CLAIMS

1. A severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) 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 modifications including:

mutation of amino acid 67 to alanine, amino acid 202 to glycine, and amino acid 229 to histidine;

wherein the RBD comprises mutation of amino acid 404 to asparagine, amino acid 471 to lysine, and amino acid 488 to tyrosine;

wherein the SD1/2 domain comprises mutation of amino acid 601 to glycine, and amino acid 668 to valine; and

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

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

2. The SARS-CoV-2S glycoprotein of claim 1 comprising or consisting of an amino acid sequence having at least 95% identity to SEQ ID NO: 115.

3. The SARS-CoV-2S glycoprotein of claim 1 comprising a signal peptide, optionally wherein the signal peptide comprises an amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 117.

4. The SARS-CoV-2S glycoprotein of claim 1 comprising a C-terminal fusion protein.

5. The SARS-CoV-2S glycoprotein of claim 4, wherein the C-terminal fusion protein is a hexahistidine tag or a foldon.

6. The SARS-CoV-2S glycoprotein of claim 5, wherein the foldon has an amino acid sequence corresponding to SEQ ID NO: 68.

7. The SARS-CoV-2S glycoprotein of any one of claims 1-6, wherein the ΔHcal is at least 2-fold greater than the ΔHcal of the wild-type CoV S glycoprotein (SEQ ID NO: 2).

8. The SARS-CoV-2S glycoprotein of any one of claims 1-7, 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: 115.

9. The SARS-CoV-2S glycoprotein of any one of claims 1-7, 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: 115.

10. An isolated nucleic acid encoding the SARS-CoV-2 S glycoprotein of any of claims 1-9.

11. A vector comprising the nucleic acid of claim 10.

12. A nanoparticle comprising the SARS-CoV-2S glycoprotein of any one of claims 1-9.

13. The nanoparticle of claim 12, wherein the nanoparticle has a Zavg diameter of between 20 nm and 35 nm; or the nanoparticle has a polydispersity index from 0.2 to 0.45.

14. A cell expressing the SARS-CoV-2S glycoprotein of any of claims 1-9.

15. A vaccine composition comprising the SARS-CoV-2S glycoprotein of any one of claims 1-9 and a pharmaceutically acceptable buffer.

16. The vaccine composition of claim 15, comprising an adjuvant.

17. The vaccine composition of claim 16, 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.

18. The vaccine composition of claim 17, wherein fraction A of *Quillaja Saponaria* Molina and fraction C of *Quillaja Saponaria* Molina account for 76.5 % to 93.5 % by weight and 13.5 % to 16.5 % 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 92 % by weight and 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.

19. An immunogenic composition comprising:

(i) a nanoparticle comprising a SARS-CoV-2 S glycoprotein of any one of claims 1-9, and a non-ionic detergent core;

(ii) a pharmaceutically acceptable buffer, and

(iii) a saponin adjuvant.

20. The immunogenic composition of claim 19, comprising from 2.7 μg to 27.5 μg of CoV S glycoprotein.

21. The immunogenic composition of claim 19, comprising 4.5 to 5.5 μg of CoV S glycoprotein.

22. The immunogenic composition of any one of claims 19-21, 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.

23. The immunogenic composition of claim 22, 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 76.5 % to 93.5 % by weight and 13.5 % to 16.5 % 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.

24. The immunogenic composition of any one of claims 19-23, comprising 45 to 55 µg of saponin adjuvant.

25. The immunogenic composition of any one of claims 19-24, 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).

26. Use of the vaccine composition of any one of claims 15-19 or the immunogenic composition of any one of claims 20-26 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.

27. The use of claim 26, wherein from 2.7 µg to 27.5 µg of CoV S glycoprotein is to be administered.

28. The use of claim 26 or 27, wherein 4.5 to 5.5 µg of CoV S glycoprotein is to be administered.

29. The use of any one of claims 26-28, wherein the vaccine composition or immunogenic composition comprises an adjuvant and 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.

30. The use of claim 29, 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 76.5 % to 93.5 % by weight and 13.5% to 16.5 % 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.

31. The use of any one of claims 26-30, wherein the vaccine composition or immunogenic composition comprises an adjuvant and the subject is to be administered 45 to 55 μg of the adjuvant.

32. The use of any one of claims 26-31, wherein the vaccine composition or immunogenic composition comprises a nanoparticle include the SARS-CoV-2 S glycoprotein and a non-ionic detergent core and 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).

33. The use of any one of claims 26-32, wherein the subject is to be administered a first dose at day 0 and a boost dose at day 21.

34. The use of any one of claims 26-32, wherein a single dose of the immunogenic composition is to be administered.

35. The use of any one of claims 26-33, wherein the subject is to be administered a second immunogenic composition different from the immunogenic composition of claim 26.

36. The use of claim 35, 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.

37. The use of any one of claims 26-36, wherein the heterogenous SARS-CoV-2 strain is selected from the group consisting of a B.1.1.7 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.

38. The use of any one of claims 26-37, wherein the efficacy of the immunogenic composition for preventing coronavirus disease-19 (COVID-19) is at least 50 %, at least 55 %, at least 60 %, at least 65 %, at least 70 %, at least 75 %, at least 80 %, at least 85 %, 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 100 % for up to 2 months, up to 2.5 months, up to 3 months, up to 3.5 months, up to 4 months, up to 4.5 months, up to 5 months, up to 5.5 months, up to 6 months, up to 6.5 months, up to 7 months, up to 7.5 months, up to 8 months, up to 8.5 months, up to 9 months, up to 9.5 months, up to 10 months, up to 10.5 months, up to 11 months, up to 11.5 months, or up to 12 months after administration of the immunogenic composition.

39. The use of any one of claims 26-38, wherein the efficacy of the immunogenic composition for preventing coronavirus disease-19 (COVID-19) is from 50 % to 99 %, from 50 % to 95 %, from 50 % to 90 %, from 50 % to 85 %, from 50 % to 80 %, from 60 % to 99 %, from 60 % to 95 %, from 60 % to 90 %, from 60 % to 85 %, from 60 % to 80 %, from 40 % to 99 %, from 40 % to 95 %, from 40 % to 90 %, from 40 % to 85 %, from 40 % to 80 %, from 40 % to 75 %, from 40 % to 70 %, from 40 % to 65 %, from 40 % to 55 %, or from

40 % to 50 % for up to 2 months, up to 2.5 months, up to 3 months, up to 3.5 months, up to 4 months, up to 4.5 months, up to 5 months, up to 5.5 months, up to 6 months, up to 6.5 months, up to 7 months, up to 7.5 months, up to 8 months, up to 8.5 months, up to 9 months, up to 9.5 months, up to 10 months, up to 10.5 months, up to 11 months, up to 11.5 months, or up to 12 months after administration of the immunogenic composition.

40. The use of claim 38 or 39, wherein the COVID-19 is mild COVID-19, a moderate COVID-19, or a severe COVID-19.

41. Use of a nanoparticle comprising a coronavirus S (CoV S) glycoprotein having the amino acid sequence of SEQ ID NO: 115, 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 1 to 60 modifications compared to a SARS-CoV-2 glycoprotein of SEQ ID NO: 1.

42. The use of claim 41, wherein the heterogeneous SARS-CoV-2 strain has a SARS-CoV-2 S glycoprotein having from 1 to 20 modifications, from 1 to 10 modifications, from 10 to 20 modifications, from 10 to 30 modifications, from 10 to 40 modifications, from 10 to 50 modifications, from 10 to 60 modifications, from 20 to 60 modifications, from 20 to 50 modifications, from 20 to 40 modifications, from 5 to 15 modifications, or from 5 to 10 modifications compared to a SARS-CoV-2 glycoprotein of SEQ ID NO: 1.