CLAIMS

What is claimed is:

1. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes at least two domains of a SARS-CoV-2 Spike protein, and less than the full length spike protein.

2. The mRNA of claim 1, wherein one of the two domains is an N-terminal domain (NTD) of a SARS-CoV-2 Spike protein.

3. The mRNA of claim 1 or 2, wherein one of the two domains is a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein.

4. The mRNA of claim 2 or 3, wherein the ORF encodes a transmembrane domain (TD) linked to the NTD and/or RBD.

5. The mRNA of claim 4, wherein the TD is an influenza hemagglutinin transmembrane domain.

6. The mRNA of claim 3 or 4, wherein the ORF comprises NTD - RBD - TM.

7. The mRNA of any one of claims 1-6, wherein the at least two domains are linked through a cleavable or non-cleavable linker.

8. The mRNA of claim 7, wherein the non-cleavable linker is a glycine-serine (GS) linker.

9. The mRNA of claim 8, wherein the GS linker 4-15 amino acids.

10. The mRNA of claim 7, wherein the linker is a pan HLA DR-binding epitope (PADRE).

11. The mRNA of any one of claims 1-10, wherein the ORF encodes a signal peptide.

12. The mRNA of claim 11, wherein the signal peptide is linked to the NTD.

13. The mRNA of claim 11, wherein the signal peptide is linked to the RBD.

14. The mRNA of any one of claims 11-13, wherein the signal peptide is heterologous to SARS-CoV-2.

15. The mRNA of any one of claims 1-3, wherein the at least two domains are soluble.

16. The mRNA of any one of claims 1-14, wherein the ORF encodes a trafficking signal domain.

17. The mRNA of claim 16, wherein the trafficking signal domain is a macrophage marker.

18. The mRNA of claim 17, wherein the macrophage marker CD86 and/or CD11b.

19. The mRNA of claim 16, wherein the trafficking signal domain is a VSV-G cytosolic tail (VSVGct).

20. The mRNA of claim 1, wherein one of the two domains is a first repetitive heptapeptide: HPPHCPC (HR1) of a SARS-CoV-2 Spike protein.

21. The mRNA of claim 1, wherein one of the two domains is a second repetitive heptapeptide: HPPHCPC (HR2) of a SARS-CoV-2 Spike protein.

22. The mRNA of claim 20 or 21, wherein the ORF encodes a transmembrane domain (TD) linked to the HR1 and/or HR2.

23. The mRNA of claim 22, wherein the TD is an influenza hemagglutinin transmembrane domain.

24. The mRNA of any one of claims 20-23, wherein the ORF encodes a fusion peptide (FP).

25. The mRNA of any one of claims 20-23, wherein the ORF encodes a CT tail.

~~26. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein.~~

~~27. The mRNA of claim 26, wherein the RBD is soluble.~~

~~28. The mRNA of claim 26, wherein the RBD is linked to a transmembrane domain, optionally an influenza hemagglutinin transmembrane domain.~~

~~29. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an N-terminal domain (NTD) of a SARS-CoV-2 Spike protein.~~

~~30. The mRNA of claim 29, wherein the NTD is linked to an RBD of a SARS-CoV-2 Spike protein to form an NTD-RBD fusion protein.~~

~~31. The mRNA of claim 30, wherein the NTD-RBD fusion is linked to a transmembrane domain (TM), optionally an influenza hemagglutinin transmembrane domain, to form an NTD-RBD-TM protein.~~

~~32. The mRNA of claim 30, wherein the NTD-RBD fusion comprises a C-terminal truncation.~~

~~33. The mRNA of any one of claims 26-32, wherein the NTD and/or RBD includes an extended region.~~

~~34. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S1 subunit, wherein the S1 subunit is linked to a transmembrane domain, optionally an influenza hemagglutinin transmembrane domain.~~

~~35. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S1 subunit, wherein the S1 subunit has been modified to remove a RBD or a portion of a RBD of S protein.~~

36. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S1 subunit linked to an S2 subunit, wherein the S1 subunit is from an HKU1 S protein.

37. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S1 subunit linked to an S2 subunit, wherein the S1 subunit is from an OC43 S protein.

38. The mRNA of any one of claims 34-37, further comprising a trafficking signal, optionally selected from macrophage markers, optionally CD86, CD11B and/or VSVGct.

39. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S2 subunit of a SARS-CoV-2 Spike protein.

40. A messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a fusion protein comprising a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein and a protein transmembrane domain.

41. The mRNA of claim 40, wherein the protein transmembrane domain is an influenza hemagglutinin transmembrane domain.

42. A messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a fusion protein comprising an amino (N)-terminal domain (NTD) of a SARS-CoV-2 Spike protein and a transmembrane domain.

43. The mRNA of claim 42, wherein the transmembrane domain is an influenza hemagglutinin transmembrane domain.

44. A messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a fusion protein comprising an amino (N)-terminal domain of a SARS-CoV-2 Spike protein linked to a receptor binding domain of a SARS-CoV-2 Spike protein.

45. The mRNA of claim 44, wherein the fusion protein further comprises a transmembrane domain.

46. The mRNA of any one of the preceding claims further comprising a 5′ cap, optionally 7mG(5’)ppp(5’)NlmpNp.

47. The mRNA of any one of claims 1-46, further comprising a polyA tail, optionally having a length of about 100 nucleotides.

48. The mRNA of any one of claims 1-47, wherein the mRNA comprises a chemical modification, optionally 1-methylpseudouridine.

49. The mRNA of any one of claims 1-48, wherein each uridine in the mRNA is a 1-methylpseudouridine.

50. A composition comprising:

(a) a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a fusion protein comprising a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein and a protein transmembrane domain; and

(b) an mRNA comprising an open reading frame encoding a fusion protein comprising an amino (N)-terminal domain (NTD) of a SARS-CoV-2 Spike protein and a transmembrane domain.

51. The composition of claim 50, wherein the protein transmembrane domain is an influenza hemagglutinin transmembrane domain.

52. The composition of claim 51, wherein the fusion protein of (a) comprises an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 77.

53. The composition of claim 52, wherein the fusion protein of (a) comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 77.

54. The composition of claim 53, wherein the fusion protein of (a) comprises the amino acid sequence of SEQ ID NO: 77.

55. The composition of any one of claims 50-54, wherein the open reading frame of (a) comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 76.

56. The composition of claim 55, wherein the open reading frame of (a) comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 76.

57. The composition of claim 56, wherein the open reading frame of (a) comprises the nucleotide sequence of SEQ ID NO: 76.

58. The composition of any one of claims 50-57, wherein the fusion protein of (b) comprises an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 47.

59. The composition of claim 58, wherein the fusion protein of (b) comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 47.

60. The composition of claim 59, wherein the fusion protein of (b) comprises the amino acid sequence of SEQ ID NO: 47.

61. The composition of any one of claims 50-60, wherein the open reading frame of (b) comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 46.

62. The composition of claim 61, wherein the open reading frame of (b) comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 46.

63. The composition of claim 62, wherein the open reading frame of (b) comprises the nucleotide sequence of SEQ ID NO: 46.

64. The composition of any one of claims 50-63, wherein the ratio of the mRNA of (a) to the mRNA of (b) is about 1:1.

65. The mRNA of any one of claims 1-49, in a composition further comprising a lipid nanoparticle.

66. The composition of any one of claims 50-64 further comprising a lipid nanoparticle.

67. The composition of claim 65 or 66, wherein the mRNA is in the lipid nanoparticle.

68. The composition of any one of claims 50-64, wherein the mRNA of (a) is in a lipid nanoparticle and the mRNA of (b) is in a lipid nanoparticle.

69. The composition of claim 68, wherein the mRNA of (a) and (b) are in the same lipid nanoparticle or wherein each of the mRNA of (a) and (b) is formulated in a separate nanoparticle, relative to each other.

70. The composition of any one of claims 65-69, wherein the lipid nanoparticle comprises a cationic lipid.

71. The composition of claim 70, wherein the lipid nanoparticle further comprises a neutral lipid.

72. The composition of claim 70 or 71, wherein the lipid nanoparticle further comprises a sterol.

73. The composition of any one of claims 70-72, wherein the lipid nanoparticle further comprises a polyethylene glycol (PEG)-modified lipid.

74. The composition of any one of claims 70-73, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.

75. The composition of claim 74, wherein the ionizable cationic lipid is heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino)octanoate (Compound 1).

76. The composition of claim 74 or 75, wherein the neutral lipid is 1,2 distearoyl-sn-glycero-3-phosphocholine (DSPC).

77. The composition of any one of claims 70-76, wherein the sterol is cholesterol.

78. The composition of any one of claims 70-77, wherein the PEG-modified lipid is 1,2-dimyristoyl-sn-glycerol, methoxypolyethyleneglycol (PEG2000-DMG).

79. The composition of any one of claims 70-78, wherein the lipid nanoparticle comprises 20-60 mol% ionizable cationic lipid, 5-25 mol% neutral lipid, 25-55 mol% sterol, and 0.5-15 mol% PEG-modified lipid.

80. The composition of claim 79, wherein the lipid nanoparticle comprises: 40-50 mol% ionizable lipid, optionally 45-50 mol%, 30-45 mol% sterol, optionally 35-40 mol%, 5-15 mol% helper lipid, optionally 10-12 mol%, 1-5% PEG lipid, optionally 1-3 mol%, or 1.5 to 2.5 mol%.

81. The composition of claim 80, wherein the lipid nanoparticle comprises: 40-50 mol% Compound 1, optionally 45-50 mol%, 30-45 mol% cholesterol, optionally 35-40 mol%, 5-15 mol% DSPC, optionally 10-12 mol%, 1-5% PEG2000DMG, optionally 1-3 mol%, or 1.5 to 2.5 mol%.

82. A method comprising administering to a subject the mRNA or the composition of any one of the preceding claims in an amount effective to induce in the subject a neutralizing antibody response against SARS-CoV-2.

83. A method comprising administering to a subject the mRNA or the composition of any one of the preceding claims in an amount effective to induce in the subject a T cell immune response against SARS-CoV-2.

84. A method comprising administering to a subject the mRNA of any one of the claims 1-49 in an amount effective to induce in the subject a neutralizing antibody response and a T cell immune response against SARS-CoV-2.

85. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes at least one domain of a SARS-CoV-2 Spike protein.

86. The mRNA of claim 85, wherein the mRNA is any one of claims 1-49.

87. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 77.

88. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 77.

89. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence of SEQ ID NO: 77.

90. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 76.

91. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 76.

92. The mRNA of claim 85 or 86, wherein the ORF comprises the nucleotide sequence of SEQ ID NO: 76.

93. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 47.

94. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 47.

95. The mRNA of claim 85 or 86, wherein the ORF encodes the amino acid sequence of SEQ ID NO: 47.

96. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 46.

97. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 46.

98. The mRNA of claim 85 or 86, wherein the ORF comprises the nucleotide sequence of SEQ ID NO: 46.

99. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 62, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 62.

100. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 61, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 61.

101. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 92, 140, or 143.

102. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the amino acid sequence of SEQ ID NO: 92, 140, or 143.

103. The mRNA of claim 85 or 86, wherein the ORF encodes the amino acid sequence of SEQ ID NO: 92, 140, or 143.

104. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 91, 139, or 142.

105. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 91, 139, or 142.

106. The mRNA of claim 85 or 86, wherein the ORF comprises the nucleotide sequence of SEQ ID NO: 91, 139, or 142.

107. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 107, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 107.

108. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 106, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 106.

109. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of any one of SEQ ID NOs: 59, 86, 89, 116, 119, or 122, optionally wherein the antigen comprises the amino acid sequence of any one of SEQ ID NOs: 59, 86, 89, 116, 119, or 122.

110. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of any one of SEQ ID NOs: 58, 85, 88, 115, 118, or 121, optionally wherein the open reading frame comprises the nucleotide sequence of any one of SEQ ID NOs: 58, 85, 88, 115, 118, or 121.

111. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an S1 subunit antigen that comprises an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 5, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 5.

112. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 3, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 3.

113. The mRNA of claim 85 or 86, wherein the antigen comprises an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 17 or 146, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 17 or 146.

114. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 16 or 145, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 16 or 145.

115. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of any one of SEQ ID NOs: 20, 23, 26, 29, 32 or 35, optionally wherein the antigen comprises the amino acid sequence of any one of SEQ ID NOs: 20, 23, 26, 29, 32, or 35.

116. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of any one of SEQ ID NOs: 19, 22, 25, 28, 31, or 34, optionally wherein the open reading frame comprises the nucleotide sequence of any one of SEQ ID NOs: 19, 22, 25, 28, 31, or 34.

117. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 38, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 38.

118. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 37, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 37.

119. The mRNA of claim 85 or 86, wherein the ORF encodes an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 41, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 41.

120. The mRNA of claim 85 or 86, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 40, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 40.

121. The mRNA of any one of the preceding claims further comprising a 5′ untranslated region (UTR), optionally comprising the nucleotide sequence of SEQ ID NO: 131 or 2.

122. The mRNA of any one of the preceding claims further comprising a 3′ untranslated region (UTR), optionally comprising the nucleotide sequence of SEQ ID NO: 132 or 4.

123. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an antigen that comprises an amino acid sequence having 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% identity to the amino acid sequence of SEQ ID NO: 8 or 65, optionally wherein the antigen comprises the amino acid sequence of SEQ ID NO: 8 or 65.

124. The mRNA of claim 123, wherein the ORF comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 7 or 64, optionally wherein the open reading frame comprises the nucleotide sequence of SEQ ID NO: 7 or 64.

~~125. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an antigen that comprises an amino acid sequence having 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% identity to the amino acid sequence of any one of SEQ ID NOs: 11, 14, 68, or 71, optionally wherein the antigen comprises the amino acid sequence of any one of SEQ ID NOs: 11, 14, 68, or 71.~~

~~126. The mRNA of claim 125, wherein the open reading frame comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of any one of SEQ ID NOs: 10, 13, 67, or 70, optionally wherein the open reading frame comprises the nucleotide sequence of any one of SEQ ID NOs: 10, 13, 67, or 70.~~

~~127. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes an antigen that comprises an amino acid sequence having 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% identity to the amino acid sequence of any one of SEQ ID NOs: 44, 50, 74, 80, 83, 101, 104 or 113, optionally wherein the antigen comprises the amino acid sequence of any one of SEQ ID NOs: 44, 50, 74, 80, 83, 101, 104 or 113.~~

~~128. The mRNA of claim 127, wherein the open reading frame comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of any one of SEQ ID NOs: 43, 49, 73, 79, 82, 100, 103, or 112, optionally wherein the open reading frame comprises the nucleotide sequence of any one of SEQ ID NOs: 43, 49, 73, 79, 82, 100, 103, or 112.~~

~~129. The mRNA of claim 109, wherein the antigen comprises an amino acid sequence having 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% identity to the amino acid sequence of any one of SEQ ID NOs: 95, 98, or 110, optionally wherein the antigen comprises the amino acid sequence of any one of SEQ ID NOs: 95, 98, or 110.~~

~~130. The mRNA of claim 129, wherein the open reading frame comprises a nucleotide sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of any one of SEQ ID NOs: 94, 97, or 109, optionally wherein the open reading frame comprises the nucleotide sequence of any one of SEQ ID NOs: 94, 97, or 109.~~

~~131. The mRNA of any one of claims 85-130, in a composition further comprising a lipid nanoparticle.~~

~~132. The composition of claim 131, wherein the mRNA is in the lipid nanoparticle.~~

~~133. The composition of any one of claims 131-132, wherein the lipid nanoparticle comprises a cationic lipid.~~

~~134. The composition of claim 133, wherein the lipid nanoparticle further comprises a neutral lipid.~~

~~135. The composition of any one of claims 131-134, wherein the lipid nanoparticle further comprises a sterol.~~

~~136. The composition of any one of claims 131-135, wherein the lipid nanoparticle further comprises a polyethylene glycol (PEG)-modified lipid.~~

~~137. The composition of any one of claims 131-136, wherein the lipid nanoparticle comprises an ionizable cationic lipid, a neutral lipid, a sterol, and a PEG-modified lipid.~~

~~138. The composition of claim 137, wherein the ionizable cationic lipid is heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (Compound 1).~~

~~139. The composition of claim 137 or 138, wherein the neutral lipid is 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).~~

~~140. The composition of any one of claims 131-139, wherein the sterol is cholesterol.~~

141. The composition of any one of claims 131-140, wherein the PEG-modified lipid is 1,2-dimyristoyl-sn-glycerol, methoxypolyethyleneglycol (PEG2000-DMG).

142. The composition of any one of claims 131-141, wherein the lipid nanoparticle comprises 20-60 mol% ionizable cationic lipid, 5-25 mol% neutral lipid, 25-55 mol% sterol, and 0.5-15 mol% PEG-modified lipid.

143. The composition of claim 142, wherein the lipid nanoparticle comprises: 40-50 mol% ionizable lipid, optionally 45-50 mol%, 30-45 mol% sterol, optionally 35-40 mol%, 5-15 mol% helper lipid, optionally 10-12 mol%, 1-5% PEG lipid, optionally 1-3 mol%, or 1.5 to 2.5 mol%.

144. The composition of claim 143, wherein the lipid nanoparticle comprises: 40-50 mol% Compound 1, optionally 45-50 mol%, 30-45 mol% cholesterol, optionally 35-40 mol%, 5-15 mol% DSPC, optionally 10-12 mol%, 1-5% PEG2000DMG, optionally 1-3 mol%, or 1.5 to 2.5 mol%.

145. The mRNA of any one of claims 85-130, wherein the mRNA comprises a chemical modification, optionally 1-methylpseudouridine.

146. The mRNA of any one of claims 85-130, wherein each uridine in the mRNA is a 1-methylpseudouridine.

147. The composition of any one of claims 131-144, wherein the mRNA comprises a chemical modification, optionally 1-methylpseudouridine.

148. The composition of any one of claims 131-144, wherein each uridine in the mRNA is a 1-methylpseudouridine.

149. A method comprising administering to a subject the mRNA of any one of claims 85-130 in an amount effective to induce in the subject a neutralizing antibody response against SARS-CoV-2.

~~150. A method comprising administering to a subject the mRNA of any one of claims 85-130 in an amount effective to induce in the subject a T cell immune response against SARS-CoV-2.~~

~~151. A method comprising administering to a subject the mRNA of any one of claims 85-130 in an amount effective to induce in the subject a neutralizing antibody response and a T cell immune response against SARS-CoV-2.~~

~~152. A method comprising administering to a subject the compostion of any one of claims 131-144 in an amount effective to induce in the subject a neutralizing antibody response against SARS-CoV-2.~~

~~153. A method comprising administering to a subject the compostion of any one of claims 131-144 in an amount effective to induce in the subject a T cell immune response against SARS-CoV-2.~~

~~154. A method comprising administering to a subject the compostion of any one of claims 131-144 in an amount effective to induce in the subject a neutralizing antibody response and a T cell immune response against SARS-CoV-2.~~

1. A messenger ribonucleic acid (mRNA) vaccine comprising:

(a) an mRNA comprising an open reading frame encoding a fusion protein comprising a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein and a protein transmembrane domain; and

(b) a lipid nanoparticle having a molar ratio of about 20-60 mol% ionizable cationic lipid, 5-25 mol% non-cationic lipid, 25-55 mol% sterol, and 0.5-15 mol% PEG-modified lipid,

wherein the mRNA comprises at least one chemical modification, wherein the at least one chemical modification is selected from the group consisting of pseudouridine (ψ), 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), 5-methoxymethyl uridine, 5-methylthio uridine, 1-methoxymethyl pseudouridine, 5-methyl cytidine, and/or 5-methoxy cytidine.

2. The mRNA vaccine of claim 1, wherein the transmembrane domain is an influenza hemagglutinin transmembrane domain.

3. A messenger ribonucleic acid (mRNA) vaccine comprising:

(a) an mRNA comprising an open reading frame encoding:

(i) a fusion protein comprising a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein and a protein transmembrane domain, wherein the open reading frame comprises a nucleotide sequence having at least 70% identity to the nucleotide sequence of SEQ ID NO: 76; or

(ii) a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein, wherein the RBD is soluble; and

(b) a lipid nanoparticle having a molar ratio of about 20-60 mol% ionizable cationic lipid, 5-25 mol% non-cationic lipid, 25-55 mol% sterol, and 0.5-15 mol% PEG-modified lipid, wherein the mRNA comprises at least one chemical modification.

4. The mRNA vaccine of claim 3, wherein the open reading frame comprises a nucleotide sequence having at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the nucleotide sequence of SEQ ID NO: 76.

5. A messenger ribonucleic acid (mRNA) comprising an open reading frame (ORF) that encodes at least two domains of a SARS-CoV-2 Spike protein, and less than the full length spike protein, wherein the first domain is a receptor binding domain (RBD) of a SARS-CoV-2 Spike protein, and wherein the second domain is an N-terminal domain (NTD) of a SARS-CoV-2 Spike protein.

6. The mRNA of claim 5, wherein the ORF encodes a transmembrane domain (TD) linked to the NTD and/or RBD, optionally wherein (i) the TD is an influenza hemagglutinin transmembrane domain, and/or (ii) the ORF comprises NTD - RBD - TM.

7. The mRNA of claim 5 or claim 6, wherein the ORF encodes a signal peptide, optionally wherein the signal peptide is linked to the RBD.

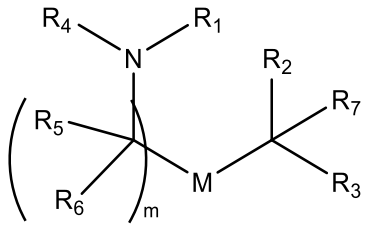
8. The mRNA of claim 7, wherein the signal peptide is heterologous to SARS-CoV-2.

9. The mRNA of any one of claims 5-8, wherein the mRNA comprises at least one chemical modification.

10. The mRNA vaccine of any one of claims 3, 4 or 9, wherein the at least one chemical modification is selected from the group consisting of pseudouridine (ψ), 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), 5-methoxymethyl uridine, 5-methylthio uridine, 1-methoxymethyl pseudouridine, 5-methyl cytidine, and/or 5-methoxy cytidine.

11. The mRNA of any one of claims 5-10, wherein the mRNA is in an mRNA vaccine further comprising a lipid nanoparticle having a molar ratio of about 20-60% ionizable cationic lipid: about 5-25% non-cationic lipid: about 25-55% sterol; and about 0.5-15% PEG-modified lipid.

12. The mRNA vaccine of any one of claims 1-4 or 11, wherein the ionizable cationic lipid comprises a compound of Formula (I):



(I),

or a salt or isomer thereof, wherein:

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

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, C_{2-14} alkenyl, -R*YR", -YR", and -R*OR", or R_2 and R_3, together with the atom to which they are attached, form a heterocycle or carbocycle;

R_4 is selected from the group consisting of a C_{3-6} carbocycle, $-(CH_2)_nQ$, $-(CH_2)_nCHQR$, -CHQR, $-CQ(R)_2$, and unsubstituted C_{1-6} alkyl, where Q is selected from a carbocycle, heterocycle, -OR, $-O(CH_2)_nN(R)_2$, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-CXH_2$, -CN, $-N(R)_2$, $-C(O)N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, -N(R)C(O)N(R)$_2$, -N(R)C(S)N(R)$_2$, $-N(R)R_8$, $-O(CH_2)_nOR$, $-N(R)C(=NR_9)N(R)_2$, $-N(R)C(=CHR_9)N(R)_2$, $-OC(O)N(R)_2$, -N(R)C(O)OR, -N(OR)C(O)R, $-N(OR)S(O)_2R$, -N(OR)C(O)OR, -N(OR)C(O)N(R)$_2$, -N(OR)C(S)N(R)$_2$, $-N(OR)C(=NR_9)N(R)_2$, $-N(OR)C(=CHR_9)N(R)_2$, $-C(=NR_9)N(R)_2$, $-C(=NR_9)R$, -C(O)N(R)OR, and –C(R)N(R)$_2$C(O)OR, and each n is independently selected from 1, 2, 3, 4, and 5;

each R_5 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

each R_6 is independently selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

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

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

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

R_9 is selected from the group consisting of H, CN, NO_2, C_{1-6} alkyl, -OR, $-S(O)_2R$, $-S(O)_2N(R)_2$, C_{2-6} alkenyl, C_{3-6} carbocycle and heterocycle;

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

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

each R" is independently selected from the group consisting of C_{3-14} alkyl and C_{3-14} alkenyl;

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

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

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

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

13. Use of the mRNA vaccine of any one of claims 1-12 in the manufacture of a medicament for inducing an antigen specific immune response in a subject.

14. Use of the mRNA vaccine of any one of claims 1-12 in the manufacture of a medicament for preventing and/or treat a coronavirus infection.

15. The mRNA vaccine of any one of claims 1-12, for use as a medicament.