CLAIMS

1. A coronavirus (CoV) Spike (S) glycoprotein comprising

(i) an S1 subunit with an inactivated furin cleavage site, wherein the S1 subunit comprises an N-terminal domain (NTD), a receptor binding domain (RBD), subdomains 1 and 2 (SD1/2), wherein the inactivated furin cleavage site has an amino acid sequence of QQAQ;

wherein the NTD optionally comprises one or more modifications selected from the group consisting of:

(a) deletion of one or more amino acids selected from the group consisting of amino acid 56, 57, 131, 132, 144, 145, 228, 229, 230, 231, 234, 235, 236, 237, 238, 239, 240 and combinations thereof;

(b) insertion of 1, 2, 3, or 4 amino acids after amino acid 132; and

(c) mutation of one or more amino acids selected from the group consisting of amino acid 5, 6, 7, 13, 51, 53, 56, 57, 62, 63, 67, 82, 125, 129, 131, 132, 133, 139, 143, 144, 145, 177, 200, 201, 202, 209, 229, 233, 240, 245, and combinations thereof;

wherein the RBD optionally comprises mutation of one or more amino acids selected from the group consisting of amino acid 333, 404, 419, 426, 439, 440, 464, 465, 471, 477, 481, 488, and combinations thereof;

wherein the SD1/2 domain optionally comprises mutation of one or more amino acids selected from the group consisting of 557, 600, 601, 642, 664, 668, and combinations thereof; and

(ii) an S2 subunit, wherein amino acids 973 and 974 are proline,

wherein the S2 subunit optionally comprises one or more modifications selected from the group consisting of:

(a) deletion of one or more amino acids from 676-685, 676-702, 702-711, 775-793, 806-815 and combinations thereof;

(b) mutation of one or more amino acids selected from the group consisting of 688, 703, 846, 875, 937, 969, 1014, 1058, 1105, and 1163 and combinations thereof; and

(c) deletion of one or more amino acids from the TMCT;

wherein the amino acids of the CoV S glycoprotein are numbered with respect to a polypeptide having the sequence of SEQ ID NO: 2.

2. The coronavirus S glycoprotein of claim 1, comprising a deletion of amino acids selected from the group consisting of:
(i) deletion of amino acids 676-685;
(ii) deletion of amino acids 702-711;
(iii) deletion of amino acids 806-815;
(iv) deletion of amino acids 775-793;
(v) deletion of amino acids 1-292 of the NTD; and
(vi) deletion of amino acids 1201-1260 of the transmembrane and cytoplasmic tail (TMCT).

3. The coronavirus S glycoprotein of claim 1 comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NOS: 85-89, 105, 106, and 112-115, 164-168.

4. The coronavirus S glycoprotein of any one of claims 1 to 3 comprising a signal peptide, optionally wherein the signal peptide comprises an amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 117.

5. The coronavirus S glycoprotein of any one of claims 1 to 4 comprising a C-terminal fusion protein.

6. The coronavirus S glycoprotein of claim 5, wherein the C-terminal fusion protein is a hexahistidine tag or a foldon.

7. The coronavirus S glycoprotein of claim 6, wherein the foldon has an amino acid sequence corresponding to SEQ ID NO: 68.

8. The coronavirus S glycoprotein of any one of claims 1-7, wherein the ΔHcal is at least 2-fold greater than the ΔHcal of the wild-type CoV S glycoprotein (SEQ ID NO: 2).

9. The coronavirus S glycoprotein of any one of claims 1-8, wherein each of the S2 subunit, NTD, RBD, and SD1/2 is 95 % identical, is 97% identical, or is 99% identical to the corresponding subunit or domain of the CoV S glycoprotein having an amino acid sequence of SEQ ID NO: 2.

10. The coronavirus S glycoprotein of any one of claims 1-8, wherein each of the S2 subunit, NTD, RBD, and SD1/2 is 99.5 % identical to the corresponding subunit or domain of the CoV S glycoprotein having an amino acid sequence of SEQ ID NO: 2.

11. An isolated nucleic acid encoding the S glycoprotein of any of claims 1-10.

12. A vector comprising the nucleic acid of claim 11.

13. A nanoparticle comprising the coronavirus S glycoprotein of any one of claims 1-10.

14. The nanoparticle of claim 13, wherein the nanoparticle has a Zavg diameter of between about 20 nm and about 35 nm; or the nanoparticle has a polydispersity index from about 0.2 to about 0.45.

15. A cell expressing the coronavirus S glycoprotein of any of claims 1-10.

16. A vaccine composition comprising the coronavirus S glycoprotein of any one of claims 1-10 and a pharmaceutically acceptable buffer.

17. The vaccine composition of claim 16, comprising an adjuvant.

18. The vaccine composition of claim 17, wherein the adjuvant comprises at least two iscom particles, wherein:

the first iscom particle comprises fraction A of *Quillaja Saponaria* Molina and not fraction C of *Quillaja Saponaria* Molina; and

the second iscom particle comprises fraction C of *Quillaja Saponaria* Molina and not fraction A of *Quillaja Saponaria* Molina.

19. The vaccine composition of claim 18, wherein fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina account for about 85 % by weight and about 15 % by weight, respectively, of the sum of weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant; or

wherein fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina account for about 92 % by weight and about 8 % by weight, respectively, of the sum of weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant.

20. The vaccine composition of claim 17-19, wherein the adjuvant is to be administered at a dose of about 50 µg.

21. An immunogenic composition comprising:

(i) a nanoparticle comprising a coronavirus S (CoV S) glycoprotein of any one of claims 1-10, and a non-ionic detergent core;

(ii) a pharmaceutically acceptable buffer, and

(iii) a saponin adjuvant.

22. The immunogenic composition of claim 21, comprising from about 3 µg to about 25 µg of CoV S glycoprotein.

23. The immunogenic composition of claim 22, comprising about 5 µg of CoV S glycoprotein.

24. The immunogenic composition of any one of claims 21-23, wherein the saponin adjuvant comprises at least two iscom particles, wherein:

the first iscom particle comprises fraction A of *Quillaja Saponaria* Molina and not fraction C of *Quillaja Saponaria* Molina; and

the second iscom particle comprises fraction C of *Quillaja Saponaria* Molina and not fraction A of *Quillaja Saponaria* Molina.

25. The immunogenic composition of claim 24, wherein fraction A of *Quillaja Saponaria* Molina accounts for 50-96% by weight and fraction C of *Quillaja Saponaria* Molina accounts for the remainder, respectively, of the sum of the weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant; or wherein fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina account for about 85 % by weight and about 15 % by

weight, respectively, of the sum of the weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant.

26. The immunogenic composition of any one of claims 21-25, comprising about 50 µg of saponin adjuvant.

27. The immunogenic composition of any one of claims 21-26, wherein the non-ionic detergent is selected from the group consisting of polysorbate-20 (PS20), polysorbate-40 (PS40), polysorbate-60 (PS60), polysorbate-65 (PS65), and polysorbate-80 (PS80).

28. Use of the vaccine composition of any one of claims 16-20 or the immunogenic composition of any one of claims 21-27 in the manufacture of a medicament for stimulating an immune response in a subject against SARS-CoV-2 or a heterogeneous SARS-CoV-2 strain.

29. The use of claim 28, wherein from about 3 µg to about 25 µg of CoV S glycoprotein is to be administered.

30. The use of claim 28 or 29, wherein about 5 µg of CoV S glycoprotein is to be administered.

31. The use of any one of claims 28-30, wherein the adjuvant comprises at least two iscom particles, wherein:

the first iscom particle comprises fraction A of *Quillaja Saponaria* Molina and not fraction C of *Quillaja Saponaria* Molina; and

the second iscom particle comprises fraction C of *Quillaja Saponaria* Molina and not fraction A of *Quillaja Saponaria* Molina.

32. The use of claim 31, wherein fraction A of *Quillaja Saponaria* Molina accounts for 50-96% by weight and fraction C of *Quillaja Saponaria* Molina accounts for the remainder, respectively, of the sum of the weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant; or wherein fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina account for about 85 % by weight and about 15 % by weight, respectively, of the sum

of the weights of fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina in the adjuvant

33. The use of any one of claims 28-32, wherein the subject is to be administered about 50 µg of the adjuvant.

34. The use of any one of claims 28-33, wherein the non-ionic detergent is selected from the group consisting of polysorbate-20 (PS20), polysorbate-40 (PS40), polysorbate-60 (PS60), polysorbate-65 (PS65), and polysorbate-80 (PS80).

35. The use of any one of claims 28-34, wherein the subject is to be administered a first dose at day 0 and a boost dose at day 21.

36. The use of any one of claims 28-34, wherein a single dose of the immunogenic composition is to be administered.

37. The use of any one of claims 28-35, wherein the subject is to be administered a second immunogenic composition different from the immunogenic composition of claim 28.

38. The use of claim 37, wherein the second immunogenic composition comprises an mRNA encoding a SARS-Cov-2 Spike glycoprotein, a plasmid DNA encoding a SARS-Cov-2 Spike glycoprotein, a viral vector encoding a SARS-Cov-2 Spike glycoprotein, or an inactivated SARS-CoV-2 virus.

39. The use of any one of claims 28-38, wherein the heterogenous SARS-CoV-2 strain is selected from the group consisting of a B.1.1.7 SARS-CoV-2 strain, B.1.351 SARS-CoV-2 strain, P.1 SARS-CoV-2 strain, B.1.617.2 SARS-CoV-2 strain, B.1.525 SARS-CoV-2 strain, B.1.526 SARS-CoV-2 strain, B.1.617.1 SARS-CoV-2 strain, a C.37 SARS-CoV-2 strain, B.1.621 SARS-CoV-2 strain, and a Cal.20C SARS-CoV-2 strain.

40. The use of any one of claims 28-39, wherein the efficacy of the immunogenic composition for preventing coronavirus disease-19 (COVID-19) is at least about 50 %, at least about 55 %, at least about 60 %, at least about 65 %, at least about 70 %, at least about 75 %, at least about 80 %, at least about 85 %, about least about 90 %, at least

about 91 %, at least about 92 %, at least about 93 %, at least about 94 %, at least about 95 %, at least about 96 %, at least about 97 %, at least about 98 %, at least about 99 %, or about 100 % for up to about 2 months, up to about 2.5 months, up to about 3 months, up to about 3.5 months, up to about 4 months, up to about 4.5 months, up to about 5 months, up to about 5.5 months, up to about 6 months, up to about 6.5 months, up to about 7 months, up to about 7.5 months, up to about 8 months, up to about 8.5 months, up to about 9 months, up to about 9.5 months, up to about 10 months, up to about 10.5 months, up to about 11 months, up to about 11.5 months, or up to about 12 months after administration of the immunogenic composition.

41. The use of any one of claims 28-40, wherein the efficacy of the immunogenic composition for preventing coronavirus disease-19 (COVID-19) is from about 50 % to about 99 %, from about 50 % to about 95 %, from about 50 % to about 90 %, from about 50 % to about 85 %, from about 50 % to about 80 %, from about 60 % to about 99 %, from about 60 % to about 95 %, from about 60 % to about 90 %, from about 60 % to about 85 %, from about 60 % to about 80 %, from about 40 % to about 99 %, from about 40 % to about 95 %, from about 40 % to about 90 %, from about 40 % to about 85 %, from about 40 % to about 80 %, from about 40 % to about 75 %, from about 40 % to about 70 %, from about 40 % to about 65 %, from about 40 % to about 55 %, or from about 40 % to about 50 % for up to about 2 months, up to about 2.5 months, up to about 3 months, up to about 3.5 months, up to about 4 months, up to about 4.5 months, up to about 5 months, up to about 5.5 months, up to about 6 months, up to about 6.5 months, up to about 7 months, up to about 7.5 months, up to about 8 months, up to about 8.5 months, up to about 9 months, up to about 9.5 months, up to about 10 months, up to about 10.5 months, up to about 11 months, up to about 11.5 months, or up to about 12 months after administration of the immunogenic composition.

42. The use of any one of claims 28-41, wherein the COVID-19 is mild COVID-19, a moderate COVID-19, or a severe COVID-19.

43. Use of a nanoparticle comprising a coronavirus S (CoV S) glycoprotein having the amino acid sequence of SEQ ID NO: 87, and a non-ionic detergent core, a pharmaceutically acceptable buffer, and (iii) a saponin adjuvant, in the manufacture of a medicament for inducing a protective immune response in a subject against a

heterogenous SARS-CoV-2 strain, wherein the heterogenous SARS-CoV-2 strain has a SARS-CoV-2 S glycoprotein having from about 1 to about 60 modifications compared to a SARS-CoV-2 glycoprotein of SEQ ID NO: 1.

44. The use of claim 43, wherein the heterogeneous SARS-CoV-2 strain has a SARS-CoV-2 S glycoprotein having from about 1 to about 20 modifications, from about 1 to about 10 modifications, from about 10 to about 20 modifications, from 10 to about 30 modifications, from about 10 to about 40 modifications, from 10 to about 50 modifications, from 10 to about 60 modifications, from 20 to about 60 modifications, from 20 to about 50 modifications, from about 20 to about 40 modifications, from about 5 to about 15 modifications, or from about 5 to about 10 modifications compared to a SARS-CoV-2 glycoprotein of SEQ ID NO: 1.