA as described in this Example). In some such embodiments, a second dose of a booster regimen may not be necessary.

[1154] In some embodiments of Regimen #6 as described in Table C above, a first dose and a second dose of a primary regimen and a first dose and a second dose of a booster regimen each comprise an RNA composition described herein (e.g., comprising RNA encoding a variant described herein such as Omicron, for example, in one embodiment RNA as described in this Example). In some such embodiments, a second dose of a booster regimen may not be necessary.

[1155] In some embodiments of Regimen #6 as described in Table C above, a first dose and a second dose of a primary regimen each comprise a BNT162b2 construct, and a first dose and a second dose of a booster regimen each comprise an RNA composition described herein (e.g., comprising RNA encoding a variant described herein

such as Omicron, for example, in one embodiment RNA as described in this Example). In some such embodiments, a second dose of a booster regimen may not be necessary.

[1156] In some embodiments of Regimen #6 as described in Table C above, a first dose and a second dose of a primary regimen and a first dose of a booster regimen each comprise a BNT162b2 construct, and a second dose of a booster regimen comprises an RNA composition described herein (e.g., comprising RNA encoding a variant described herein such as Omicron, for example, in one embodiment RNA as described in this Example).

Certain exemplary embodiments below are also within the scope of the present disclosure:

Embodiment 1. A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5, XBB.1.16, BA.4/5, XBB, XBB.1, XBB.2.3, XBB.2.3.2, or BQ.1.1 Omicron variant or sublineages thereof.

Embodiment 2. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1.5 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 3. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.4/5 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 4. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.2.75 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 5. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.2.75.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N.

Embodiment 6. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.4.6/BF.7 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F,

S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N658S, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 7. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 8. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 9. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1.16 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, E180V, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 10. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.2.3 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 11. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.2.3.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, G184V, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

Embodiment 12. The composition of embodiment 1, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BQ.1.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F,

S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

Embodiment 13. The composition of any one of embodiments 1-12, wherein the SARS-CoV-2 S protein comprises one or more mutations that stable a prefusion-confirmation.

Embodiment 14. The composition of any one of embodiments 1-13, wherein the SARS-CoV-2 S protein comprises proline substitutions at positions corresponding to K986 and V987 of SEQ ID NO: 1.

Embodiment 15. The composition of any one of embodiments 1 to 14, wherein the RNA molecule comprises at least at least one modified uridine in place of a uridine.

Embodiment 16. The composition of embodiment 15, wherein the RNA molecule comprises a modified uridine in place of each uridine.

Embodiment 17. The composition of any one of embodiments 1 to 16, wherein the RNA molecule comprises a 5′ cap.

Embodiment 18. The composition of embodiment 17, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 19. The composition of any one of embodiments 1 to 18, wherein the RNA molecule comprises a 5′ untranslated region (UTR).

Embodiment 20. The composition of embodiment 19, wherein the 5′ UTR comprises a human alpha-globin 5′-UTR.

Embodiment 21. The composition of embodiment 20, wherein the human alpha-globin 5′ untranslated region (UTR) comprises SEQ ID NO: 12.

Embodiment 22. The composition of any one of embodiments 1 to 21, wherein the RNA molecule comprises a 3′ UTR.

Embodiment 23. The composition of embodiment 22, wherein the 3′ UTR comprises a first sequence from the amino terminal enhancer of split (AES) messenger RNA and a second sequence from the mitochondrial encoded 12S ribosomal RNA.

Embodiment 24. The composition of embodiment 23, wherein the 3′ UTR comprises SEQ ID NO: 13.

Embodiment 25. The composition of any one of embodiments 1 to 24, wherein the RNA molecule comprises a poly-A sequence of at least 100 A nucleotides.

Embodiment 26. The composition of embodiment 25, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 27. The composition of embodiment 26, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 28. The composition of any one of embodiments 1-27, wherein the nucleotide sequence encoding the SARS-CoV-2 S protein is encoded by a sequence that is codon-optimized (e.g., codon-optimized for expression in human cells) and/or which has a G/C content that is increased compared to a wild type coding sequence.

Embodiment 29. The composition of embodiment 1, 8, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.1.5 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 158, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 159; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 161.

Embodiment 30. The composition of embodiment 1, 2, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.4/5 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 69, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 70; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 71.

Embodiment 31. The composition of embodiment 1, 3, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.2.75 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 80, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 81; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 83.

Embodiment 32. The composition of embodiment 1, 4, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.2.75.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 85, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 86; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 88.

Embodiment 33. The composition of embodiment 1, 5, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.4.6/BF.7 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 90, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 91; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 93.

Embodiment 34. The composition of embodiment 1, 6, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 95, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 96; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 98.

Embodiment 35. The composition of embodiment 1, 7, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BQ.1.1 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 100, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 101; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 103.

Embodiment 36. The composition of embodiment 1, 9, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.1.16 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 163, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 164; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 166.

Embodiment 37. The composition of embodiment 1, 10, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.2.3 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 168, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 169; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 171.

Embodiment 38. The composition of embodiment 1, 11, or 13 to 28, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.2.3.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 173, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 174; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 176.

Embodiment 39. The composition of any one of embodiments 1 to 38, wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP).

Embodiment 40. The composition of embodiment 39, wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

Embodiment 41. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 42. The composition of embodiment 41, wherein the nucleotide sequence comprises modified uridines in place of all uridines.

Embodiment 43. The composition of embodiment 41 or 42, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 44. The composition of any one of embodiments 41 to 43, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 45. The composition of any one of embodiments 41 to 44, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 46. The composition of embodiment 45, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 47. The composition of embodiment 46, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 48. The composition of any one of embodiments 41 to 47, wherein the RNA comprises SEQ ID NO: 161.

Embodiment 49. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 80 and comprises the nucleotide sequence of SEQ ID NO: 81 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 81, and wherein the RNA comprises:

(a) at least one modified uridine;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 50. The composition of embodiment 49, wherein the nucleotide sequence comprises modified uridines in place of all uridines.

Embodiment 51. The composition of embodiment 49 or 50, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 52. The composition of any one of embodiments 49 to 51, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 53. The composition of any one of embodiments 49 to 52, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 54. The composition of embodiment 53, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 55. The composition of embodiment 54, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 56. The composition of any one of embodiments 49 to 55, wherein the RNA comprises SEQ ID NO: 83.

Embodiment 57. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 58. The composition of embodiment 57, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 59. The composition of embodiment 57 or 58, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 60. The composition of any one of embodiments 57 to 59, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 61. The composition of any one of embodiments 57 to 60, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 62. The composition of embodiment 61, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 63. The composition of embodiment 62, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 64. The composition of any one of 57 to 63, wherein the RNA comprises SEQ ID NO: 88.

Embodiment 65. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 90 and comprises the nucleotide sequence of SEQ ID NO: 91 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 91, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 66. The composition of embodiment 65, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 67. The composition of embodiment 65 or 66, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 68. The composition of any one of embodiments 65 to 67, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 69. The composition of any one of embodiments 65 to 68, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 70. The composition of embodiment 69, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 71. The composition of embodiment 70, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 72. The composition of any one of embodiments 65 to 71, wherein the RNA comprises SEQ ID NO: 93.

Embodiment 73. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 95 and comprises the nucleotide sequence of SEQ ID NO: 96 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 96, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 74. The composition of embodiment 73, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 75. The composition of embodiment 73 or 74, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 76. The RNA molecule any one of embodiments 73 to 75, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 77. The composition of any one of embodiments 73 to 76, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 78. The composition of embodiment 77, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 79. The composition of embodiment 78, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 80. The composition of any one of embodiments 73 to 79, wherein the RNA comprises SEQ ID NO: 98.

Embodiment 81. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 82. The composition of embodiment 81, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 83. The composition of embodiment 81 or 82, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 84. The composition any one of embodiments 81 to 83, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 85. The composition of any one of embodiments 81 to 84, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5' untranslated region (UTR) comprising SEQ ID NO: 12;

a 3' untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 86. The composition of embodiment 85, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 87. The composition of embodiment 86, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 88. The composition of any one of embodiments 81 to 87, wherein the RNA comprises SEQ ID NO: 103.

Embodiment 89. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 163 and comprises the nucleotide sequence of SEQ ID NO: 164 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 164, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5' cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 90. The composition of embodiment 89, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 91. The composition of embodiment 89 or 90, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 92. The composition of any one of embodiments 89 to 91, wherein the 5' cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 93. The composition of any one of embodiments 89 to 92, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5' untranslated region (UTR) comprising SEQ ID NO: 12;

a 3' untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 94. The composition of embodiment 93, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 95. The composition of embodiment 94, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 96. The composition of any one of embodiments 89 to 95, wherein the RNA comprises SEQ ID NO: 166.

Embodiment 97. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 168 and comprises the nucleotide sequence of SEQ ID NO: 169 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 169, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 98. The composition of embodiment 97, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 99. The composition of embodiment 97 or 98, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 100. The composition of any one of embodiments 97 to 99, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 101. The composition of any one of embodiments 97 to 100, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 102. The composition of embodiment 101, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 103. The composition of embodiment 102, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 104. The composition of any one of embodiments 97 to 103, wherein the RNA comprises SEQ ID NO: 171.

Embodiment 105. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 173 and comprises the nucleotide sequence of SEQ ID NO: 174 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 174, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 106. The composition of embodiment 105, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 107. The composition of embodiment 105 or 106, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 108. The composition of any one of embodiments 105 to 107, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 109. The composition of any one of embodiments 105 to 108, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5' untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 110. The composition of embodiment 109, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 111. The composition of embodiment 110, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 112. The composition of any one of embodiments 105 to 111, wherein the RNA comprises SEQ ID NO: 176.

Embodiment 113. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%,

at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 114. The composition of embodiment 113, wherein the nucleotide sequence includes modified uridines in place of all uridines.

Embodiment 115. The composition of embodiment 113 or 114, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 116. The composition of any one of embodiments 113 to 115, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 117. The composition of any one of embodiments 113 to 116, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 118. The composition of embodiment 117, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 119. The composition of embodiment 118, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 120. The composition of any one of embodiments 113 to 119, wherein the RNA comprises SEQ ID NO: 72.

Embodiment 121. The composition of any one of embodiments 1 to 120, further comprising one or more additional RNA molecules, each comprising a nucleotide sequence that encodes a SARS-CoV-2 S protein of a SARS-CoV-2 variant.

Embodiment 122. A composition comprising the RNA molecule of embodiment 2 or 29, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.5.

Embodiment 123. The composition of embodiment 122, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

Embodiment 124. A composition comprising the RNA molecule of embodiment 3 or 30, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not BA.4/5.

Embodiment 125. The composition of embodiment 124, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

Embodiment 126. A composition comprising the RNA molecule of embodiment 5 or 32, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not BA.2.75.2.

Embodiment 127. The composition of embodiment 126, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant.

Embodiment 128. A composition comprising the RNA molecule of embodiment 9 or 36, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.16.

Embodiment 129. The composition of embodiment 128, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

Embodiment 130. A composition comprising the RNA molecule of embodiment 10 or 37, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3.

Embodiment 131. The composition of embodiment 130, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

Embodiment 132. A composition comprising the RNA molecule of embodiment 11 or 38, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3.2.

Embodiment 133. The composition of embodiment 132, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

Embodiment 134. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 135. The composition of embodiment 134, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 136. The composition of embodiment 134, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 137. The composition of any one of embodiments 134 to 136, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 138. The composition of any one of embodiments 134 to 137, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 139. The composition of any one of embodiments 134 to 138, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 140. The composition of any one of embodiments 134 to 139, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 141. The composition of embodiment 140, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 142. The composition of embodiment 141, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 143. The composition of any one of embodiments 134 to 142, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72.

Embodiment 144. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 145. The composition of embodiment 144, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 146. The composition of embodiment 144, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 147. The composition of any one of embodiments 144 to 146, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 148. The composition of any one of embodiments 144 to 147, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 149. The composition of any one of embodiments 144 to 148, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 150. The composition of any one of embodiments 144 to 149, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 151. The composition of embodiment 150, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 152. The composition of embodiment 151, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 153. The composition of any one of embodiments 144 to 152, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

Embodiment 154. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 155. The composition of embodiment 154, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 156. The composition of embodiment 154, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 157. The composition of any one of 154 to 156, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 158. The composition of any one of embodiments 154 to 157, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 159. The composition of any one of embodiments 154 to 158, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 160. The composition of any one of embodiments 154 to 159, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 161. The composition of embodiment 160, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 162. The composition of 161, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 163. The composition of any one of embodiments 154 to 162, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

Embodiment 164. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 101 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 165. The composition of embodiment 164, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 166. The composition of embodiment 164, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 167. The composition of any one of embodiments 164 to 166, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 168. The composition of any one of embodiments 164 to 167, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 169. The composition of any one of embodiments 164 to 168, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 170. The composition of any one of embodiments 164 to 169, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5' untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 171. The composition of embodiment 170, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 172. The composition of embodiment 171, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 173. The composition of any one of embodiments 164 to 172, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

Embodiment 174. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 175. The composition of embodiment 174, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 176. The composition of embodiment 174, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 177. The composition of any one of embodiments 174 to 176, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 178. The composition of any one of embodiments 174 to 177, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 179. The composition of any one of embodiments 174 to 178, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 180. The composition of any one of embodiments 174 to 179, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 181. The composition of embodiment 180, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 182. The composition of embodiment 181, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 183. The composition of any one of embodiments 174 to 182, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

Embodiment 184. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 185. The composition of embodiment 184, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 186. The composition of embodiment 185, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 187. The composition of any one of embodiments 184 to 186, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 188. The composition of any one of embodiments 184 to 187, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 189. The composition of any one of embodiments 184 to 188, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

Embodiment 190. The composition of any one of embodiments 184 to 189, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 191. The composition of embodiment 190, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 192. The composition of embodiment 191, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 193. The composition of any one of embodiments 184 to 192, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

Embodiment 194. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

Embodiment 195. The composition of embodiment 194, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

Embodiment 196. The composition of embodiment 194, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

Embodiment 197. The composition of any one of embodiments 194 to 196, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

Embodiment 198. The composition of any one of embodiments 194 to 197, wherein the modified uridines are each N1-methyl-pseudouridine.

Embodiment 199. The composition of any one of embodiments 194 to 198, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 200. The composition of any one of embodiments 194 to 199, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5' untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

Embodiment 201. The composition of embodiment 200, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

Embodiment 202. The composition of embodiment 201, wherein the poly-A sequence comprises SEQ ID NO: 14.

Embodiment 203. The composition of any one of embodiments 194 to 202, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

Embodiment 204. The composition of any one of embodiments 1 to 203, which is formulated as a liquid, a solid, or a combination thereof.

Embodiment 205. The composition of any one of embodiments 1 to 204, which is formulated for injection.

Embodiment 206. The composition of embodiment 205, which is formulated for intramuscular administration.

Embodiment 207. The composition of any one of embodiments 1 to 206, wherein the RNA is mRNA or saRNA.

Embodiment 208. The composition of any one of embodiments 1 to 207, which is a pharmaceutical composition.

Embodiment 209. The composition of embodiment 208, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

Embodiment 210. The composition of any one of embodiments 1 to 209, which is a vaccine.

Embodiment 211. A method of eliciting an immune response in a subject, comprising administering the composition of any one of embodiments 1 to 210.

Embodiment 212. The method of embodiment 211, wherein the immune response is elicited against an Omicron variant of SARS-CoV-2.

Embodiment 213. The method of embodiment 212, wherein the immune response is elicited against a Wuhan strain, an Omicron variant, a Beta variant, an Alpha variant, and a Delta variant of SARS-CoV-2.

Embodiment 214. The method of any one of embodiments 211 to 213, wherein the subject has not been previously infected with and/or has not been previously administered a SARS-CoV-2 vaccine.

Embodiment 215. The method of any one of embodiments 211 to 214, wherein the subject has previously been infected with SARS-CoV-2 and/or has been previously administered a SARS-CoV-2 vaccine.

Embodiment 216. The method of any one of embodiments 211 to 215, wherein the subject has previously received a vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

Embodiment 217. The method of embodiment 216, wherein the subject has previously been administered RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

Embodiment 218. The method of embodiment 217, wherein the subject has previously been administered two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain.

Embodiment 219. The method of any one of embodiments 211 to 218, wherein the subject has previously been administered:

(i) two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., BNT162b2); and

(ii) one or more doses of a bivalent vaccine comprising:

(a) a first RNA comprising a nucleotide sequence encoding a SARS-CoV-2 S protein of a Wuhan strain; and

(b) a second RNA comprising a nucleoside sequence encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant.

Embodiment 220. The method of embodiment 219, wherein the first RNA comprises a nucleotide sequence of that is at least 90% identical to that set forth in SEQ ID NO: 20 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical), and the second RNA comprises a nucleotide sequence that is at least 90% identical to that set forth in SEQ ID NO: 72 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical).

Embodiment 221. The method of any one of embodiments 211 to 220, wherein the composition of any one of embodiments 1 to 210 comprises about 3 μg to about 30 μg of RNA (e.g., about 3 μg, about 10 μg, or about 30 μg of RNA).

Embodiment 222. The method of embodiment 221, wherein the composition of any one of embodiments 1 to 210 comprises about 3 μg of RNA, and the subject is about 6 months to less than about 5 years old.

Embodiment 223. The method of embodiment 222, wherein the composition of any one of embodiments 1 to 210 comprises about 10 μg of RNA, and the subject is about 5 years old to less than about 12 years old.

Embodiment 224. The method of embodiment 223, wherein the composition of any one of embodiments 1 to 210 comprises about 30 μg of RNA, and the subject is about 12 years or older.

Embodiment 225. The method of any one of embodiments 211 to 224, where in the composition of any one of embodiments 1 to 210 is co-administered with one or more vaccines against a non-SARS-CoV-2 disease (e.g., a non-SARS-CoV-2 respiratory disease).

Embodiment 226. The method of embodiment 225, wherein the one or more vaccines against a non-SARS-CoV-2 disease comprises an influenza vaccine, an RSV vaccine, or a combination thereof.

Embodiment 227. A kit comprising the composition of any one of embodiments 1 to 210.

Embodiment 228. The kit of embodiment 227, further comprising instructions for use of the composition for inducing an immune response against coronavirus in a subject.

Embodiment 229. The composition of any one of embodiments 1 to 210, for pharmaceutical use.

Embodiment 230. The composition of embodiment 229, wherein the pharmaceutical use comprises inducing an immune response against coronavirus in a subject.

Embodiment 231. The composition of embodiment 229 or 230, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus infection.

Embodiment 232. The composition of any one of embodiments 1 to 210, which is for administration to a human.

Embodiment 233. The composition of embodiment 230 or 231, wherein the coronavirus is a betacoronavirus.

Embodiment 234. The composition of any one of embodiments 230, 231, or 233, wherein the coronavirus is a sarbecovirus.

Embodiment 235. The composition of any one of embodiments 230, 231, 233, or 234, wherein the coronavirus is SARS-CoV-2.

Embodiment 236. The method of any one of embodiments 211 to 226, wherein the subject is a human.

Embodiment 237. The method of any one of embodiments 211 to 226 or 236, wherein the immune response is induced against a coronavirus.

Embodiment 238. The method of embodiment 237, wherein the coronavirus is a betacoronavirus.

Embodiment 239. The method of embodiment 238, wherein the betacoronavirus is a sarbecovirus.

Embodiment 240. The method of any one of embodiments 237 to 239, wherein the coronavirus is SARS-CoV-2.

Embodiment 241. The composition of any one of embodiments 1 to 210, for pharmaceutical use.

Embodiment 242. The composition of embodiment 241, wherein the pharmaceutical use comprises inducing an immune response against coronavirus in a subject.

Embodiment 243. The composition of embodiment 241 or 242, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus infection.

Embodiment 244. The composition of embodiment 242 or 243, wherein the coronavirus is a betacoronavirus.

Embodiment 245. The composition of embodiment 244, wherein the betacoronavirus is a sarbecovirus.

Embodiment 246. The composition of embodiment 245, wherein the sarbecovirus is a SARS-CoV-2 virus.

Embodiment 247. Use of the composition of any one of embodiments 1 to 210 for the manufacture of a medicament for inducing an immune response against coronavirus in a subject.

Embodiment 248. The use of embodiment 247, wherein the medicament is for therapeutic or prophylactic treatment of a coronavirus infection.

Embodiment 249. The use of embodiment 247 or 248, wherein the coronavirus is a betacoronavirus.

Embodiment 250. The composition of embodiment 249, wherein the betacoronavirus is a sarbecovirus.

Embodiment 251. The composition of embodiment 250, wherein the sarbecovirus is a SARS-CoV-2 virus.

Embodiment 252. A composition comprising an RNA molecule having:

(a) a nucleotide sequence that is at least 99% identical to SEQ ID NO: 161;

(b) a nucleotide sequence that is at least 95% identical to SEQ ID NO: 161, and which encodes a SARS-CoV-2 S protein comprising the following mutations relative to SEQ ID NO: 1: T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N,

N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, K986P, and V987P; or

(c) a nucleotide sequence as set forth in SEQ ID NO: 161; and

wherein the RNA molecule comprises:

(i) a 5′ cap; and

(ii) a modified uridine in place of each uridine.

Embodiment 253.The composition of embodiment 252, wherein the modified uridine is N1-methyl-pseudouridine.

Embodiment 254.The composition of embodiment 252 or embodiment 253, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

Embodiment 255.The composition of any one of embodiments 252 to 254, wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP), preferably wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

Embodiment 256.The composition of any one of embodiments 252 to 255, wherein the composition comprises one or more additional RNA molecules, each having a nucleotide sequence encoding an S protein of a SARS-CoV-2 strain or variant that is not XBB.1.5, preferably wherein the one or more additional RNA molecules comprise a sequence that is at least 95% identical to that set forth in SEQ ID NO: 20, 72, or 103.

Embodiment 257.The composition of any one of embodiments 252 to 256, wherein the RNA molecule comprises:

(i) N1-methyl-pseudouridine in place of each uridine; and

(ii) a 5′ cap that comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG;

wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP); and

wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

Embodiment 258.The composition of any one of embodiments 252 to 257, comprising about 10 mM Tris buffer and about 10% sucrose.

Embodiment 259.The composition of any one of embodiments 252 to 258, wherein the composition comprises at least one unit dose of LNP-encapsulated RNA molecules, optionally wherein the unit dose comprises the RNA molecule in an amount of about 30 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 10 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 3 μg.

Embodiment 260.The composition of any one of embodiments 252 to 259, wherein the composition is formulated as a multi-dose formulation in a vial.

Embodiment 261.A composition of any one of embodiments 252 to 260 for use in a method of inducing an immune response against coronavirus in a subject, said method comprising administering to a subject the composition.

Embodiment 262.The composition for use of embodiment 261, wherein:

the subject is 12 years or older, and the composition comprises 30 µg of the RNA molecule, or

the subject is 5 years to less than 12 years old, and the composition comprises 10 µg of the RNA molecule, or

the subject is 6 months to less than 5 years old, and the composition comprises 3 µg of the RNA molecule.

Embodiment 263.The composition for use of embodiment 261 or embodiment 262, wherein the composition is administered in a volume of about 200 µL to 300 µL.

Embodiment 264.The composition for use of any one of embodiments 261 to 263, wherein the subject was previously administered one or more doses of a SARS-CoV-2 vaccine, preferably wherein the subject was previously administered a complete dosing regimen of a SARS-CoV-2 vaccine.

Embodiment 265.The composition for use of any one of embodiments 262 to 264, wherein the subject was previously administered a first dose and a second dose of BNT162b2, wherein the first dose and the second dose were administered about 21 days apart, and/or wherein the subject was previously administered as a booster dose a bivalent vaccine that delivers (i) a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and (ii) a SARS-CoV-2 S protein of a Wuhan strain.

Embodiment 266.The composition for use of any one of embodiments 261 to 266, wherein said method further comprises administering one or more vaccines against a non-SARS-CoV-2 disease, preferably wherein the one or more vaccines comprises an RSV vaccine, an influenza vaccine, or a combination thereof.

Citation of documents and studies referenced herein is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the contents of these documents are based on the information available to the applicants and do not constitute any admission as to the correctness of the contents of these documents.
The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

Examples

Example 1: Further Studies Characterizing Variant-Adapted Vaccines in Vaccine-Naïve Mice

[1157] The present Example provides exemplary dosing regimens in vaccine-naïve subjects, as well as data confirming that certain variant-adapted vaccines provided in the present disclosure can produce a strong immune response (in particular, high neutralizing antibody titers) in vaccine naïve subjects (mice in the present Example). The present Example also provides further data demonstrating that variant-adapted vaccines can produce a strong immune response against the SARS-CoV-2 variant they are directed against, and that bivalent vaccines (e.g., Wuhan + BA.4/5 bivalent vaccines) can result in broader cross-neutralization as compared to monovalent vaccines.

[1158] Vaccine-naïve mice were administered a monovalent or bivalent vaccines comprising a variant-adapted vaccines, as summarized in the Table shown in Fig. 10. As shown in Fig. 10, vaccine naïve mice were administered two doses of one of the following compositions:

- Buffer (negative control)
- A composition comprising 1 μg of an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2);
- A bivalent composition comprising 0.5 μg of a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and 0.5 μg of a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant;
- A composition comprising 1 μg of an RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant;
- A composition comprising 1 μg of an RNA encoding a SARS-CoV-2 S protein of an Omicron BQ.1.1 variant;
- A composition comprising 1 μg of an RNA encoding a SARS-CoV-2 S protein of an Omicron XBB variant; or
- A composition comprising 1 μg of an RNA encoding a SARS-CoV-2 S protein of an Omicron BA.2.75.2 variant.

[1159] In the present Example, each of the RNAs administered was a modRNA, comprising N1-methyl-pseudouridine in place of each uridine. RNA was also formulated in LNPs. In the case of the bivalent composition (Wuhan + BA.4/5), RNA was mixed prior to LNP formulation.

[1160] Vaccines were administered on days 0 and 21, sera samples were collected on days 0, 14, 21, and 35, and on day 35 mice were sacrificed and the experiment concluded.

[1161] Pseudovirus neutralization titers were collected as described in the previous Examples. Pseudovirus neutralization titers in sera samples collected 14 days after a second dose of vaccine (35 days after the start of the experiment) are shown in Fig. 11.

[1162] As shown in Fig. 11, the bivalent (Wuhan + Omicron BA.4/5) composition produced high neutralization titers against each pseudovirus tested, including high neutralization titers against new, highly immune-escaping variants (e.g., BA.4/5, BA.2.75.2, BQ.1.1 and XBB). These results demonstrate that a bivalent Wuhan + Omicron BA.4/5 vaccine (e.g., a bivalent described herein) can produce strong cross-neutralization titers when administered to vaccine naïve subjects.

[1163] The results also show, surprisingly, that certain variant-adapted vaccines produce particularly strong cross-neutralization titers. In particular, a BA.2.75.2-adapted vaccine was found to induce surprisingly broad cross neutralization titers.

[1164] Many of the variant-adapted monovalent vaccines were also found to surprisingly induce a strong immune response against a Wuhan strain, even though a Wuhan-adapted vaccine was not found to induce strong neutralization of those variants. For example, BA.4/5, BA.1.1, XBB, and BA.2.75.2 monovalent vaccines were each

found to induce strong neutralization titers against a Wuhan pseudovirus, but a Wuhan-adapted vaccine was not found to induce high neutralization titers against any of these variants.

[1165] In a follow-up experiment, pseudovirus neutralization titers were determined in sera collected from vaccine naïve subjects (mice) administered (i) two doses of an RNA composition that delivers a Wuhan S protein (BNT162b2), (ii) two doses of a bivalent composition comprising a first RNA that encodes a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2) and a second RNA that encodes an S protein of a BA.4/5 Omicron variant, or (iii) a first dose of an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second dose of a bivalent (Wuhan + BA.4/5) RNA composition. Again, pseudovirus neutralization titers were collected using methods described in the previous Examples.

[1166] Neutralization titers are shown in Fig. 12. As shown in the figure, two doses of a bivalent vaccine were found to induce significantly higher neutralization titers against new immune-escaping SARS-CoV-2 variants (specifically, BQ.1.1, BA.2.75.2, XBB, and XBB.1.5 SARS-CoV-2 variants) as compared to a Wuhan-adapted vaccine (see Figs. 12 (A) and (B)). Surprisingly, two doses of a bivalent vaccine was also found to induce significantly higher neutralization titers against variants as compared to a first dose of a Wuhan-adapted vaccine and a second dose of a bivalent vaccine (see Fig. 12(C)). These results demonstrate that a bivalent Wuhan + BA.4/5 RNA composition described herein can produce a strong cross-neutralization response against new variants of concern (e.g., against BQ.1.1, BA.2.75.2, XBB, and XBB.1.5 variants). The results also demonstrate that two doses of such a bivalent vaccine can produce surprisingly strong immune responses when administered as a primary dosing regimen to vaccine-naïve subjects.

Example 2: Further Studies of Variant-Adapted Bi- and Trivalent Vaccines in Vaccine-Naïve Mice

[1167] The present Example provides data characterizing certain bivalent and trivalent variant-adapted vaccines in vaccine naïve mice. The particular vaccines tested are shown in Fig. 13. As shown in the Figure, vaccines were administered on days 0 and 21, sera samples were collected on days 0, 14, and 21, and on day 35 a final sera sample was collected and mice were sacrificed.

[1168] Pseudovirus neutralization titers from sera samples collected on day 35 (14 days after administering a second dose of vaccine) are shown in Fig. 14. As shown in the figure, each of the tested bi- and trivalent composition can produce a strong neutralization titer against their corresponding variants, and can also induce broad cross-neutralization of other variants of concern. The BA.4/5 + BQ.1.1 combination in particular was found to produce strong cross-neutralization titers.

Example 3: Further Studies of Variant-Adapted Bi- and Trivalent Vaccines in Vaccine-Experienced Mice

[1169] The present Example describes a study to characterize immune responses induced by certain variant-adapted vaccines in vaccine-experienced subjects (mice in the present Example). In particular, the present Example describes an experiment to characterize immune responses induced in subjects previously administered (i) at least one dose of a composition that delivers a SARS-CoV-2 S protein of a Wuhan strain, and (ii) at least one dose of a bivalent composition comprising a first RNA that encodes a SARS-COV-2 S protein of a Wuhan strain and a second RNA that encodes a SARS-CoV-2 S protein of a BA.4/5 Omicron variant.

[1170] Two sets of experimental dosing regimens are summarized in Figs. 15 and 16.

[1171] In a first set of experiments (summarized in Fig. 15), BALB/C mice are administered a first dose of an RNA vaccine encoding a SARS-CoV-2 S protein of a Wuhan variant (BNT162b2), and, 21 days later, a second dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding SARS-COV-2 S protein of a BA.4/5 Omicron variant. About 10 weeks after administered the second dose, mice are then administered one of the following compositions (comprising RNAs encoding SARS-CoV-2 S proteins from the listed strains/variants):

- Wuhan + BA.4/5
- XBB.1.5
- BA.2.75.2
- BQ.1.1
- Wuhan + BA.4/5 + XBB.1.5
- Wuhan + BA.4/5 + BA.2.75.2
- BA.4/5 + XBB.1.5
- BA.4/5 + BA.2.75.2
- BA.4/5 + BQ.1.1

[1172] About 28 days after the third dose, mice are sacrificed and final neutralization titers are collected.

[1173] In a related experiment, neutralization titers are determined in mice administered two doses of a composition that delivers a Wuhan S protein, a third dose of a bivalent vaccine, and a fourth dose of one of the vaccines listed below (comprising RNAs encoding SARS-CoV-2 S proteins from the listed variants). The design of this experiment is summarized in Fig. 16.

- XBB.1.5
- BA.2.75.2
- BQ.1.1
- BA.4/5 + XBB.1.5
- BA.4/5 + BA.2.75.2
- BA.4/5 + BQ.1.1

Example 4: Further Studies Investigating Variant-Adapted Vaccines Administered to Vaccine-Naïve Mice

[1174] The present Example provides data characterizing certain monovalent and bivalent variant-adapted vaccines in vaccine naïve mice. The particular vaccines tested are shown in Fig. 17. As shown in the Figure, vaccines were administered vaccines on days 0 and 21 (the same vaccine composition and dose was administered on each day; dose amounts indicated in Fig. 17), and sera samples were collected on day 35 (14 days after the second dose of a vaccine).

[1175] Pseudovirus neutralization titers from sera samples collected on day 35 are shown in Fig. 18. As shown in the figure, each of the tested compositions can produce strong neutralization titers against the corresponding strain or variant. In particular, a monovalent composition comprising an RNA encoding an S protein of an XBB.1.5 Omicron variant was shown to induce high neutralization titers against XBB.1.5 when administered as a primary series. A bivalent composition comprising an RNA encoding an S protein of an XBB.1.5 Omicron variant and an RNA encoding an S protein of an Omicron BA.4/5 variant was also shown to induce high neutralization titers against

XBB.1.5 when administered as a primary series, although titers were lower than those induced by an XBB.1.5 monovalent vaccine.

[1176] Each of the compositions comprising an RNA encoding an S protein of a SARS-CoV-2 variant (i.e., WT + BA.4/5, BA.4/5, XBB.1.5, and BA.4/5 + XBB.1.5) was also found to induce broad cross-neutralization of other variants of concern. In particular, the BA.4/5 + XBB.1.5 bivalent vaccine was found to induce high neutralization titers both against the XBB.1.5 variant as well as other strains. Neutralization titers against XBB.1.16 are expected to be similar to those induced against XBB.1.5, as neutralization data shows that the XBB.1.16 variant possesses no escape advantage relative to XBB.1.5 (see, e.g., Fig. 20). Similarly, neutralization titers for XBB.1.9.1/1.9.2 are expected to match those for XBB.1.5, as XBB.1.9.1/1.9.2 does not comprise any additional S protein mutations relative to XBB.1.5.

[1177] A similar experiment (summarized in the schematic at the top of Fig. 21) was also performed in which vaccine-naïve mice were administered two doses of (i) a bivalent composition comprising RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, (ii) a monovalent composition comprising RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant, or (iii) a bivalent composition comprising RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant. The two doses of RNA were administered 21 days apart, and neutralization titers were collected 4 weeks after administering the second dose. As shown in Fig. 21, an XBB.1.5-adapted monovalent vaccine (e.g., as described herein) induced the highest neutralization titers against each of an XBB.1.5 variant, an XBB.1.16 variant, and an XBB.2.3 variant as compared to the other compositions tested.

Example 5: Further Studies Investigating Variant-Adapted Vaccines Administered to Vaccine-Experienced Mice

[1178] The present Example provides exemplary immune response data generated using certain monovalent and bivalent variant-adapted vaccines in vaccine-experienced mice. In particular, the present Example provides data demonstrating that vaccines (e.g., monovalent or bivalent vaccines) comprising an RNA encoding an XBB.1.5 S protein can induce strong neutralization titers against an XBB.1.5 Omicron variant in previously vaccinated subjects (e.g., subjects previously administered RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, as in the present Example).

[1179] The particular vaccines tested are shown in Fig. 19. As shown in the Figure, mice in all groups were administered the following vaccines (listed in order of administration): (1) a first dose of a vaccine comprising RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2 in the present example), (2) a second dose of a vaccine comprising an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (again, BNT162b2 in the present example; second dose administered about 21 days after the first dose), (3) a third dose of a bivalent vaccine comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant (administered about 84 days after the second dose), and (4) a fourth dose of one of the monovalent or bivalent vaccines listed in the Figure (administered about 29 days after the third dose). Sera samples were collected 134 days after administration of the first dose of vaccine (immediately before administering the 4th dose), and 160 days after administering the 1st dose. Mice were administered 0.5 μg of each vaccine (for monovalent vaccines: 0.5 μg of an RNA, for bivalent vaccines: 0.25 μg of each RNA). On day 160, lymph nodes and spleen samples were also collected for T cell and B cell analysis.

[1180] Pseudovirus neutralization titers are shown in Fig. 20. As shown in the figure, vaccines comprising an RNA encoding an XBB.1.5 S protein were found to induce a strong neutralization response when administered as either a monovalent or bivalent (e.g., BA.4/5 + XBB.1.5) vaccine. In particular, the data demonstrates that such vaccines are especially effective when administered as a booster dose (e.g., to subjects previously administered one or more vaccines that deliver a SARS-CoV-2 S protein of a Wuhan strain and one or more bivalent vaccines (delivering a SARS-CoV-2 S protein of a Wuhan strain and an Omicron BA.4/5 variant), as tested in the present Example). In the present experiment, neutralization titers induced by an XBB.1.5 monovalent vaccine (in particular, neutralization titers against an XBB.1.5, XBB.1.16, and XBB.2.3-adapted pseudovirus) were found to be higher than those induced by a bivalent vaccine (BA.4/5 + XBB.1.5). Other studies confirmed that monovalent or bivalent vaccine comprising an RNA encoding an XBB.1.5 S protein can induce a strong immune response against XBB variants (in particular, when administered as a booster), and further showed that, while a bivalent vaccine can induce higher neutralization titers at early time points, neutralization titers induced by a bivalent vaccine decreased faster than those induced by a monovalent vaccine, such that, 4 weeks after a booster dose, neutralization titers induced by a monovalent vaccine were higher than those induced by a bivalent vaccine (data not shown). As noted in previous Example 4, neutralization titers for XBB.1.9.1/1.9.2 are expected to match those induced for XBB.1.5, as XBB.1.9.1/1.9.2 does not comprise any additional S protein mutations relative to XBB.1.5.

[1181] A similar experiment was also performed to test the efficacy of an XBB.1.16-adapted vaccine (schematic summarizing the experimental protocol used is shown in Fig. 22). In short, mice were divided into groups of 10, and administered two doses (21 days apart) of an RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (BNT162b2 in the present example), followed by a third dose (administered 14 days after the second dose) of a candidate vaccine encoding (i) a bivalent composition comprising a first RNA encoding a SARS-CoV-2 S protein of a Wuhan strain and a second RNA encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant, (ii) a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant, (iii) a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an XBB.1.16 variant. 14 days after administering a third dose of vaccine, mice were bled and neutralization titers collected (e.g., using a pseudovirus neutralization assay described in one of the previous examples).

[1182] As shown in Fig. 22, a monovalent composition comprising an RNA encoding a SARS-CoV-2 S protein of an XBB.1.5 variant (e.g., an RNA described herein) induced the highest neutralization titers against each of the XBB.1.5, XBB.1.16, and XBB.2.3 variants. Surprisingly, an XBB.1.5 monovalent composition induced higher titers against an XBB.1.16 variant than a monovalent comprising an RNA encoding a SARS-CoV-2 S protein of an XBB.1.16 variant.

Claims

1. A composition comprising an RNA molecule having:

(a) a nucleotide sequence that is at least 99% identical to SEQ ID NO: 161;

(b) a nucleotide sequence that is at least 95% identical to SEQ ID NO: 161, and which encodes a SARS-CoV-2 S protein comprising the following mutations relative to SEQ ID NO: 1: T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, K986P, and V987P; or

(c) a nucleotide sequence as set forth in SEQ ID NO: 161; and

wherein the RNA molecule comprises:

(i) a 5′ cap; and

(ii) a modified uridine in place of each uridine.

2. The composition of claim 1, wherein the modified uridine is N1-methyl-pseudouridine.

3. The composition of claim 1 or 2, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$.

4. The composition of any one of claims 1 to 3, wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP), preferably wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

5. The composition of any one of claims 1 to 4, wherein the composition comprises one or more additional RNA molecules, each having a nucleotide sequence encoding an S protein of a SARS-CoV-2 strain or variant that is not XBB.1.5, preferably wherein the one or more additional RNA molecules comprise a sequence that is at least 95% identical to that set forth in SEQ ID NO: 20, 72, or 103.

6. The composition of any one of claims 1 to 5, wherein the RNA molecule comprises:

(i) N1-methyl-pseudouridine in place of each uridine; and

(ii) a 5′ cap that comprises $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$;

wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP); and

wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

7. The composition of any one of claims 1 to 6, comprising about 10 mM Tris buffer and about 10% sucrose.

8. The composition of any one of embodiments 1 to 7, wherein the composition comprises at least one unit dose of LNP-encapsulated RNA molecules, optionally wherein the unit dose comprises the RNA molecule in an amount of about 30 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 10 μg, or wherein the unit dose comprises the RNA molecule in an amount of about 3 μg.

9. The composition of any one of claims 1 to 8, wherein the composition is formulated as a multi-dose formulation in a vial.

10. The composition of any one of claims 1 to 9, for use in a method of inducing an immune response against coronavirus in a subject, said method comprising administering to a subject the composition.

11. The composition for use of embodiment 10, wherein:

the subject is 12 years or older, and the composition comprises 30 µg of the RNA molecule, or

the subject is 5 years to less than 12 years old, and the composition comprises 10 µg of the RNA molecule, or

the subject is 6 months to less than 5 years old, and the composition comprises 3 µg of the RNA molecule.

12. The composition for use of claim 10 or claim 11, wherein the composition is administered in a volume of about 200 µL to 300 µL.

13. The composition for use of any one of claims 10 to 12, wherein the subject was previously administered one or more doses of a SARS-CoV-2 vaccine, preferably wherein the subject was previously administered a complete dosing regimen of a SARS-CoV-2 vaccine.

14. The composition for use of any one of embodiments 10 to 13, wherein the subject was previously administered a first dose and a second dose of BNT162b2, wherein the first dose and the second dose were administered about 21 days apart, and/or wherein the subject was previously administered as a booster dose a bivalent vaccine that delivers (i) a SARS-CoV-2 S protein of an Omicron BA.4/5 variant and (ii) a SARS-CoV-2 S protein of a Wuhan strain.

15. The composition for use of any one of embodiments 10 to 14, wherein said method further comprises administering one or more vaccines against a non-SARS-CoV-2 disease, preferably wherein the one or more vaccines comprises an RSV vaccine, an influenza vaccine, or a combination thereof.

16. A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5, XBB.1.16, BA.4/5, XBB, XBB.1, XBB.2.3, XBB.2.3.2, or BQ.1.1 Omicron variant or sublineages thereof.

17. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1.5 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

18. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.4/5 variant, wherein the one or more mutations are selected from the

group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

19. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.2.75 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, Q498R, N501Y, Y505H D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

20. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.2.75.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, G142D, K147E, W152R, F157L, I210V, V213G, G257S, G339H, R346T, N354D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, N460K, S477N, T478K, E484A, F486S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, and D1199N.

21. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BA.4.6/BF.7 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N658S, N679K, P681H, N764K, D796Y, Q954H, and N969K.

22. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

23. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486S, F490S, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

24. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.1.16 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ145, H146Q, E180V, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

25. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.2.3 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

26. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of an XBB.2.3.2 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, V83A, G142D, Δ144, H146Q, Q183E, G184V, V213E, D253G, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, P521S, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K.

27. The composition of claim 16, wherein the SARS-CoV-2 S protein or immunogenic fragment thereof comprises one or more mutations characteristic of a BQ.1.1 variant, wherein the one or more mutations are selected from the group consisting of T19I, Δ24-26, A27S, Δ69/70, G142D, V213G, G339D, R346T, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, K444T, L452R, N460K, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

28. The composition of any one of claims 16-28, wherein the SARS-CoV-2 S protein comprises one or more mutations that stable a prefusion-confirmation.

29. The composition of any one of claims 16-28, wherein the SARS-CoV-2 S protein comprises proline substitutions at positions corresponding to K986 and V987 of SEQ ID NO: 1.

30. The composition of any one of claims 1 to 29, wherein the RNA molecule comprises at least at least one modified uridine in place of a uridine.

31. The composition of claim 30, wherein the RNA molecule comprises a modified uridine in place of each uridine.

32. The composition of any one of claims 1 to 31, wherein the RNA molecule comprises a 5′ cap.

33. The composition of claim 32, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

34. The composition of any one of claims 1 to 33, wherein the RNA molecule comprises a 5′ untranslated region (UTR).

35. The composition of claim 34, wherein the 5′ UTR comprises a human alpha-globin 5′-UTR.

36. The composition of claim 35, wherein the human alpha-globin 5′ untranslated region (UTR) comprises SEQ ID NO: 12.

37. The composition of any one of claims 1 to 36, wherein the RNA molecule comprises a 3′ UTR.

38. The composition of claim 37, wherein the 3′ UTR comprises a first sequence from the amino terminal enhancer of split (AES) messenger RNA and a second sequence from the mitochondrial encoded 12S ribosomal RNA.

39. The composition of claim 38, wherein the 3′ UTR comprises SEQ ID NO: 13.

40. The composition of any one of claims 1 to 39, wherein the RNA molecule comprises a poly-A sequence of at least 100 A nucleotides.

41. The composition of claim 40, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

42. The composition of claim 41, wherein the poly-A sequence comprises SEQ ID NO: 14.

43. The composition of any one of claims 1 to 42, wherein the nucleotide sequence encoding the SARS-CoV-2 S protein is encoded by a sequence that is codon-optimized (e.g., codon-optimized for expression in human cells) and/or which has a G/C content that is increased compared to a wild type coding sequence.

44. The composition of claim 16, 23, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.1.5 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 158, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 159; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 161.

45. The composition of claim 16, 17, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.4/5 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 69, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 70; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 71.

46. The composition of claim 16, 18, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.2.75 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 80, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 81; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 83.

47. The composition of claim 16, 19, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.2.75.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 85, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 86; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 88.

48. The composition of claim 16, 20, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BA.4.6/BF.7 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 90, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 91; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 93.

49. The composition of claim 16, 21, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 95, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 96; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 98.

50. The composition of claim 16, 22, or 18 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron BQ.1.1 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 100, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 101; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 103.

51. The composition of claim 16, 24, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.1.16 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 163, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 164; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 166.

52. The composition of claim 16, 26, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.2.3 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 168, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 169; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 171.

53. The composition of claim 16, 26, or 28 to 43, wherein the SARS-CoV-2 S protein comprises one or more mutations characteristic of an Omicron XBB.2.3.2 variant and wherein:

a) the SARS-CoV-2 S protein comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 173, or an immunogenic fragment thereof; and/or

b) the RNA molecule encoding the SARS-CoV-2 S protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 174; and/or at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to SEQ ID NO: 176.

54. The composition of any one of claims 16 to 53, wherein the RNA molecule is encapsulated in a lipid nanoparticle (LNP).

55. The composition of claim 54, wherein the LNP comprises molar ratios of 20-60% ionizable cationic lipid, 5-25% neutral lipid, 25-55% sterol, and 0.5-15% PEG-modified lipid.

56. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

57. The composition of claim 56, wherein the nucleotide sequence comprises modified uridines in place of all uridines.

58. The composition of claim 56 or 57, wherein the modified uridines are each N1-methyl-pseudouridine.

59. The composition of any one of claims 56 to 58, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

60. The composition of any one of claims 56 to 59, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3’ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

61. The composition of claim 60, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

62. The composition of claim 61, wherein the poly-A sequence comprises SEQ ID NO: 14.

63. The composition of any one of claims 56 to 62, wherein the RNA comprises SEQ ID NO: 161.

64. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 80 and comprises the nucleotide sequence of SEQ ID NO: 81 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 81, and wherein the RNA comprises:

(a) at least one modified uridine;

(b) a 5’ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

65. The composition of claim 64, wherein the nucleotide sequence comprises modified uridines in place of all uridines.

66. The composition of claim 64 or 65, wherein the modified uridines are each N1-methyl-pseudouridine.

67. The composition of any one of claims 64 to 66, wherein the 5’ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

68. The composition of any one of claims 64 to 67, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3’ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

69. The composition of claim 68, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

70. The composition of claim 69, wherein the poly-A sequence comprises SEQ ID NO: 14.

71. The composition of any one of claims 64 to 70, wherein the RNA comprises SEQ ID NO: 83.

72. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

73. The composition of claim 72, wherein the nucleotide sequence includes modified uridines in place of all uridines.

74. The composition of claim 72 or 73, wherein the modified uridines are each N1-methyl-pseudouridine.

75. The composition of any one of claims 72 to 74, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

76. The composition of any one of claims 72 to 75, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

77. The composition of claim 76, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

78. The composition of claim 77, wherein the poly-A sequence comprises SEQ ID NO: 14.

79. The composition of any one of 72 to 78, wherein the RNA comprises SEQ ID NO: 88.

80. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 90 and comprises the nucleotide sequence of SEQ ID NO: 91 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 91, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

81. The composition of claim 80, wherein the nucleotide sequence includes modified uridines in place of all uridines.

82. The composition of claim 80 or 81, wherein the modified uridines are each N1-methyl-pseudouridine.

83. The composition of any one of claims 80 to 82, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

84. The composition of any one of claims 80 to 83, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

85. The composition of claim 84, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

86. The composition of claim 85, wherein the poly-A sequence comprises SEQ ID NO: 14.

87. The composition of any one of claims 80 to 86, wherein the RNA comprises SEQ ID NO: 93.

88. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 95 and comprises the nucleotide sequence of SEQ ID NO: 96 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 96, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

89. The composition of claim 88, wherein the nucleotide sequence includes modified uridines in place of all uridines.

90. The composition of claim 88 or 89, wherein the modified uridines are each N1-methyl-pseudouridine.

91. The RNA molecule any one of claims 88 to 90, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

92. The composition of any one of claims 88 to 91, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

93. The composition of claim 92, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

94. The composition of claim 93, wherein the poly-A sequence comprises SEQ ID NO: 14.

95. The composition of any one of claims 88 to 94, wherein the RNA comprises SEQ ID NO: 98.

96. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

97. The composition of claim 96, wherein the nucleotide sequence includes modified uridines in place of all uridines.

98. The composition of claim 96 or 97, wherein the modified uridines are each N1-methyl-pseudouridine.

99. The composition any one of claims 96 to 98, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

100. The composition of any one of claims 96 to 99, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

101. The composition of claim 100, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

102. The composition of claim 101, wherein the poly-A sequence comprises SEQ ID NO: 14.

103. The composition of any one of claims 96 to 102, wherein the RNA comprises SEQ ID NO: 103.

104. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 163 and comprises the nucleotide sequence of SEQ ID NO: 164 or a nucleotide sequence

that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 164, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

105. The composition of claim 104, wherein the nucleotide sequence includes modified uridines in place of all uridines.

106. The composition of claim 104 or 105, wherein the modified uridines are each N1-methyl-pseudouridine.

107. The composition of any one of claims 104 to 106, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

108. The composition of any one of claims 104 to 107, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

109. The composition of claim 108, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

110. The composition of claim 109, wherein the poly-A sequence comprises SEQ ID NO: 14.

111. The composition of any one of claims 104 to 110, wherein the RNA comprises SEQ ID NO: 166.

112. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 168 and comprises the nucleotide sequence of SEQ ID NO: 169 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 169, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

113. The composition of claim 112, wherein the nucleotide sequence includes modified uridines in place of all uridines.

114. The composition of claim 112 or 113, wherein the modified uridines are each N1-methyl-pseudouridine.

115. The composition of any one of claims 112 to 114, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

116. The composition of any one of claims 112 to 115, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

117. The composition of claim 116, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

118. The composition of claim 117, wherein the poly-A sequence comprises SEQ ID NO: 14.

119. The composition of any one of claims 112 to 118, wherein the RNA comprises SEQ ID NO: 171.

120. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 173 and comprises the nucleotide sequence of SEQ ID NO: 174 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 174, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

106. The composition of claim 105, wherein the nucleotide sequence includes modified uridines in place of all uridines.

122. The composition of claim 120 or 121, wherein the modified uridines are each N1-methyl-pseudouridine.

123. The composition of any one of claims 120 to 122, wherein the 5′ cap comprises $m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG.

124. The composition of any one of claims 120 to 123, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

125. The composition of claim 124, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

126. The composition of claim 125, wherein the poly-A sequence comprises SEQ ID NO: 14.

127. The composition of any one of claims 120 to 126, wherein the RNA comprises SEQ ID NO: 176.

128. A composition comprising: a lipid nanoparticle (LNP) comprising an RNA, wherein the RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and wherein the RNA comprises:

(a) modified uridines;

(b) a 5′ cap; and

wherein the LNP comprises a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

129. The composition of claim 128, wherein the nucleotide sequence includes modified uridines in place of all uridines.

130. The composition of claim 128 or 129, wherein the modified uridines are each N1-methyl-pseudouridine.

131. The composition of any one of claims 128 to 130, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$.

132. The composition of any one of claims 128 to 131, wherein the RNA further comprises at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

133. The composition of claim 132, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

134. The composition of claim 133, wherein the poly-A sequence comprises SEQ ID NO: 14.

135. The composition of any one of claims 128 to 134, wherein the RNA comprises SEQ ID NO: 72.

136. The composition of any one of claims 16 to 134, further comprising one or more additional RNA molecules, each comprising a nucleotide sequence that encodes a SARS-CoV-2 S protein of a SARS-CoV-2 variant.

137. A composition comprising the RNA molecule of claim 17 or 44, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.5.

128. The composition of claim 137, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

139. A composition comprising the RNA molecule of claim 18 or 45, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not BA.4/5.

140. The composition of claim 139, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

141. A composition comprising the RNA molecule of claim 20 or 47, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not BA.2.75.2.

142. The composition of claim 141, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant,

or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant.

143. A composition comprising the RNA molecule of claim 24 or 52, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.1.16.

144. The composition of claim 143, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

145. A composition comprising the RNA molecule of claim 25 or 52, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3.

146. The composition of claim 145, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3.2 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

147. A composition comprising the RNA molecule of claim 26 or 54, and one or more additional RNA molecules, wherein the one or more additional RNA molecules each comprise one or more mutations that is associated with a SARS-CoV-2 variant that is not XBB.2.3.2.

148. The composition of claim 147, wherein the one or more additional RNA molecules comprise a nucleotide sequence that encodes:

(i) a SARS-CoV-2 S protein of a Wuhan strain,

(ii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.5 variant,

(iii) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.1.16 variant,

(iv) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an XBB.2.3 variant,

(v) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant, or

(vi) a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

149. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

150. The composition of claim 159, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

151. The composition of claim 149, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

152. The composition of any one of claims 149 to 151, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

153. The composition of any one of claims 149 to 152, wherein the modified uridines are each N1-methyl-pseudouridine.

154. The composition of any one of claims 149 to 153, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG.

155. The composition of any one of claims 149 to 164, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

156. The composition of claim 155, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

157. The composition of claim 156, wherein the poly-A sequence comprises SEQ ID NO: 14.

158. The composition of any one of claims 159 to 157, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72.

159. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

160. The composition of claim 159, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

161. The composition of claim 159, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

162. The composition of any one of claims 159 to 161, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

163. The composition of any one of claims 159 to 162, wherein the modified uridines are each N1-methyl-pseudouridine.

164. The composition of any one of claims 159 to 163, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$.

165. The composition of any one of claims 159 to 164, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

166. The composition of claim 165, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

167. The composition of claim 166, wherein the poly-A sequence comprises SEQ ID NO: 14.

168. The composition of any one of claims 159 to 167, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

169. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

170. The composition of claim 169, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

171. The composition of claim 169, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

172. The composition of any one of 169 to 171, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

173. The composition of any one of claims 169 to 172, wherein the modified uridines are each N1-methyl-pseudouridine.

174. The composition of any one of claims 169 to 173, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

175. The composition of any one of claims 169 to 174, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‵ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

176. The composition of claim 175, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

177. The composition of 176, wherein the poly-A sequence comprises SEQ ID NO: 14.

178. The composition of any one of claims 169 to 177, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

179. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 7 and comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 9, and

the second RNA encodes the polypeptide of SEQ ID NO: 101 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

180. The composition of claim 179, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

181. The composition of claim 179, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

182. The composition of any one of claims 179 to 182, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

183. The composition of any one of claims 179 to 182, wherein the modified uridines are each N1-methyl-pseudouridine.

184. The composition of any one of claims 179 to 183, wherein the 5′ cap comprises $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$.

185. The composition of any one of claims 179 to 184, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

186. The composition of claim 185, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

187. The composition of claim 186, wherein the poly-A sequence comprises SEQ ID NO: 14.

188. The composition of any one of claims 179 to 187, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 20; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

189. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 158 and comprises the nucleotide sequence of SEQ ID NO: 159 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least

92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 159, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

190. The composition of claim 189, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

191. The composition of claim 189, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

192. The composition of any one of claims 189 to 191, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

193. The composition of any one of claims 189 to 192, wherein the modified uridines are each N1-methyl-pseudouridine.

194. The composition of any one of claims 189 to 193, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG.

195. The composition of any one of claims 189 to 194, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

196. The composition of claim 195, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

197. The composition of claim 196, wherein the poly-A sequence comprises SEQ ID NO: 14.

198. The composition of any one of claims 189 to 197, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 161.

199. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 85 and comprises the nucleotide sequence of SEQ ID NO: 86 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 86, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

200. The composition of claim 199, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

201. The composition of claim 200, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

202. The composition of any one of claims 199 to 201, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

203. The composition of any one of claims 199 to 202, wherein the modified uridines are each N1-methyl-pseudouridine.

204. The composition of any one of claims 199 to 203, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG.

205. The composition of any one of claims 199 to 204, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3′ untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

206. The composition of claim 205, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

207. The composition of claim 206, wherein the poly-A sequence comprises SEQ ID NO: 14.

208. The composition of any one of claims 199 to 207, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 88.

209. A composition comprising a first RNA and a second RNA, wherein:

the first RNA encodes the polypeptide of SEQ ID NO: 69 and comprises the nucleotide sequence of SEQ ID NO: 70 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 70, and

the second RNA encodes the polypeptide of SEQ ID NO: 100 and comprises the nucleotide sequence of SEQ ID NO: 101 or a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 101, and

wherein each of the first RNA and the second RNA comprise:

(a) modified uridines; and

(b) a 5′ cap, and

wherein the first RNA and the second RNA are formulated in lipid nanoparticles (LNPs), wherein the LNPs comprise a cationically ionizable lipid, a neutral lipid, a sterol and a polymer-lipid conjugate.

210. The composition of claim 209, wherein the first RNA and the second RNA are formulated in the same lipid nanoparticles.

211. The composition of claim 209, wherein the first RNA and the second RNA are formulated in separate lipid nanoparticles.

212. The composition of any one of claims 209 to 211, wherein each of the first RNA and the second RNA include modified uridines in place of all uridines.

213. The composition of any one of claims 209 to 212, wherein the modified uridines are each N1-methyl-pseudouridine.

214. The composition of any one of claims 207 to 213, wherein the 5′ cap comprises $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$.

215. The composition of any one of claims 209 to 214, wherein the first RNA and the second RNA each independently comprise at least one, at least two, or all of the following features:

a 5‘ untranslated region (UTR) comprising SEQ ID NO: 12;

a 3' untranslated region (UTR) comprising SEQ ID NO: 13; and

a poly-A sequence of at least 100 A nucleotides.

216. The composition of claim 215, wherein the poly-A sequence comprises 30 adenine nucleotides followed by 70 adenine nucleotides, wherein the 30 adenine nucleotides and 70 adenine nucleotides are separated by a linker sequence.

217. The composition of claim 216, wherein the poly-A sequence comprises SEQ ID NO: 14.

218. The composition of any one of claims 207 to 217, wherein:

the first RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 72; and

the second RNA molecule comprises a nucleotide sequence that is at least 80% (e.g., at 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 97%, at least 98%, or 99% or higher) identical to SEQ ID NO: 103.

219. The composition of any one of claims 16 to 218, which is formulated as a liquid, a solid, or a combination thereof.

220. The composition of any one of claims 16 to 219, which is formulated for injection.

221. The composition of claim 220, which is formulated for intramuscular administration.

222. The composition of any one of claims 16 to 221, wherein the RNA is mRNA or saRNA.

223. The composition of any one of claims 16 to 222, which is a pharmaceutical composition.

224. The composition of claim 223, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

225. The composition of any one of claims 16 to 224, which is a vaccine.

226. A method of eliciting an immune response in a subject, comprising administering the composition of any one of claims 1 to 225.

227. The method of claim 226, wherein the immune response is elicited against an Omicron variant of SARS-CoV-2.

228. The method of claim 227, wherein the immune response is elicited against a Wuhan strain, an Omicron variant, a Beta variant, an Alpha variant, and a Delta variant of SARS-CoV-2.

229. The method of any one of claims 226 to 228, wherein the subject has not been previously infected with and/or has not been previously administered a SARS-CoV-2 vaccine.

230. The method of any one of claims 226 to 229, wherein the subject has previously been infected with SARS-CoV-2 and/or has been previously administered a SARS-CoV-2 vaccine.

231. The method of any one of claims 226 to 230, wherein the subject has previously received a vaccine that delivers a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

232. The method of claim 231, wherein the subject has previously been administered RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., a full length protein or an antigenic fragment thereof).

233. The method of claim 232, wherein the subject has previously been administered two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain.

234. The method of any one of claims 226 to 233, wherein the subject has previously been administered:

(i) two or more doses of RNA encoding a SARS-CoV-2 S protein of a Wuhan strain (e.g., BNT162b2); and

(ii) one or more doses of a bivalent vaccine comprising:

(a) a first RNA comprising a nucleotide sequence encoding a SARS-CoV-2 S protein of a Wuhan strain; and

(b) a second RNA comprising a nucleoside sequence encoding a SARS-CoV-2 S protein of an Omicron BA.4/5 variant.

235. The method of claim 234, wherein the first RNA comprises a nucleotide sequence of that is at least 90% identical to that set forth in SEQ ID NO: 20 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical), and the second RNA comprises a nucleotide sequence that is at least 90% identical to that set forth in SEQ ID NO: 72 (e.g., at least 95% identical, at least 96% identical, at least 97% identical, at least 99% identical, or 100% identical).

236. The method of any one of claims 226 to 235, wherein the composition of any one of claims 1 to 210 comprises about 3 μg to about 30 μg of RNA (e.g., about 3 μg, about 10 μg, or about 30 μg of RNA).

237. The method of claim 236, wherein the composition of any one of claims 1 to 225 comprises about 3 μg of RNA, and the subject is about 6 months to less than about 5 years old.

238. The method of claim 237, wherein the composition of any one of claims 1 to 225 comprises about 10 μg of RNA, and the subject is about 5 years old to less than about 12 years old.

239. The method of claim 238, wherein the composition of any one of claims 1 to 225 comprises about 30 μg of RNA, and the subject is about 12 years or older.

240. The method of any one of claims 226 to 239, where in the composition of any one of claims 1 to 225 is co-administered with one or more vaccines against a non-SARS-CoV-2 disease (e.g., a non-SARS-CoV-2 respiratory disease).

241. The method of claim 240, wherein the one or more vaccines against a non-SARS-CoV-2 disease comprises an influenza vaccine, an RSV vaccine, or a combination thereof.

242. A kit comprising the composition of any one of claims 1 to 225.

243. The kit of claim 242, further comprising instructions for use of the composition for inducing an immune response against coronavirus in a subject.

244. The composition of any one of claims 1 to 225, for pharmaceutical use.

245. The composition of claim 244, wherein the pharmaceutical use comprises inducing an immune response against coronavirus in a subject.

246. The composition of claim 244 or 245, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus infection.

247. The composition of any one of claims 16 to 210, which is for administration to a human.

248. The composition of claim 245 or 246, wherein the coronavirus is a betacoronavirus.

249. The composition of any one of claims 245, 246, or 248, wherein the coronavirus is a sarbecovirus.

250. The composition of any one of claims 245, 246, 248, or 249, wherein the coronavirus is SARS-CoV-2.

251. The method of any one of claims 226 to 241, wherein the subject is a human.

252. The method of any one of claims 226 to 251, wherein the immune response is induced against a coronavirus.

253. The method of claim 252, wherein the coronavirus is a betacoronavirus.

254. The method of claim 253, wherein the betacoronavirus is a sarbecovirus.

255. The method of any one of claims 251 to 254, wherein the coronavirus is SARS-CoV-2.

256. The composition of any one of claims 1 to 9 or 16 to 225, for pharmaceutical use.

257. The composition of claim 256, wherein the pharmaceutical use comprises inducing an immune response against coronavirus in a subject.

258. The composition of claim 256 or 257, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a coronavirus infection.

259. The composition of claim 257 or 258, wherein the coronavirus is a betacoronavirus.

260. The composition of claim 259, wherein the betacoronavirus is a sarbecovirus.

261. The composition of claim 260, wherein the sarbecovirus is a SARS-CoV-2 virus.

262. Use of the composition of any one of claims 1 to 9 or 16 to 225 for the manufacture of a medicament for inducing an immune response against coronavirus in a subject.

263. The use of claim 262, wherein the medicament is for therapeutic or prophylactic treatment of a coronavirus infection.

264. The use of claim 262 or 263, wherein the coronavirus is a betacoronavirus.

265. The composition of claim 264, wherein the betacoronavirus is a sarbecovirus.

266. The composition of claim 265, wherein the sarbecovirus is a SARS-CoV-2 virus.

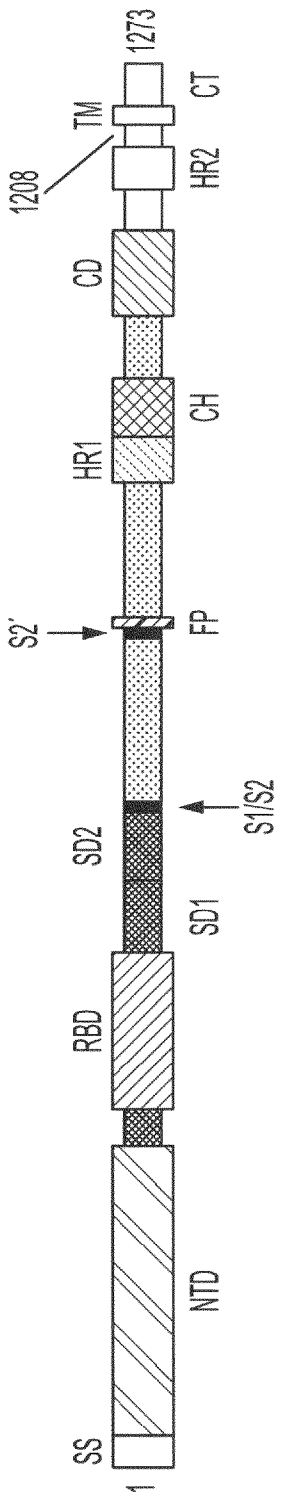
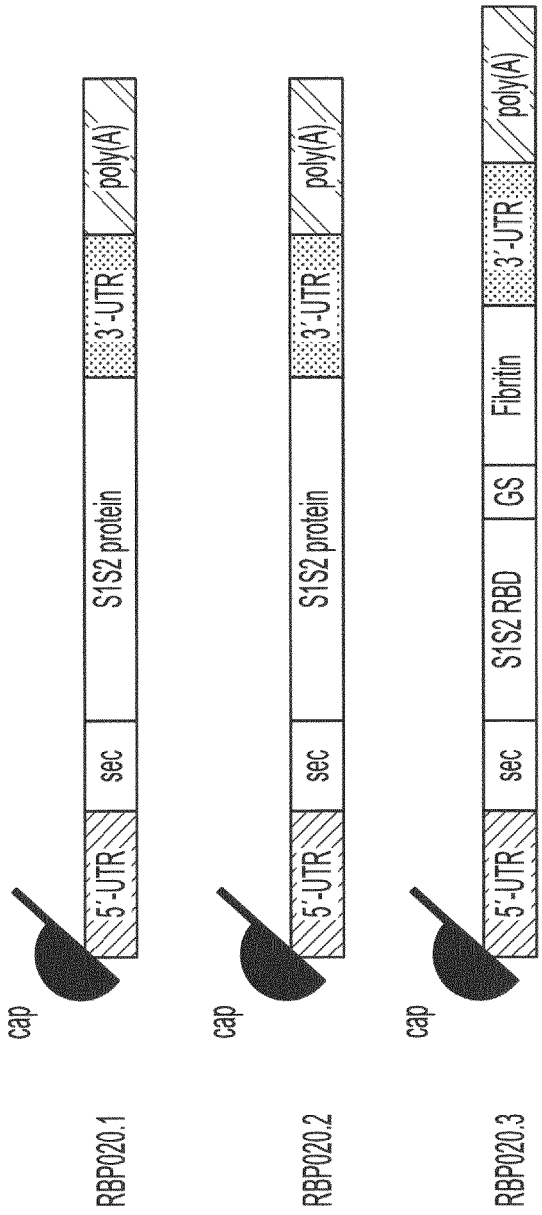


Figure 1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3'-UTR
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cap
5'-UTR
sec
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3'-UTR
poly(A)
RBP020.2
cap
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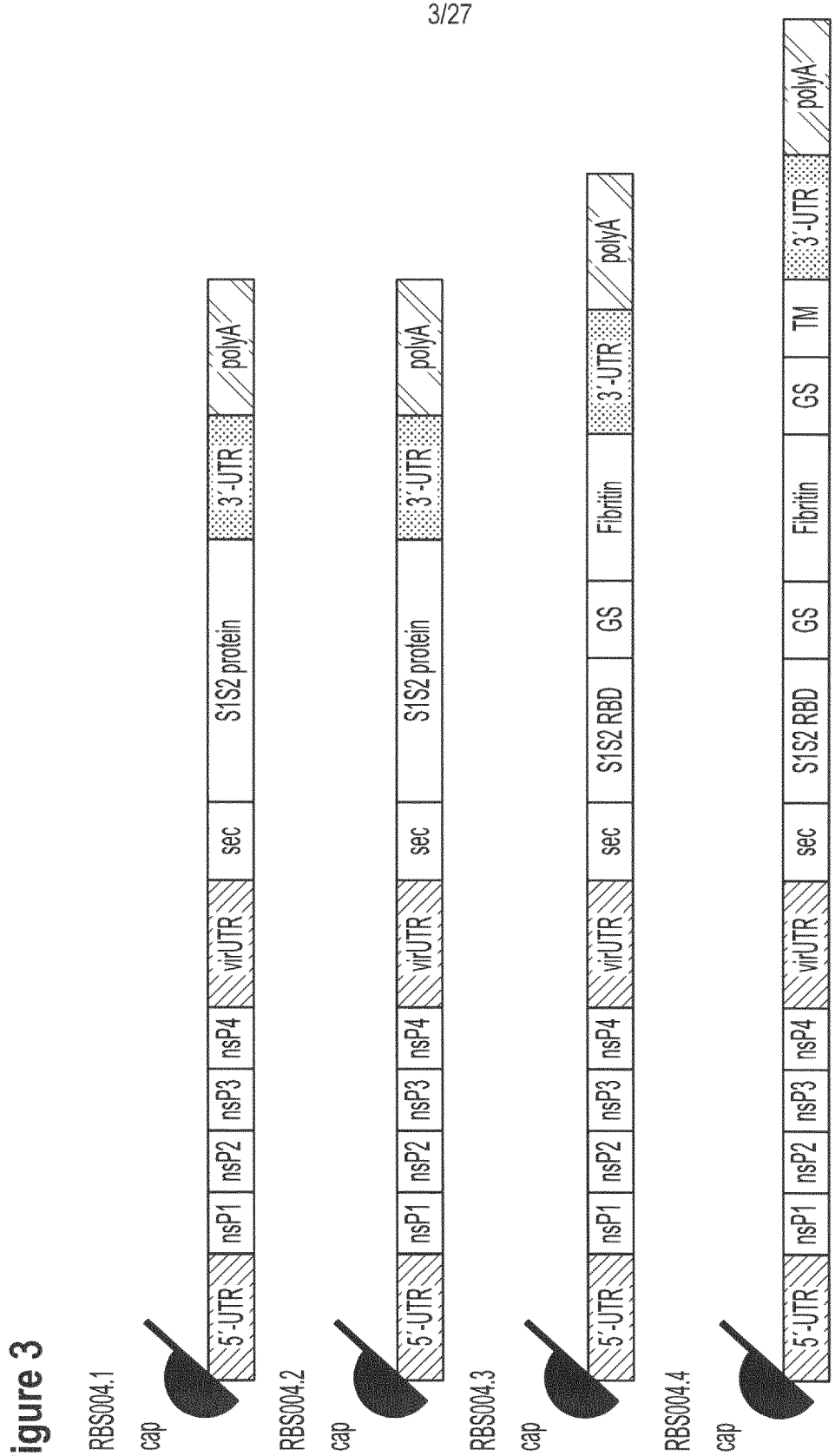
sec
S1S2 RBD
GS
Fibritin
3'-UTR
poly(A)
RBP020.3

Figure 2

Figure 3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nsP1
nsP2
nsP3
nsP4
virUTR
sec
S1S2 protein
3´-UTR
polyA
RBS004.3
cap
5´-UTR
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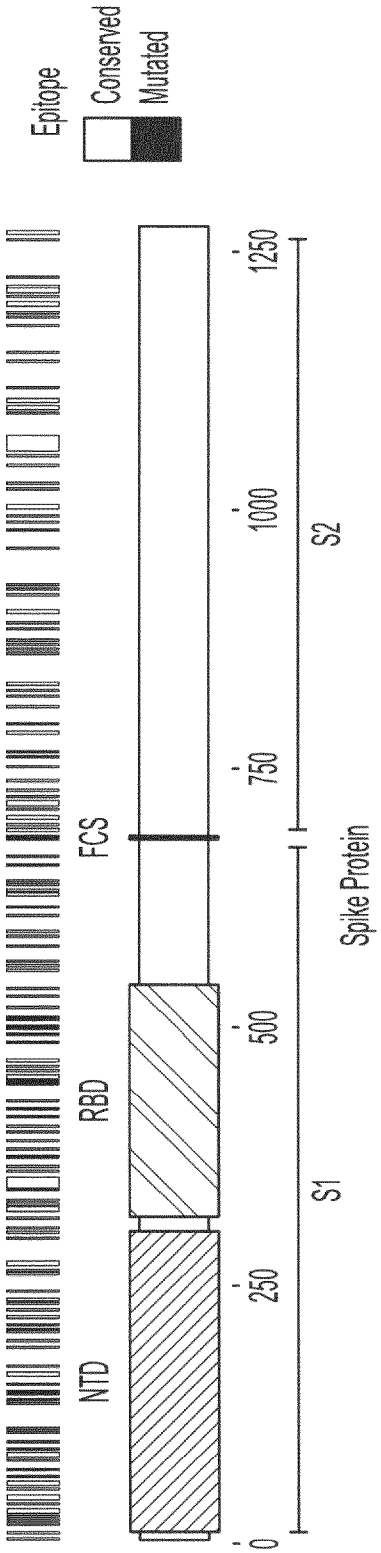
nsP3
nsP4
virUTR
sec
S1S2 RBD
GS
Fibritin
3´-UTR
polyA
RBS004.4
cap
5´-UTR
nsP1
nsP2
nsP3
nsP4
virUTR
sec
S1S2 RBD
GS
Fibritin
GS
TM
3´-UTR
polyA

Figure 4

HLA-Allele	No of MHC-I epitopes*	No. of epitopes affected by mutations in different VOCs				
		Alpha	Beta	Gamma	Delta	Omicron
A*01:01	1	0	0	0	0	0
A*02:01	2	0	0	0	0	0
A*03:01	**2**	0	0	0	0	**1**
A*11:01	2	0	0	0	0	0
A*24:02	**5**	0	0	0	**1**	**1**
A*26:01	2	0	0	0	0	0
A*29:02	1	0	0	0	0	**1**
A*68:01	4	0	0	0	0	**1**
B*07:02	1	0	0	0	0	0
B*15:01	**3**	**1**	**2**	**1**	**1**	**2**
B*35:01	6	0	0	0	0	0
C*03:03	1	0	0	0	0	0
C*04:01	1	0	0	0	0	0
Total affected **Total unaffected**	31	**1 (4%)** **30 (96%)**	**2 (7%)** **26 (93%)**	**1 (4%)** **30 (96%)**	**2 (7%)** **26 (93%)**	**6 (22%)** **25 (78%)**

Figure 5


Epitope
Conserved
Mutated
NTD
RBD
FCS
0
250
500
750
1000
1250
S1
S2
Spike Protein

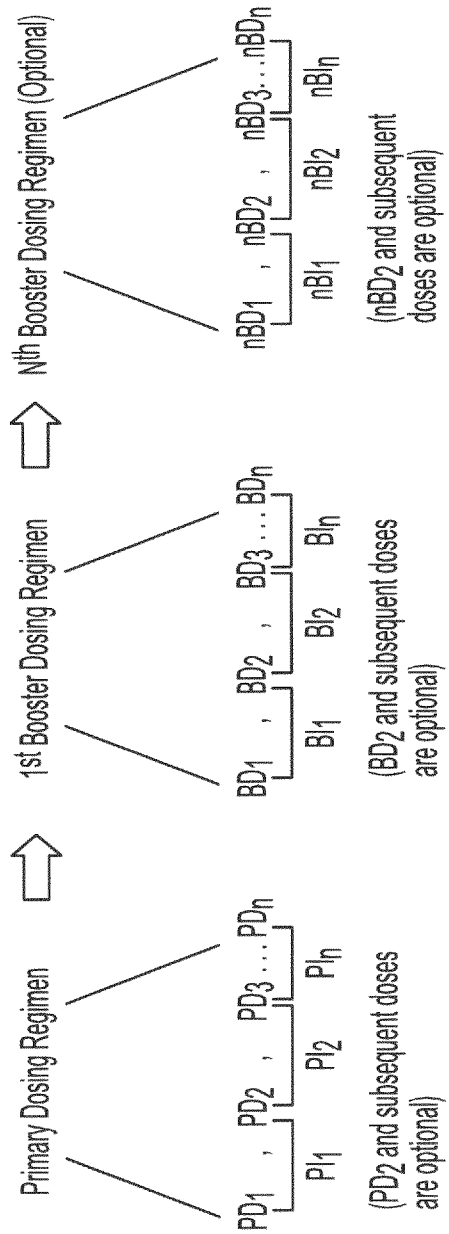

Primary Dosing Regimen
1st Booster Dosing Regimen
Nth Booster Dosing Regimen (Optional)
PD1 , PD2 , PD3 ....PDn
PI1 PI2 PIn
(PD2 and subsequent doses are optional)
BD1 , BD2 , BD3 ....BDn
BI1 BI2 BIn
(BD2 and subsequent doses are optional)
nBD1 , nBD2 , nBD3...nBDn
nBI1 nBI2 nBIn
(nBD2 and subsequent doses are optional)

Figure 6

Figure 7

RBD
Wuhan WT strain
VOD ALPHA
VOC DELTA
VOC OMICRON BA.1
VOC OMICRON BA.4/5

```
301  CTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASV
301  CTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASV
301  CTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASV
301  CTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFDEVFNATRFASV
301  CTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFDEVFNATRFASV

351  YAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSF
351  YAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSF
351  YAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSF
351  YAWNRKRISNCVADYSVLYNLAPFFTFKCYGVSPTKLNDLCFTNVYADSF
351  YAWNRKRISNCVADYSVLYNFAPFFAFKCYGVSPTKLNDLCFTNVYADSF

401  VIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN
401  VIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN
401  VIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYN
401  VIRGDEVRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVSGNYN
401  VIRGNEVSQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNKLDSKVGGNYN

451  YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPT
451  YLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPT
451  YRYRLFRKSNLKPFERDISTEIYQAGSKPCNGVEGFNCYFPLQSYGFQPT
451  YLYRLFRKSNLKPFERDISTEIYQAGNKPCNGVAGVNCYFPLRSYSFRPT
451  YRYRLFRKSNLKPFERDISTEIYQAGNKPCNGVAGVNCYFPLQSTGFRPT

501  NGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTG
501  YGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTG
501  NGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTG
501  YGVGHQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLKGTG
501  YGVGHQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTG
```

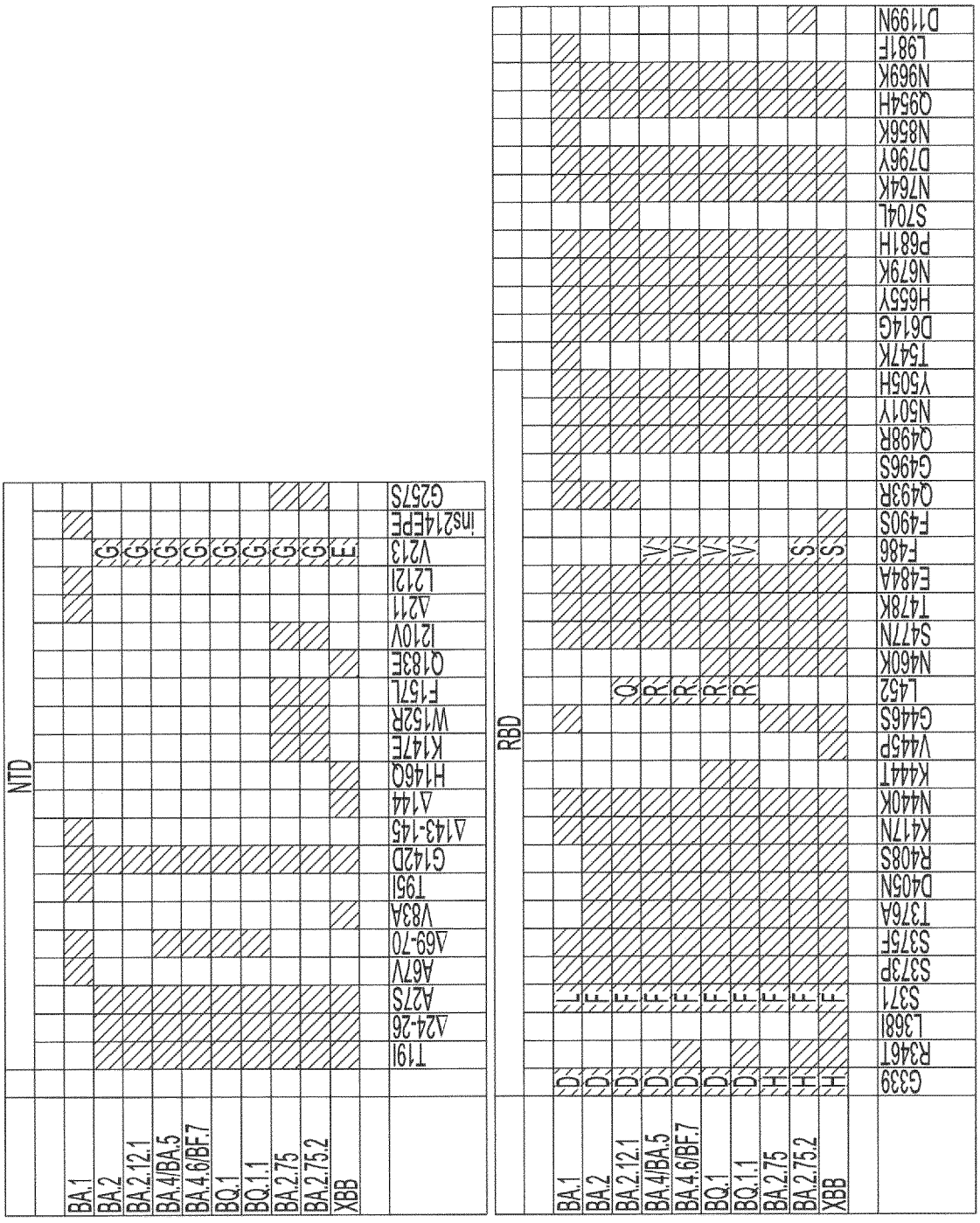

NTD
T19I
Δ24-26
A27S
A67V
Δ69-70
V83A
T95I
G142D
Δ143-145
Δ144
H146Q
K147E
W152R
F157L
Q183E
I210V
Δ211
L212I
V213
ins214EPE
G257S
RBD
G339
R346T
L368I
S371
S373P
S375F
T376A
D405N
R408S
K417N
N440K
K441T
V445P
G446S
L452
N460K
S477N
T478K
E484A
F486
F490S
Q493R
G496S
Q498R
N501Y
Y505H
T547K
D614G
H655Y
N679K
P681H
S704L
N764K
D796Y
N856K
Q954H
N969K
L981F
D1199N
BA.1
BA.2
BA.2.12.1
BA.4/BA.5
BA.4.6/BF.7
BQ.1
BQ.1.1
BA.2.75
BA.2.75.2
XBB

Figure 8

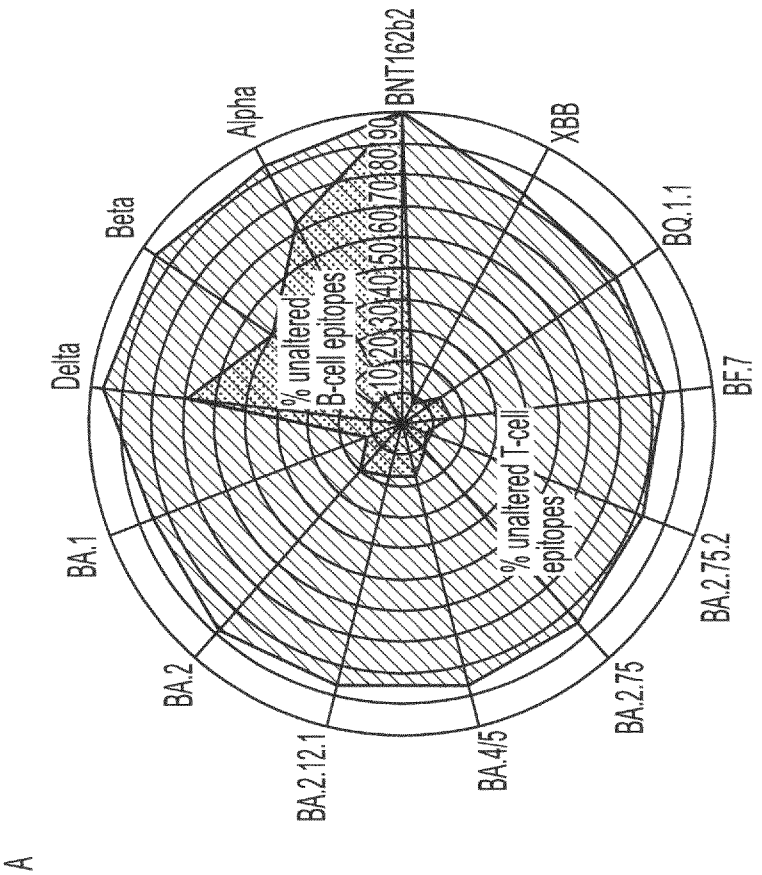

A
BNT162b2
Alpha
Beta
Delta
BA.1
BA.2
BA.2.12.1
BA.4/5
BA.2.75
BA.2.75.2
BF.7
BQ.1.1
XBB
% unaltered B-cell epitopes
10
20
30
40
50
60
70
80
90
% unaltered T-cell epitopes

Figure 9

Figure 9 (Continued)

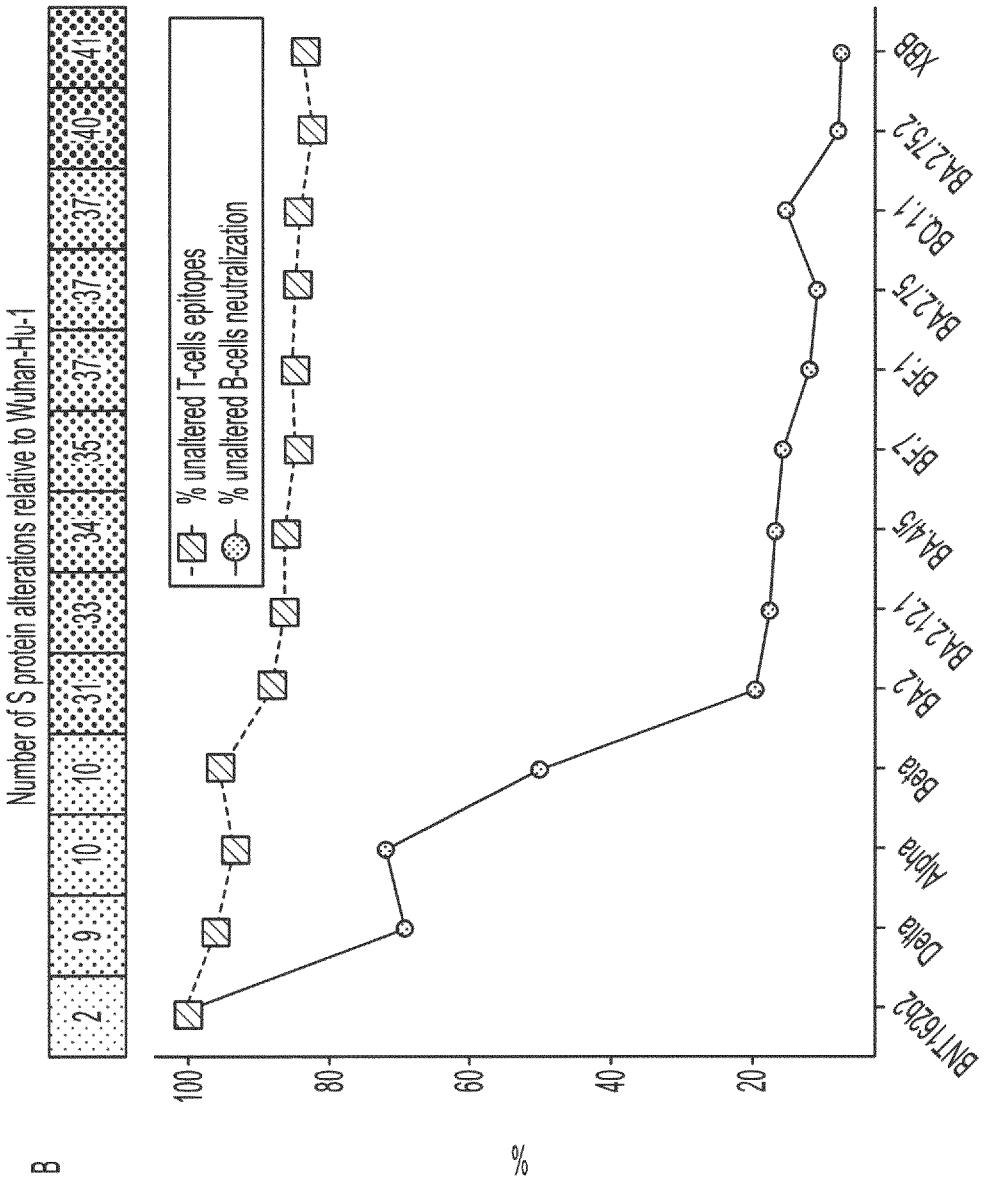
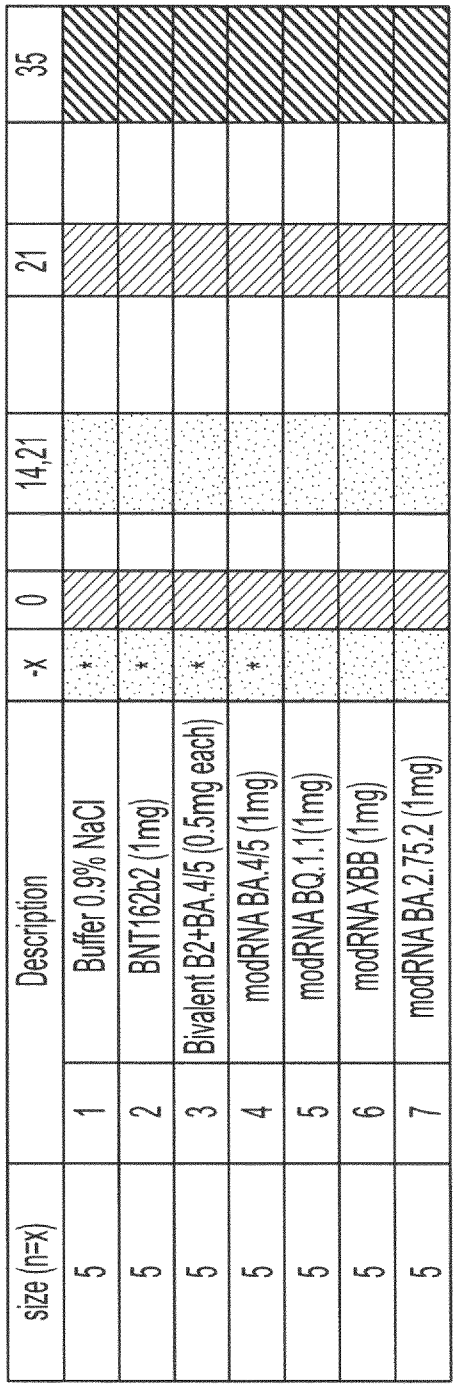


Figure 10



size (n=x)		Description	-x	0	14,21	21	35
5	1	Buffer 0.9% NaCl	*				
5	2	BNT162b2 (1mg)	*				
5	3	Bivalent B2+BA.4/5 (0.5mg each)	*				
5	4	modRNA BA.4/5 (1mg)	*				
5	5	modRNA BQ.1.1(1mg)					
5	6	modRNA XBB (1mg)					
5	7	modRNA BA.2.75.2 (1mg)					

Figure 11

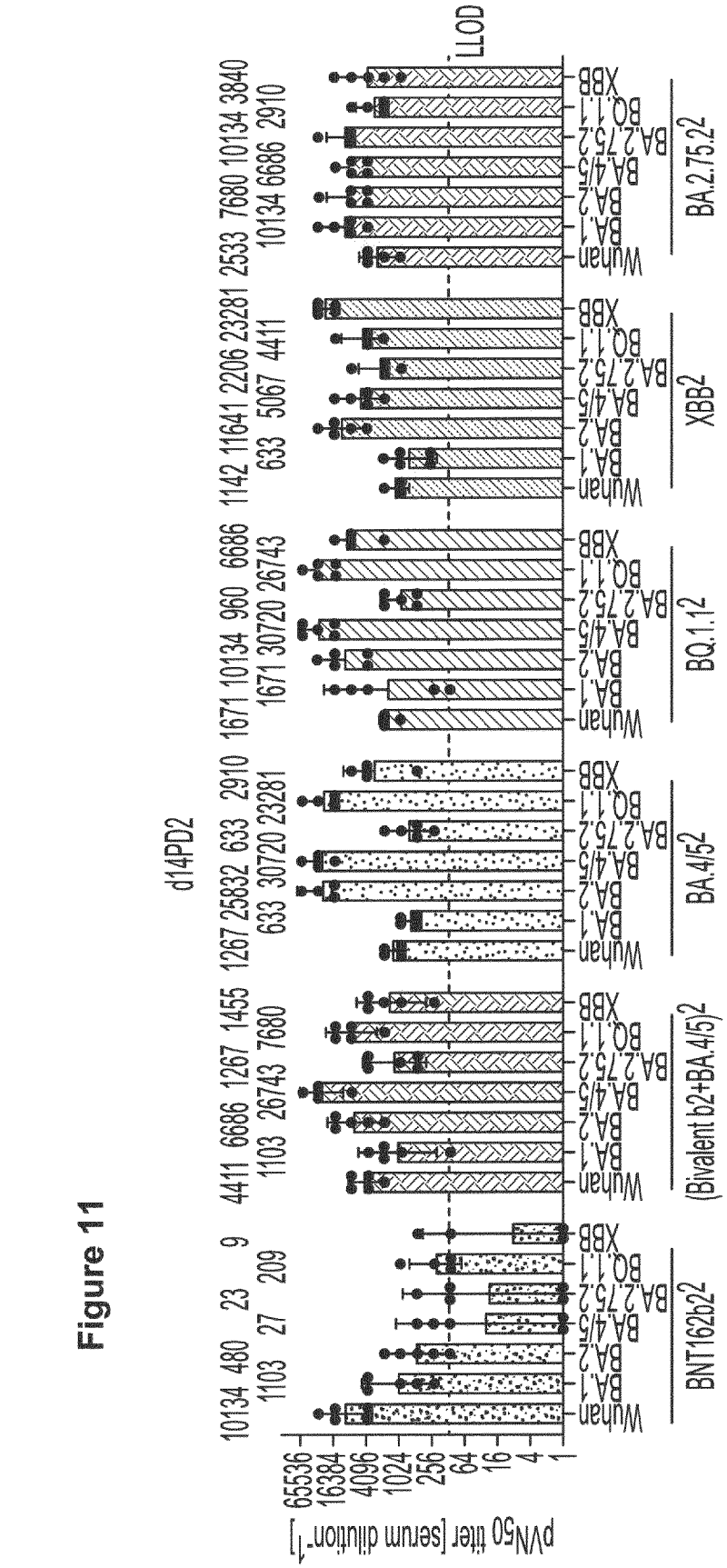

d14PD2
pVN50 titer [serum dilution-1]
65536
16384
4096
1024
256
64
16
4
1
LLOD
10134 480 23 9 4411 6686 1267 1455 1267 25832 633 2910 1671 10134 960 6686 1142 11641 2206 23281 2533 7680 10134 3840
1103 27 209 1103 26743 7680 633 30720 23281 1671 30720 26743 633 5067 4411 10134 6686 2910
Wuhan
BA.1
BA.2
BA.4/5
BA.2.75.2
BQ.1.1
XBB
BNT162b2 2
(Bivalent b2+BA.4/5) 2
BA.4/5 2
BQ.1.1 2
XBB 2
BA.2.75.2 2

Figure 12

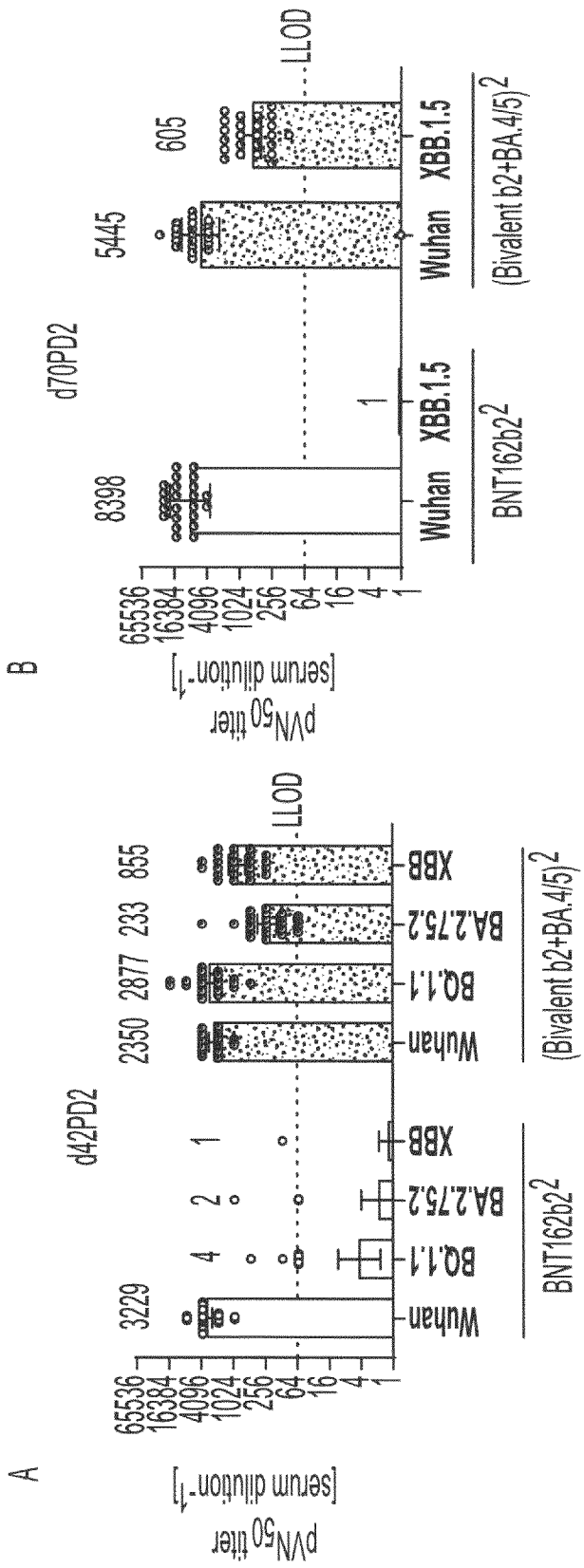

A
pVN50 titer [serum dilution-1]
65536
16384
4096
1024
256
64
16
4
1
d42PD2
3229
4
2
1
2350
2877
233
855
LLOD
Wuhan
BQ.1.1
BA.2.75.2
XBB
Wuhan
BQ.1.1
BA.2.75.2
XBB
BNT162b2 2
(Bivalent b2+BA.4/5) 2
B
pVN50 titer [serum dilution-1]
65536
16384
4096
1024
256
64
16
4
1
d70PD2
8398
1
5445
605
LLOD
Wuhan
XBB.1.5
Wuhan
XBB.1.5
BNT162b2 2
(Bivalent b2+BA.4/5) 2

Figure 12 (Continued)

C

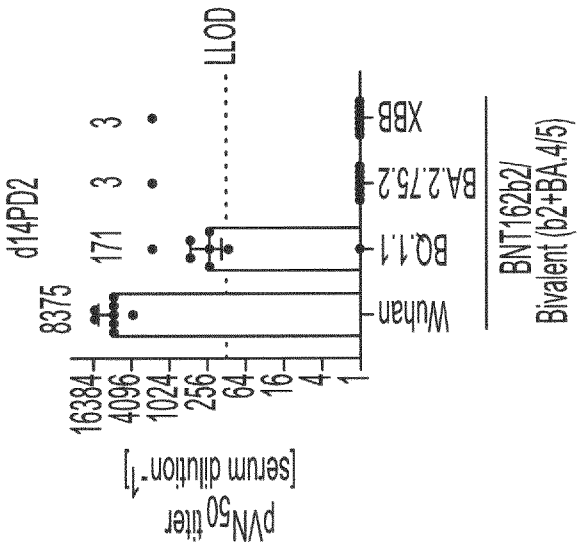
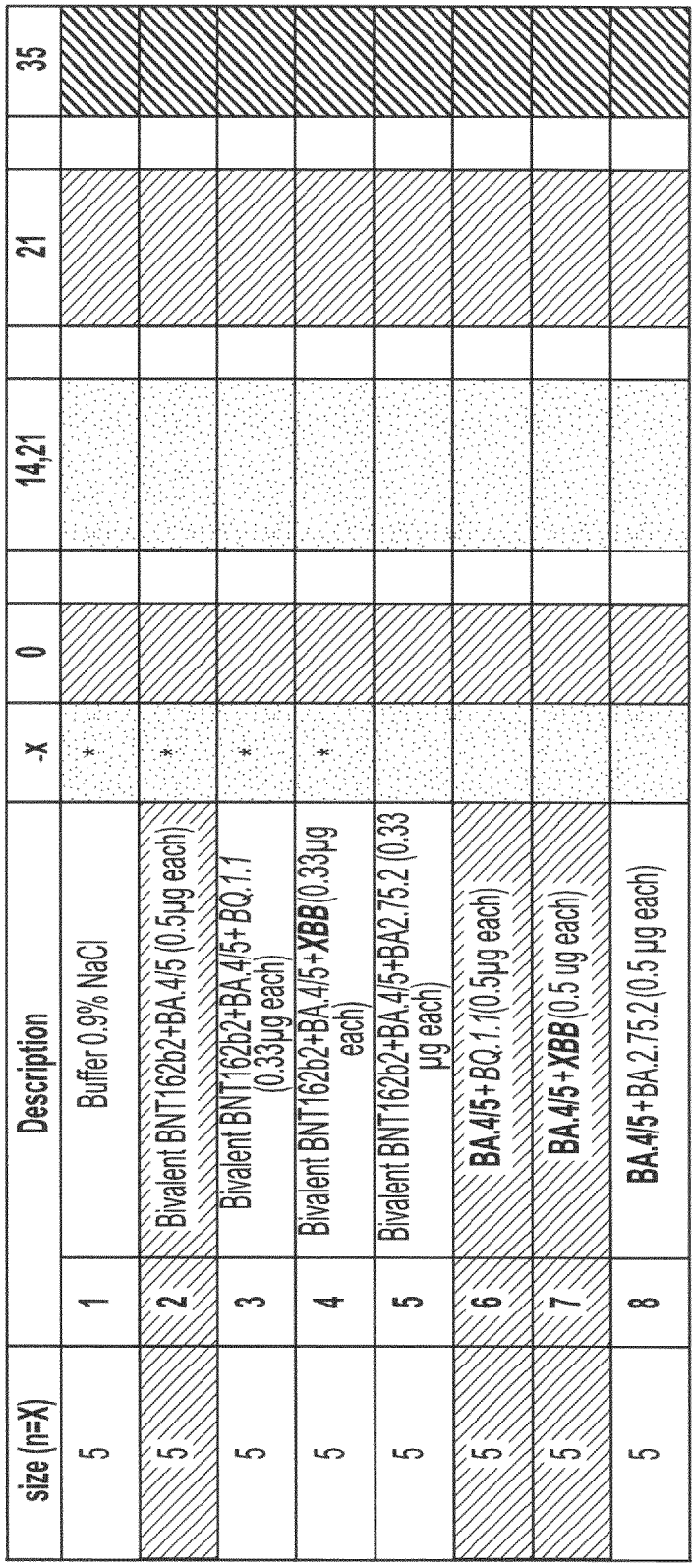


Figure 13



size (n=X)		Description	-X	0		14,21		21		35
5	1	Buffer 0.9% NaCl	*							
5	2	Bivalent BNT162b2+BA.4/5 (0.5µg each)	*							
5	3	Bivalent BNT162b2+BA.4/5+*BQ.1.1* (0.33µg each)	*							
5	4	Bivalent BNT162b2+BA.4/5+**XBB** (0.33µg each)	*							
5	5	Bivalent BNT162b2+BA.4/5+BA2.75.2 (0.33 µg each)								
5	6	**BA.4/5**+*BQ.1.1* (0.5µg each)								
5	7	**BA.4/5**+**XBB** (0.5 ug each)								
5	8	**BA.4/5**+BA.2.75.2 (0.5 µg each)								

Figure 14

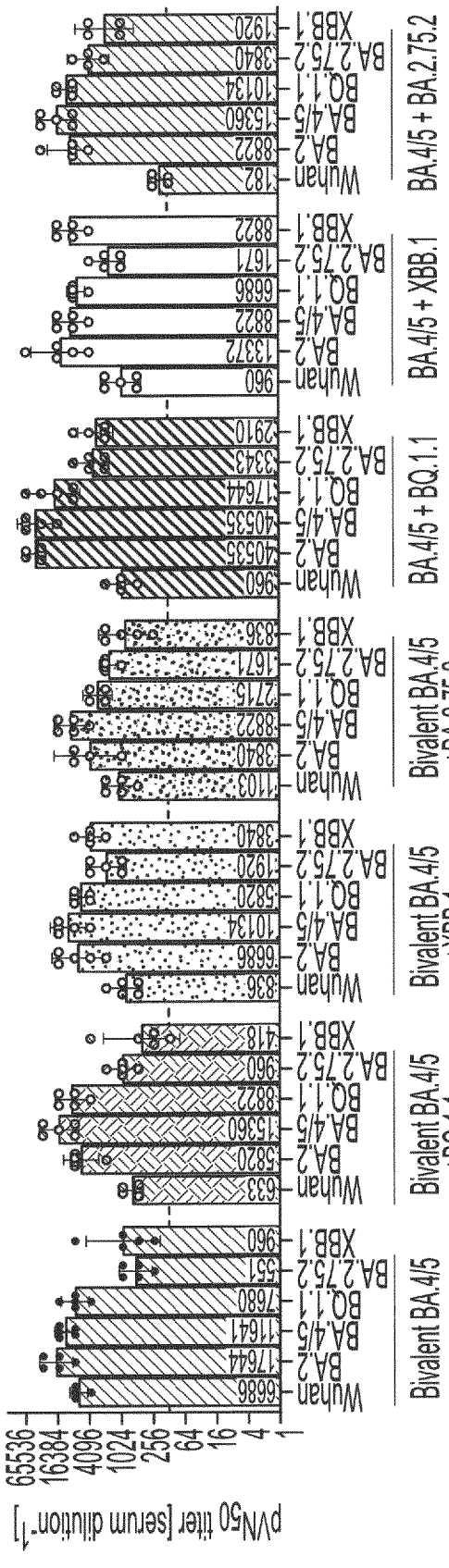
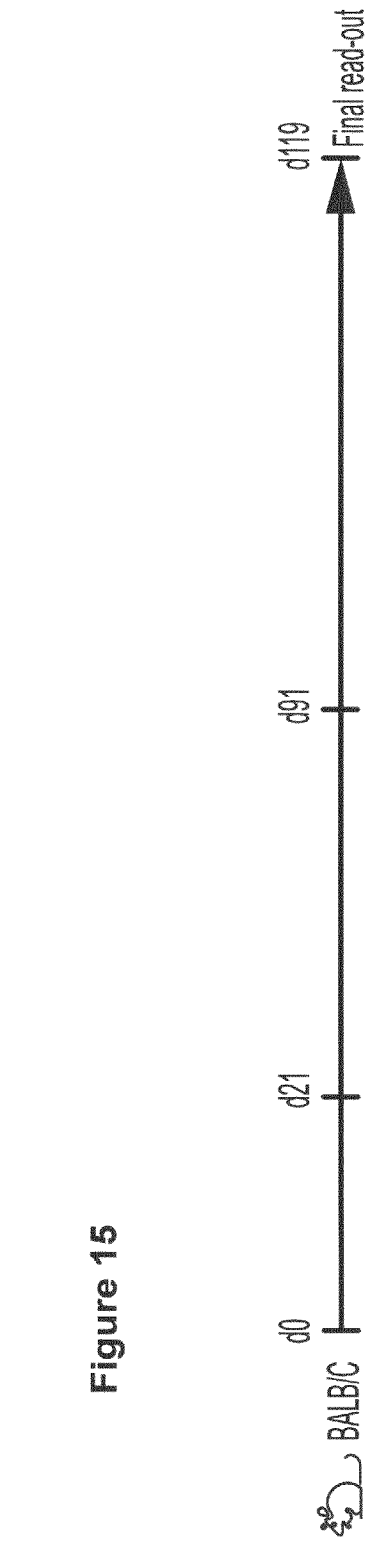
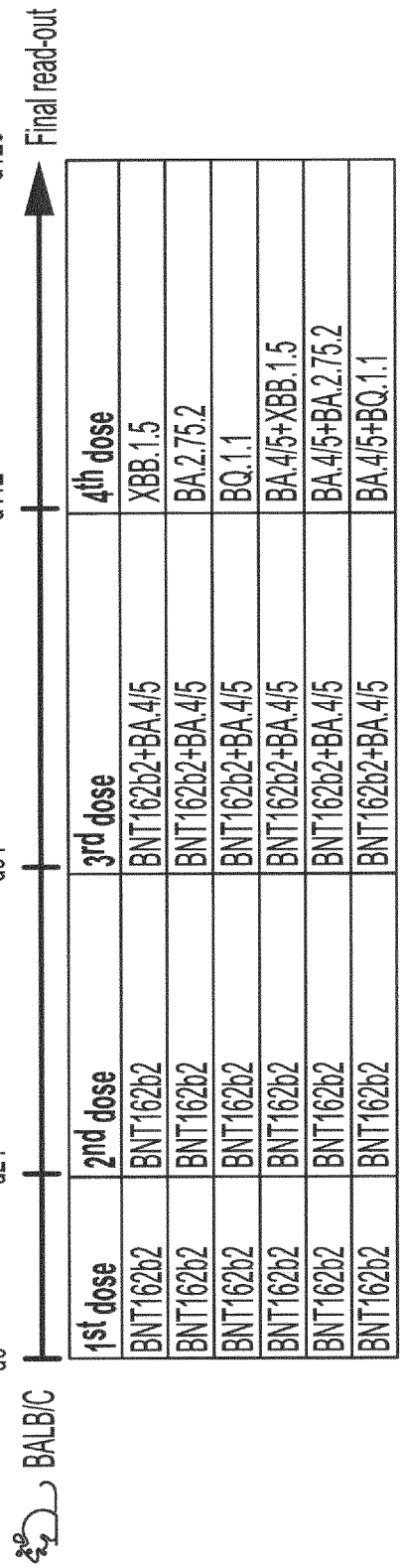

14 days post-boost
pVN50 titer [serum dilution-1]
65536
16384
4096
1024
256
64
16
4
1
Wuhan
BA.2
BA.4/5
BQ.1.1
BA.2.75.2
XBB.1
Bivalent BA.4/5
Bivalent BA.4/5 +BQ.1.1
Bivalent BA.4/5 +XBB.1
Bivalent BA.4/5 +BA.2.75.2
BA.4/5 + BQ.1.1
BA.4/5 + XBB.1
BA.4/5 + BA.2.75.2
6686
17644
11641
7680
551
960
633
5820
15360
8822
960
418
836
6686
10134
5820
1920
3840
1103
3840
8822
2715
1671
836
960
40535
40535
17644
3343
2910
960
13372
8822
6686
1671
8822
182
8822
15360
10134
3840
1920

Figure 15



1st dose	2nd dose	3rd dose
BNT162b2	BNT162b2+BA.4/5	BNT162b2+BA.4/5
BNT162b2	BNT162b2+BA.4/5	XBB.1.5
BNT162b2	BNT162b2+BA.4/5	BA.2.75.2
BNT162b2	BNT162b2+BA.4/5	BQ.1.1
BNT162b2	BNT162b2+BA.4/5	BNT162b2+BA.4/5+XBB.1.5
BNT162b2	BNT162b2+BA.4/5	BNT162b2+BA.4/5+BA.2.75.2
BNT162b2	BNT162b2+BA.4/5	BA.4/5+XBB.1.5
BNT162b2	BNT162b2+BA.4/5	BA.4/5+BA.2.75.2
BNT162b2	BNT162b2+BA.4/5	BA.4/5+BQ.1.1

Figure 16



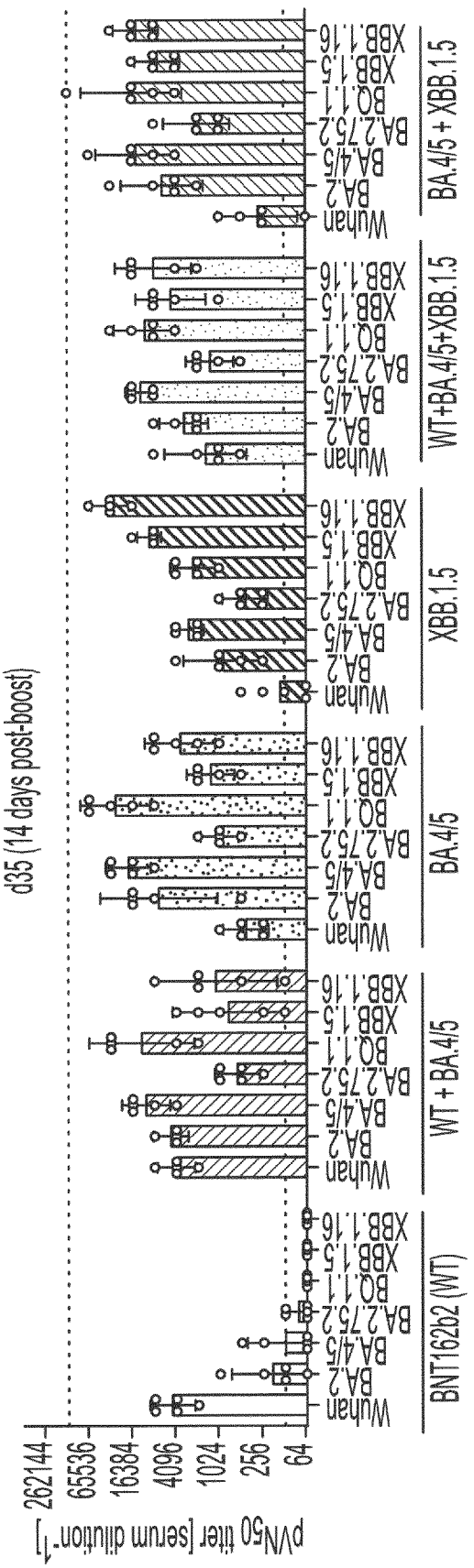
1st dose	2nd dose	3rd dose	4th dose
BNT162b2	BNT162b2	BNT162b2+BA.4/5	XBB.1.5
BNT162b2	BNT162b2	BNT162b2+BA.4/5	BA.2.75.2
BNT162b2	BNT162b2	BNT162b2+BA.4/5	BQ.1.1
BNT162b2	BNT162b2	BNT162b2+BA.4/5	BA.4/5+XBB.1.5
BNT162b2	BNT162b2	BNT162b2+BA.4/5	BA.4/5+BA.2.75.2
BNT162b2	BNT162b2	BNT162b2+BA.4/5	BA.4/5+BQ.1.1

Figure 17

Vaccine dose: monovalent (1 mg); bivalent (0.5 mg + 0.5 mg)
5 groups of mice; 5 mice per group, 1 group received saline in place of vaccinations.
Pseudovirus neutralization on sera collected at day 35 (final bleed).

Figure 18

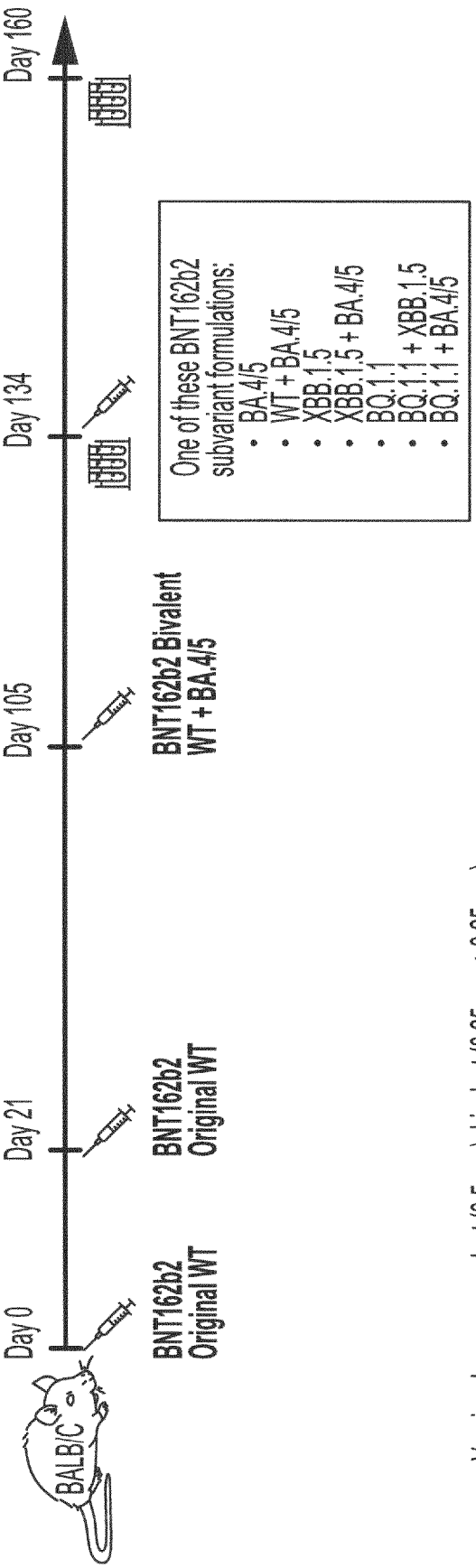
A



B

	Pseudovirus						
2 doses vaccine	Wuhan	BA.2	BA.4/5	BA.2.75.2	BQ.1.1	XBB.1.5	XBB.1.16
WT	44111	182	120	79	60	60	60
WT+BA.4/5	3840	4567	10134	551	11641	728	1103
BA.4/5	418	6686	17644	960	26743	1267	3343
XBB.1.5	1383	836	2533	418	2206	8822	30720
WT+BA.4/5 + XBB.1.5	1455	2910	11641	1267	10134	4411	7680
BA.4/5 + XBB.1.5	2761	5820	13372	1920	15360	6686	13372

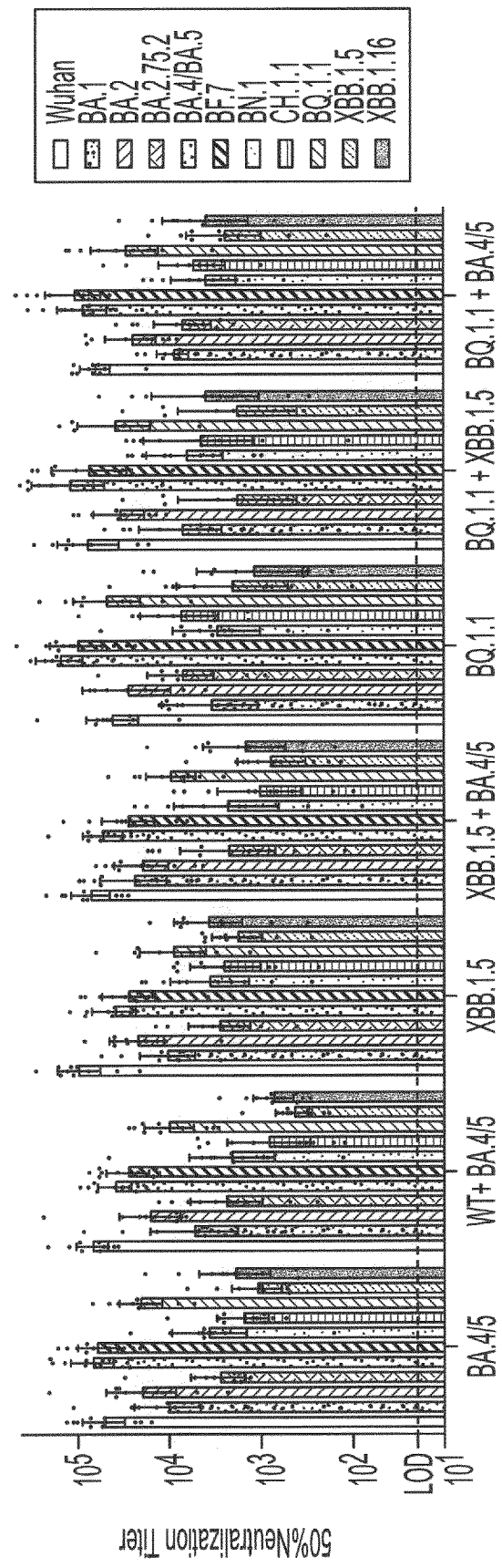
Figure 19



Vaccine dose: monovalent (0.5 mg); bivalent (0.25 mg + 0.25 mg)
8 groups of mice; 10 mice per group, 1 group received saline in place of vaccinations.
Pseudovirus neutralization on sera collected at bleed timepoints; T cell and B cell analysis from lymph nodes/spleen at terminal timepoint.

Figure 20

A



B

4th Dose Vaccine	Wuhan	Omicron								
		BA.1	BA.2	BA.2.75.2	BA.4/BA.5	BF.7	BN.1	CH.1.1	BQ.1.1	XBB.1.5	XBB.1.16
BNT162b2 BA.4/5	54379	10793	20741	2963	71457	63209	3745	1589	21297	1120	1831
BNT162b2 WT+ BA.4/5	71748	5374	16799	2448	40689	28425	2100	835	10138	444	733
BNT162b2 XBB.1.5	100108	10685	22796	2832	41055	28248	3692	2480	9243	1800	3766
BNT162b2 BA.4/5 +XBB.1.5	74398	25025	20254	2288	54232	28420	2361	1036	9556	773	1523
BNT162b2 BQ.1.1	42337	3600	29414	7452	159692	105315	3046	7742	49217	2042	1226*
BNT162b2 XBB.1.5 + BQ.1.1	77816	7437	34923	1817	125142	76331	6618	4611	40286	1817	4008
BNT162b2 BA.4/5 + BQ.1.1	64623	9014	26229	7113	89562	112025	4151	5549	30654	2511	3990

Figure 20 (Continued)

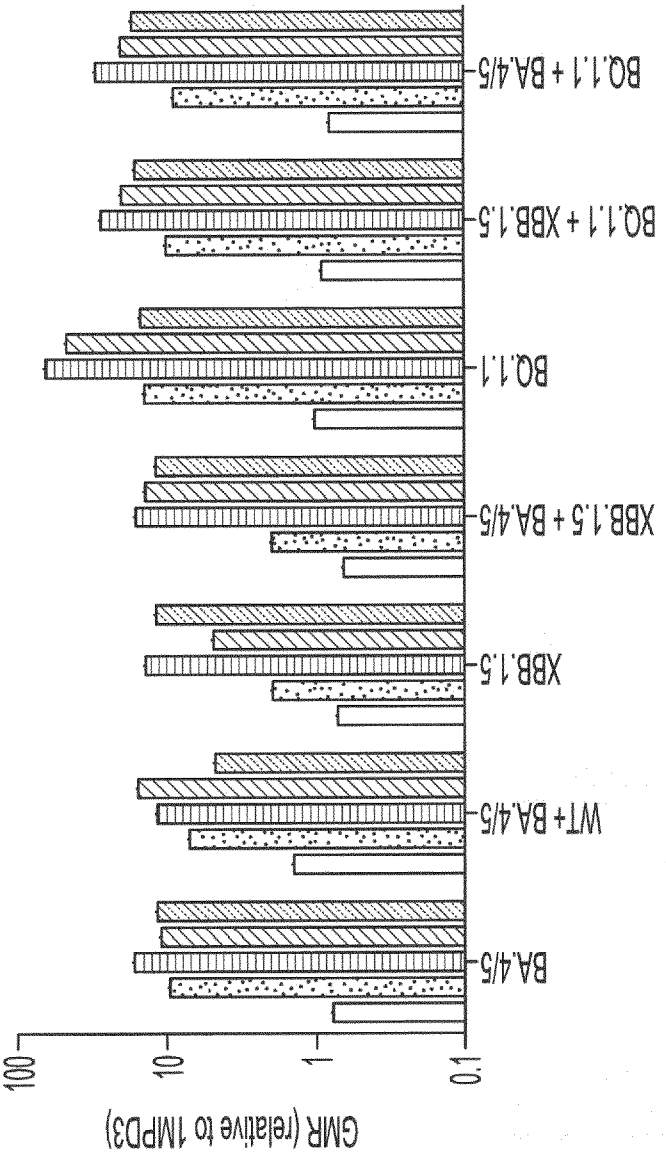
C

D

4th Dose Vaccine	Wuhan	Omicron									
		BA.1	BA.2	BA.2.75.2	BA.4/BA.5	BF.7	BN.1	CH.1.1	BQ.1.1	XBB.1.5	XBB.1.16
BNT162b2 BA.4/5	0.8	2.0	1.2	1.2	1.8	2.2	1.8	1.9	2.1	2.5	2.5
BNT162b2 WT+ BA.4/5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
BNT162b2 XBB.1.5	1.4	2.0	1.4	1.2	1.0	1.0	1.8	3.0	0.9	4.1	5.1
BNT162b2 BA.4/5 + XBB.1.5	1.0	4.7	1.2	0.9	1.3	1.0	1.1	1.2	0.9	1.7	2.1
BNT162b2 BQ.1.1	0.6	0.7	1.8	3.0	3.9	3.7	1.5	9.3	4.9	4.6	1.7
BNT162b2 XBB.1.5 + BQ.1.1	1.1	1.4	2.1	0.7	3.1	2.7	3.2	5.5	4.0	4.1	5.5
BNT162b2 BA.4/5 + BQ.1.1	0.9	1.7	1.6	2.9	2.2	3.9	2.0	6.6	3.0	5.7	5.4

Figure 20 (Continued)

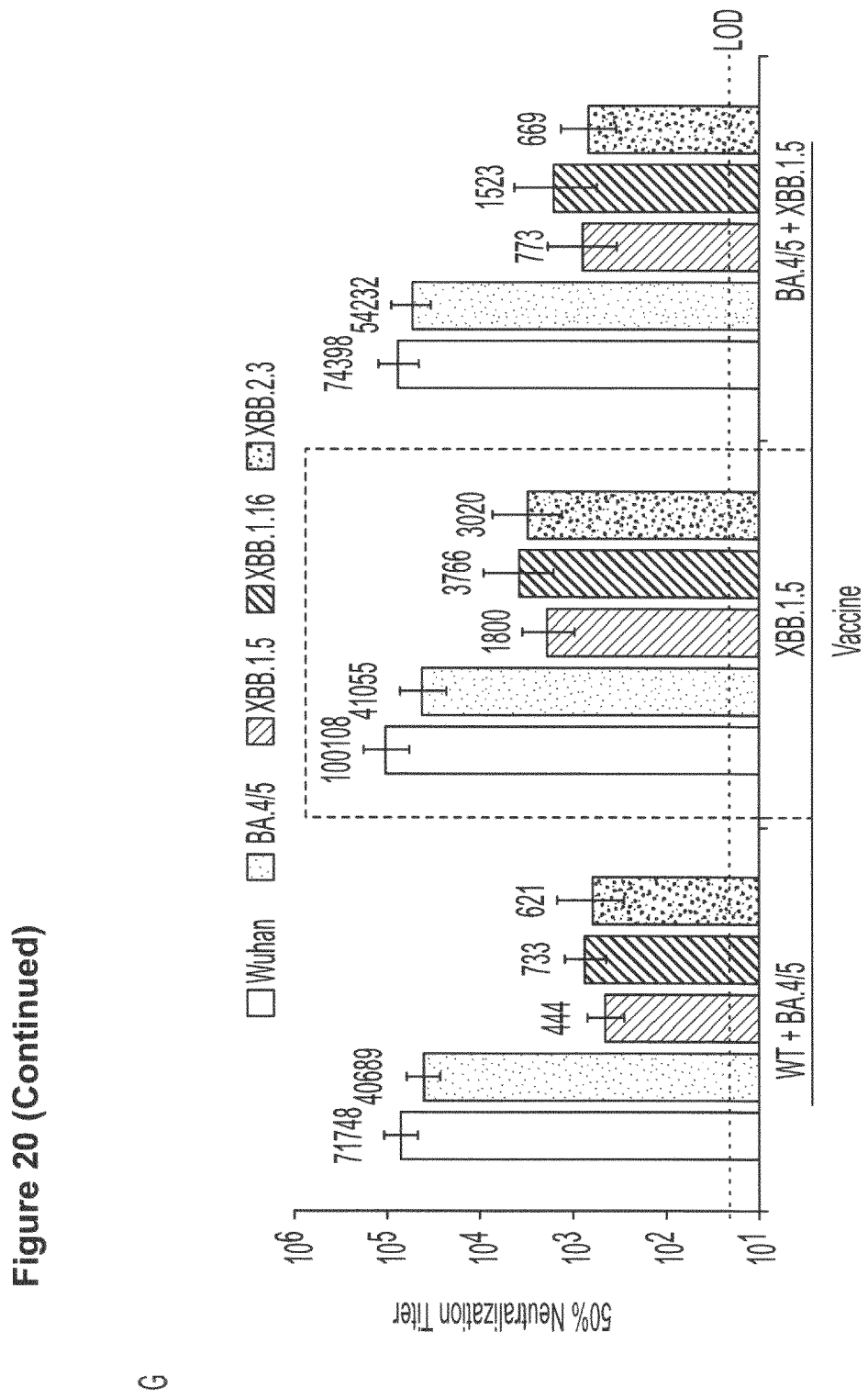
E



F

4th Dose Vaccine	Wuhan	Omicron			
		BA.4/BA.5	CH.1.1	BQ.1.1	XBB.1.5
BNT162b2 BA.4/5	0.8	9.7	16.8	11.1	11.8
BNT162b2 WT+ BA.4/5	1.4	7.2	11.8	15.8	4.9
BNT162b2 XBB.1.5	0.7	2.0	13.9	4.9	12.5
BNT162b2 BA.4/5 +XBB.1.5	0.7	1.9	15.6	13.6	12.1
BNT162b2 BQ.1.1	1.0	14.3	64.6	47.4	14.9
BNT162b2 XBB.1.5 + BQ.1.1	0.9	10.2	27.7	20.4	16.1
BNT162b2 BA.4/5 + BQ.1.1	0.8	8.5	30.0	20.2	17.0

Figure 20 (Continued)



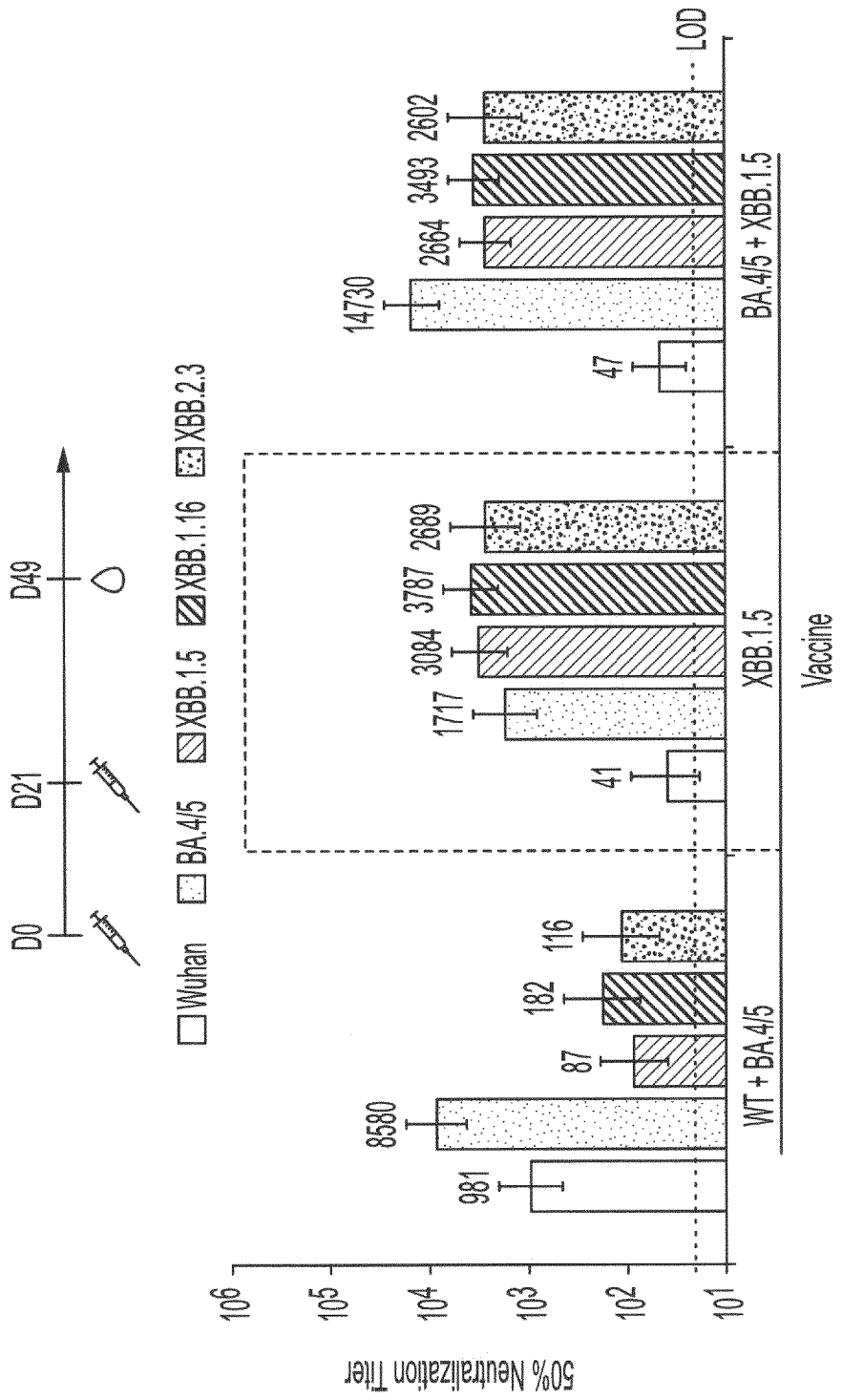
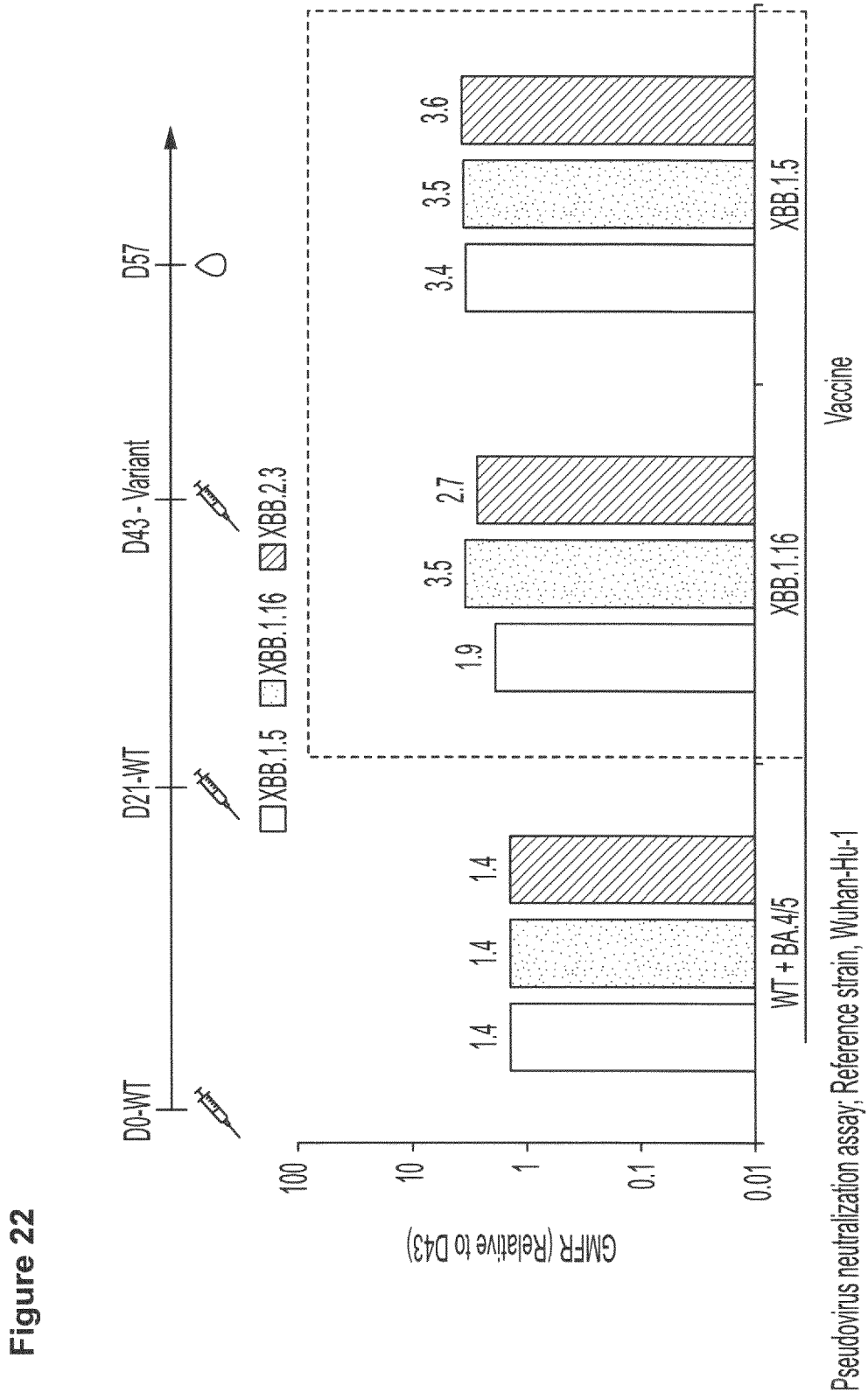

D0
D21
D49
Wuhan
BA.4/5
XBB.1.5
XBB.1.16
XBB.2.3
50% Neutralization Tiler
10^6
10^5
10^4
10^3
10^2
10^1
LOD
981
8580
87
182
116
41
1717
3084
3787
2689
47
14730
2664
3493
2602
WT + BA.4/5
XBB.1.5
BA.4/5 + XBB.1.5
Vaccine

Figure 21

Figure 22


D0-WT
D21-WT
D43 - Variant
D57
XBB.1.5
XBB.1.16
XBB.2.3
GMFR (Relative to D43)
100
10
1
0.1
0.01
1.4
1.4
1.4
1.9
3.5
2.7
3.4
3.5
3.6
WT + BA.4/5
XBB.1.16
XBB.1.5
Vaccine
Pseudovirus neutralization assay; Reference strain, Wuhan-Hu-1
N = 10 mice per vaccine group

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/067350

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/067350

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-15, 17, 44, 56-63, 137, 138, 159-168(completely); 16, 28-43, 54, 55, 136 189-198, 219-266(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/067350

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/12 A61P31/14 C07K14/165
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C12N A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/226436 A1 (TRANSLATE BIO INC [US]; SANOFI PASTEUR INC [US]) 11 November 2021 (2021-11-11) paragraphs [0003], [0013], [0014], [0016], [0017], [0019] - [0027], [0030] paragraphs [0037], [0108] - [0112], [0199] - [0204] paragraphs [0210] - [0211], [0228] - [0229], [0307] paragraphs [0325] - [0328]; example 13 ----- -/--	1-17, 28-44, 54-63, 136-138, 159-168, 189-198, 219-239, 242-266

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2023	01/12/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Noë, Veerle

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/159118 A2 (RNALMMUNE INC [US]) 12 August 2021 (2021-08-12) page 3, paragraph 3 page 4, paragraph 2-4 page 7, last paragraph - page 8, line 15 page 8, paragraph 3 page 9, last paragraph page 10, last paragraph - page 11, paragraph 1 page 11, paragraph 3 -----	16,17, 28-34, 37,40, 43,44, 54, 219-229, 236, 242-266
X	WO 2021/160346 A1 (PASTEUR INSTITUT [FR]) 19 August 2021 (2021-08-19) paragraphs [0006], [0016] - [0020], [0033], [0035], [0037] paragraphs [0053] - [0054], [0056], [0060], [0073] - [0077] claims 4,6,8,18 -----	16,17, 28-30, 32,34, 37,40, 43,44, 54, 219-230, 242-266
X	WO 2021/237174 A1 (VAXESS TECH INC [US]) 25 November 2021 (2021-11-25) page 5, paragraph 3 page 91, last paragraph page 92, paragraph 1 page 92, last line - page 93, paragraph 1 page 94, paragraph 1-2 claims 80,186 ----- -/--	16,17, 28-30, 44,54, 219-230, 236, 240-266

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Uk Health Security Agency: "SARS-CoV-2 variants of concern and variants under investigation in England : Technical briefing 29", , 26 November 2021 (2021-11-26), XP093032319, Retrieved from the Internet: URL:https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1036501/Technical_Briefing_29_published_26_November_2021.pdf [retrieved on 2023-03-16] page 18	1-10, 39-44, 219-232
X	Tegally Houriiyah ET AL: "Continued Emergence and Evolution of Omicron in South Africa: New BA.4 and BA.5 lineages", medRxiv, 2 May 2022 (2022-05-02), XP093032398, DOI: 10.1101/2022.05.01.22274406 Retrieved from the Internet: URL:https://www.medrxiv.org/content/10.1101/2022.05.01.22274406v1.full.pdf [retrieved on 2023-03-16] the whole document	4-10
X,P	WO 2022/137133 A1 (CUREVAC AG [DE]; GLAXOSMITHKLINE BIOLOGICALS SA [BE]) 30 June 2022 (2022-06-30) the whole document	16,17
E	EP 4 226 938 A2 (BIONTECH SE [DE]) 16 August 2023 (2023-08-16) the whole document	16,17
X,P	WO 2023/073190 A9 (BIONTECH SE [DE]) 22 June 2023 (2023-06-22) the whole document	16,17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/067350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021226436 A1	11-11-2021	AU 2021269042 A1	02-02-2023
		CA 3177940 A1	11-11-2021
		EP 4146265 A1	15-03-2023
		IL 297962 A	01-01-2023
		JP 2023524767 A	13-06-2023
		KR 20230008801 A	16-01-2023
		WO 2021226436 A1	11-11-2021
WO 2021159118 A2	12-08-2021	AU 2021216443 A1	08-09-2022
		BR 112022015626 A2	11-10-2022
		CA 3167257 A1	12-08-2021
		CN 115297892 A	04-11-2022
		EP 4100066 A2	14-12-2022
		IL 295360 A	01-10-2022
		JP 2023512833 A	29-03-2023
		KR 20220143684 A	25-10-2022
		US 2022040292 A1	10-02-2022
		US 2023108926 A1	06-04-2023
		WO 2021159118 A2	12-08-2021
WO 2021160346 A1	19-08-2021	CA 3167611 A1	19-08-2021
		EP 4103228 A1	21-12-2022
		US 2022401550 A1	22-12-2022
		WO 2021160346 A1	19-08-2021
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		CA 3183930 A1	25-11-2021
		CN 116406285 A	07-07-2023
		EP 4153139 A1	29-03-2023
		JP 2023527175 A	27-06-2023
		KR 20230013274 A	26-01-2023
		US 2023270842 A1	31-08-2023
		WO 2021237174 A1	25-11-2021
WO 2022137133 A1	30-06-2022	NONE	
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		GB 2615177 A	02-08-2023
		JP 2023081859 A	13-06-2023
		WO 2023094713 A2	01-06-2023
WO 2023073190 A9	22-06-2023	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15, 17, 44, 56-63, 137, 138, 159-168(completely); 16, 28-43, 54, 55, 136, 189-198, 219-266(partially)

A composition comprising an RNA molecule having: (a) a nucleotide sequence that is at least 99% identical to SEQ ID NO: 161, corresponding to XBB.1.5 Omicron variant ; (b) a nucleotide sequence that is at least 95% identical to SEQ ID NO: 161, and which encodes a SARS-CoV-2 S protein comprising the following mutations relative to SEQ ID NO: 1: T19I, ?24-26, A27S, V83A, G142D, ?145, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, K986P, and V987P; or (c) a nucleotide sequence as set forth in SEQ ID NO: 161; and wherein the RNA molecule comprises: (i) a 5' cap; and (ii) a modified uridine in place of each uridine.

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2. claims: 18, 45, 128-135, 139, 140, 149-158(completely); 16, 28-43, 54, 55, 136, 189-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.4/5 variant.

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3. claims: 19, 46, 64-71(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75 variant.

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4. claims: 20, 47, 72-79, 141, 142, 169-178(completely); 16, 28-43, 54, 55, 136, 199-208, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an BA.2.75.2 variant.

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5. claims: 21, 48, 80-87(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

BA.4.6/BF.7 variant.

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6. claims: 22, 49, 88-95(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a XBB variant.

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7. claims: 23(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a XBB.1 variant.

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8. claims: 24, 51, 104-111, 143, 144(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a XBB.1.16 variant.

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9. claims: 25, 52, 112-119, 145, 146(completely); 16, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a XBB.2.3 variant.

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10. claims: 26, 53, 120-127, 147, 148(completely); 16, 28-43, 54, 55, 136, 219-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a XBB.2.3.2 variant.

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11. claims: 27, 50, 96-103, 179-188(completely); 16, 28-43, 54, 55, 136, 209-266(partially)

A composition comprising an RNA molecule comprising a nucleotide sequence encoding a SARS-CoV-2 S protein comprising one or more mutations characteristic of a BQ.1.1 variant.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210