

ANTIBODIES AGAINST SARS-COV-2 AND METHODS OF USING THE SAME

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format
5 in lieu of a paper copy, and is hereby incorporated by reference into the specification.
The name of the text file containing the Sequence Listing is 930585_402WO
_SEQUENCE_LISTING.txt. The text file is 328 KB, was created on February 24,
2021, and is being submitted electronically via EFS-Web.

BACKGROUND

10 A novel betacoronavirus emerged in Wuhan, China, in late 2019. As of
February 19, 2021, approximately 110 million cases of infection by this virus (termed,
among other names, SARS-CoV-2 and originally identified as Wuhan coronavirus),
were confirmed worldwide, and had resulted in approximately 2.45 million deaths.
Modalities for preventing or treating SARS-CoV-2 infection, and diagnostic tools for
15 diagnosing a SARS-CoV-2 infection, are needed.

SUMMARY

In one aspect, the present disclosure refers to an isolated antibody, or an
antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) that
20 comprises the complementarity determining region (CDR)H1 amino acid sequence set
forth in SEQ ID NO.:106, the CDRH2 amino acid sequence set forth in SEQ ID
NO.:121, and the CDRH3 amino acid sequence set forth in SEQ ID NO.:108, and a
light chain variable domain (VL) that comprises the CDRL1 amino acid sequence set
forth in SEQ ID NO.:169, the CDRL2 amino acid sequence set forth in SEQ ID
25 NO.:170, and the CDRL3 amino acid sequence set forth in SEQ ID NO.:171,
wherein the antibody or antigen-binding fragment is capable of binding to a SARS-
CoV-2 surface glycoprotein (S).

In another aspect, the present disclosure refers to an isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113 and the VL comprises or consists of the amino acid sequence set forth in SEQ ID NO.:168.

In another aspect, the present disclosure refers to the use of a SARS-CoV-2 neutralizing antibody or antigen-binding fragment in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody or antigen-binding fragment comprises:

- (i) a heavy chain variable domain (VH) that comprises: the complementarity determining region (CDR)H1 amino acid sequence set forth in SEQ ID NO.:106, the CDRH2 amino acid sequence set forth in SEQ ID NO.:121, and the CDRH3 amino acid sequence set forth in SEQ ID NO.:108; and
- (ii) a light chain variable domain (VL) that comprises: the CDRL1 amino acid sequence set forth in SEQ ID NO.:169, the CDRL2 amino acid sequence set forth in SEQ ID NO.:170, and the CDRL3 amino acid sequence set forth in SEQ ID NO.:171.

In another aspect, the present disclosure refers to the use of a SARS-CoV-2 neutralizing antibody or antigen-binding fragment in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody or antigen-binding fragment comprises a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113 and the VL comprises or consists of the amino acid sequence set forth in SEQ ID NO.:168.

In another aspect, the present disclosure refers to an isolated antibody that comprises: (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:173; and (ii) 5 a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

In another aspect, the present disclosure refers to an isolated antibody that comprises: (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that 10 comprises or consists of the amino acid sequence set forth in SEQ ID NO.:175; and (ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

15 In another aspect, the present disclosure refers to the use of a SARS-CoV-2 neutralizing antibody in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody comprises: (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists 20 of the amino acid sequence set forth in SEQ ID NO.:173; and (ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

In another aspect, the present disclosure refers to the use of a SARS-CoV-2 neutralizing antibody in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody comprises: (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:175; and (ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

10 In another aspect, the present disclosure refers to an isolated polynucleotide encoding the antibody or antigen-binding fragment as disclosed herein, or encoding a VH, a heavy chain, a VL, and/or a light chain of the antibody or the antigen-binding fragment.

In another aspect, the present disclosure refers to a recombinant vector
15 comprising the polynucleotide as disclosed herein.

In another aspect, the present disclosure refers to a method for producing an antibody or antigen-binding fragment as disclosed herein, wherein the method comprises culturing a host cell expressing the antibody or antigen-binding fragment under conditions and for a time sufficient to produce the antibody, or the antigen-binding fragment.
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In another aspect, the present disclosure refers to a composition comprising the antibody or antigen-binding fragment as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the present disclosure refers to a composition comprising the polynucleotide as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent.
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In another aspect, the present disclosure refers to a composition comprising the recombinant vector as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the present disclosure refers to a host cell comprising the polynucleotide as disclosed herein and/or the vector as disclosed herein, wherein the polynucleotide is heterologous to the host cell.

5 In another aspect, the present disclosure refers to a human B cell comprising the polynucleotide as disclosed herein, wherein the polynucleotide is heterologous to the human B cell and/or wherein the human B cell is immortalized.

In yet another aspect, the present disclosure refers to a composition comprising the host cell as disclosed herein or the human B cell as disclosed herein and a pharmaceutically acceptable carrier, excipient, or diluent.

10 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figures 1A and 1B show binding by antibodies (1A) S303 (VH SEQ ID NO.:63; VL SEQ ID NO.:67) and (1B) S309 (VH SEQ ID NO.:105; VL SEQ ID NO.:168) of the present disclosure to recombinant SARS-CoV-2 RBD, as described in Example 2.

15 **Figures 2A and 2B** show SARS-CoV-2 neutralization of infection by certain antibodies of the present disclosure, as described in Example 4.

Figures 3A-3I show SARS-CoV-2 neutralization of infection, as described in Example 4. Figure 3A shows neutralization by donor plasma from SARS-CoV-1 survivors. Figures 3B-3D and 3I show neutralization by supernatant from B cells
20 expressing certain antibodies of the present disclosure. Figures 3E-3H show neutralization by certain recombinant IgG1 antibodies.

CLAIMS

What is claimed is:

1. An isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) that comprises the complementarity determining region (CDR)H1 amino acid sequence set forth in SEQ ID NO.:106, the CDRH2 amino acid sequence set forth in SEQ ID NO.:121, and the CDRH3 amino acid sequence set forth in SEQ ID NO.:108, and a light chain variable domain (VL) that comprises the CDRL1 amino acid sequence set forth in SEQ ID NO.:169, the CDRL2 amino acid sequence set forth in SEQ ID NO.:170, and the CDRL3 amino acid sequence set forth in SEQ ID NO.:171,

wherein the antibody or antigen-binding fragment is capable of binding to a SARS-CoV-2 surface glycoprotein (S).

2. The isolated antibody or antigen-binding fragment of claim 1, which is capable of binding to a surface glycoprotein (S) of:

- (i) a SARS-CoV-2 Wuhan-Hu-1 (SEQ ID NO.:165);
- (ii) a SARS-CoV-2 B.1.1.7;
- (iii) a SARS-CoV-2 B.1.351;
- (iv) a SARS-CoV-2 comprising any one or more of the following substitution mutations relative to SEQ ID NO.:165: N501Y; S477N; N439K; L452R; E484K; Y453F; A520S; K417N; K417V; S494P; N501T; S477R; V367F; P384L; A522S; A522V; V382L; P330S; T478I; S477I; P479S; or
- (v) any combination of (i)-(iv).

3. An isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113 and the VL comprises or consists of the amino acid sequence set forth in SEQ ID NO.:168.

4. The isolated antibody or antigen-binding fragment of claim 1 or 3, which is capable of neutralizing a SARS-CoV-2 infection:

- (i) in an *in vitro* model of infection;
- (ii) in an *in vivo* animal model of infection;
- (iii) in a human; or
- (iv) any combination of (i)-(iii).

5. Use of a SARS-CoV-2 neutralizing antibody or antigen-binding fragment in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody or antigen-binding fragment comprises:

(i) a heavy chain variable domain (VH) that comprises: the complementarity determining region (CDR)H1 amino acid sequence set forth in SEQ ID NO.:106, the CDRH2 amino acid sequence set forth in SEQ ID NO.:121, and the CDRH3 amino acid sequence set forth in SEQ ID NO.:108; and

(ii) a light chain variable domain (VL) that comprises: the CDRL1 amino acid sequence set forth in SEQ ID NO.:169, the CDRL2 amino acid sequence set forth in SEQ ID NO.:170, and the CDRL3 amino acid sequence set forth in SEQ ID NO.:171.

6. The use of claim 5, wherein the SARS-CoV-2 comprises:

- (i) a SARS-CoV-2 Wuhan-Hu-1;
- (ii) a SARS-CoV-2 B.1.1.7;
- (iii) a SARS-CoV-2 B.1.351;
- (iv) a SARS-CoV-2 comprising, in a surface glycoprotein (S) thereof, any

one or more of the following substitution mutations relative to SEQ ID NO.:165:
N501Y; S477N; N439K; L452R; E484K; Y453F; A520S; K417N; K417V; S494P;
N501T; S477R; V367F; P384L; A522S; A522V; V382L; P330S; T478I; S477I; P479S;
or

- (v) any combination of (i)-(iv).

7. Use of a SARS-CoV-2 neutralizing antibody or antigen-binding fragment in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody or antigen-binding fragment comprises a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113 and the VL comprises or consists of the amino acid sequence set forth in SEQ ID NO.:168.

8. The use of claim 5 or 7 wherein the SARS-CoV-2 neutralizing antibody or antigen-binding fragment is to be administered intravenously.

9. The isolated antibody or antigen-binding fragment of claim 1 or the use of claim 5, wherein:

- (i) the VH comprises or consists of an amino acid sequence having at least 85% identity to the amino acid sequence set forth in SEQ ID NO.:113; and/or
- (ii) the VL comprises or consists of an amino acid sequence having at least 85% identity to the amino acid sequence set forth in SEQ ID NO.:168.

10. The isolated antibody or antigen-binding fragment of claim 9 or the use of claim 9, wherein:

- (i) the VH comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:113; and/or
- (ii) the VL comprises or consists of an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO.:168.

11. The isolated antibody or antigen-binding fragment of claim 9 or the use of claim 9, wherein:

- (i) the VH comprises or consists of an amino acid sequence having at least 95% identity to the amino acid sequence set forth in SEQ ID NO.:113; and/or

(ii) the VL comprises or consists of an amino acid sequence having at least 95% identity to the amino acid sequence set forth in SEQ ID NO.:168.

12. The isolated antibody or antigen-binding fragment of claim 9 or the use of claim 9, wherein:

(i) the VH comprises or consists of an amino acid sequence having at least 99% identity to the amino acid sequence set forth in SEQ ID NO.:113; and/or

(ii) the VL comprises or consists of an amino acid sequence having at least 99% identity to the amino acid sequence set forth in SEQ ID NO.:168.

13. The isolated antibody or antigen-binding fragment of claim 1 or 3 or the use of claim 5 or 7, wherein the antibody or antigen-binding fragment is capable of inhibiting an interaction between:

(i) SARS-CoV-2 and a human DC-SIGN;

(ii) SARS-CoV-2 and a human L-SIGN;

(iii) SARS-CoV-2 and a human SIGLEC-1; or

(iv) any combination of (i)-(iii).

14. The isolated antibody or antigen-binding fragment of claim 1 or the use of claim 5, wherein the antibody or antigen-binding fragment comprises a human antibody, a monoclonal antibody, a purified antibody, a single chain antibody, a Fab, a Fab', a F(ab')₂, a Fv, a scFv, or a scFab.

15. The isolated antibody or antigen-binding fragment of claim 1 or 3 or the use of claim 5 or 7, wherein the antibody or antigen-binding fragment further comprises a Fc polypeptide or a fragment thereof.

16. The isolated antibody or antigen-binding fragment of claim 1 or 3 or the use of claim 5 or 7, wherein the antibody or antigen-binding fragment is a IgG, IgA, IgM, IgE, or IgD isotype.

17. The isolated antibody or antigen-binding fragment of claim 15 or the use of claim 15, wherein the Fc polypeptide or fragment thereof comprises:

- (i) a mutation that enhances binding to a FcRn as compared to a reference Fc polypeptide that does not comprise the mutation; and/or
- (ii) a mutation that enhances binding to a FcγR as compared to a reference Fc polypeptide that does not comprise the mutation.

18. The isolated antibody or antigen-binding fragment of claim 17 or the use of claim 17, wherein the mutation that enhances binding to a FcRn comprises:

- (i) M428L/N434S;
- (ii) M252Y/S254T/T256E;
- (iii) T250Q/M428L;
- (iv) P257I/Q311I;
- (v) P257I/N434H;
- (vi) D376V/N434H;
- (vii) T307A/E380A/N434A; or
- (viii) any combination of (i)-(vii).

19. The isolated antibody or antigen-binding fragment of claim 18 or the use of claim 18, wherein the mutation that enhances binding to a FcRn comprises M428L/N434S.

20. The isolated antibody or antigen-binding fragment of claim 17 or the use of claim 17, wherein the mutation that enhances binding to a FcγR comprises S239D, I332E, A330L, G236A, or any combination thereof.

21. The isolated antibody or antigen-binding fragment of claim 20 or the use of claim 20, wherein the mutation that enhances binding to a FcγR comprises:

- (i) S239D/I332E;
- (ii) S239D/A330L/I332E;

- (iii) G236A/S239D/I332E; or
- (iv) G236A/A330L/I332E.

22. The isolated antibody or antigen-binding fragment of claim 1 or 3 or the use of claim 5 or 7, wherein the antibody or antigen-binding fragment further comprises a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:265 or 266.

23. An isolated antibody that comprises:

- (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:173; and
- (ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

24. An isolated antibody that comprises:

- (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:175; and
- (ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

25. Use of a SARS-CoV-2 neutralizing antibody in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody comprises:

- (i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:173; and

(ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

26. Use of a SARS-CoV-2 neutralizing antibody in the manufacture of a medicament for treating a SARS-CoV-2 infection in a subject, wherein the SARS-CoV-2 neutralizing antibody comprises:

(i) a heavy chain comprising (i)(1) a VH that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:113, and (i)(2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:175; and

(ii) a light chain comprising (ii)(1) a VL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.: 168, and (ii)(2) a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:174.

27. An isolated polynucleotide encoding the antibody or antigen-binding fragment of any one of claims 1 to 4 or 9 to 24, or encoding a VH, a heavy chain, a VL, and/or a light chain of the antibody or the antigen-binding fragment.

28. The isolated polynucleotide of claim 27, wherein the polynucleotide comprises deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), wherein the RNA optionally comprises messenger RNA (mRNA).

29. The isolated polynucleotide of claim 27 or 28, which is codon-optimized for expression in a host cell.

30. The isolated polynucleotide of claim 29, which is codon-optimized for expression in a mammalian host cell.

31. The isolated polynucleotide of any one of claims 27 to 30, wherein the polynucleotide further comprises a nucleotide sequence encoding a signal peptide.

32. The isolated polynucleotide of any one of claims 27-31, comprising a polynucleotide having at least 50% identity to, or comprising the polynucleotide sequence of, any one of SEQ ID NOs.:257-262.

33. A recombinant vector comprising the polynucleotide of any one of claims 27-32.

34. A method for producing an antibody or antigen-binding fragment of any one of claims 1 to 4 or 9 to 24, wherein the method comprises culturing a host cell expressing the antibody or antigen-binding fragment under conditions and for a time sufficient to produce the antibody, or the antigen-binding fragment.

35. The method for producing an antibody or antigen-binding fragment of claim 34, wherein the host cell comprises a recombinant vector comprising a polynucleotide of any one of claims 27 to 32.

36. The method for producing an antibody or antigen-binding fragment of claim 34 or 35, wherein the host cell is a mammalian cell.

37. The method for producing an antibody or antigen-binding fragment of any one of claims 34-36, wherein the method comprises culturing the host cell in batch cell culture.

38. The method for producing an antibody or antigen-binding fragment of any one of claims 34-37, wherein the method further comprises purifying the antibody or antigen-binding fragment.

39. A composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 4 or 9 to 24 and a pharmaceutically acceptable carrier, excipient, or diluent.

40. A composition comprising the polynucleotide of any one of claims 27-32 and a pharmaceutically acceptable carrier, excipient, or diluent.

41. A composition comprising the recombinant vector of claim 33 and a pharmaceutically acceptable carrier, excipient, or diluent.

42. A host cell comprising the polynucleotide of any one of claims 27-32 and/or the vector of claim 33, wherein the polynucleotide is heterologous to the host cell.

43. A human B cell comprising the polynucleotide of any one of claims 27-32, wherein the polynucleotide is heterologous to the human B cell and/or wherein the human B cell is immortalized.

44. A composition comprising the host cell of claim 42 or the human B cell of claim 43 and a pharmaceutically acceptable carrier, excipient, or diluent.