

since the efficacy and pharmacokinetic properties of each antibody differ, are difficult to formulate in order to maintain reliable administration schemes.

The present invention, however, provides monoclonal antibodies which show an advantageous binding profile to the S1-protein of SARS-CoV-2 allowing the binding and neutralization of SARS-CoV-2-activity of seven different “escape”-mutants reported up to date, as well as also the binding specifically to the “7-PM-mutant”, which comprises all seven known “escape”-mutations in one molecule.

Summary

In one aspect, there is provided a humanized or a human therapeutic monoclonal antibody or antigen-binding fragment, or a substantially similar variant thereof that binds specifically to SARS-CoV-2 glycoprotein S with the amino acid sequence of SEQ ID NO: 02 and neutralizes the infectious activity of SARS-CoV-2.

In another aspect, there is provided an isolated nucleic acid molecule encoding the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof as defined above.

In another aspect, there is provided an expression vector comprising the nucleic acid molecule as defined above.

In another aspect, there is provided a method of producing the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof as defined above comprising the steps of introducing the expression vector as defined above into an isolated host cell, growing the cell under conditions permitting production of the antibody or antigen-binding fragment thereof, recovering the antibody or fragment so produced.

In another aspect, there is provided a pharmaceutical composition comprising the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof as defined above, and a pharmaceutically acceptable carrier.

In another aspect, there is provided a therapeutic antibody or antigen-binding as defined above for the use in the prevention and/or treatment of a SARS-CoV-2-related disease or condition in a patient.

In another aspect, there is provided a use of a therapeutic antibody or antigen-binding fragment as defined above in the manufacture of a medicament for preventing and/or treating a SARS-CoV-2-related disease or condition in a patient.

Detailed Description

In a first embodiment, the present invention pertains to a therapeutic antibody or antigen-binding fragment thereof that binds specifically to SARS-CoV-2 glycoprotein S with the amino acid sequence of SEQ ID NO: 02 and neutralizes the infectious activity of SARS-CoV-2.

In a second embodiment, the present invention pertains to a therapeutic antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes for binding to the SARS-CoV-2 glycoprotein S with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 406; and a light chain variable region of the amino acid sequence in SEQ ID NO: 408.

In another embodiment, the present invention pertains to a therapeutic antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof competes for binding to the SARS-CoV-2 glycoprotein S with an antibody comprising at least one, two, three or all of the amino acid sequences of SEQ ID NO: 909 – 928 (YU505-A02); SEQ ID NO: 349 – 368 (YU536-D04); SEQ ID NOs: 389 - 408 (YU537-H11) and/or SEQ ID NO: 1305 - 1312 (STE90-C11).

In a fourth embodiment, the present invention pertains to a therapeutic antibody or antigen-binding fragment thereof, comprising a variable heavy chain with an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 46, 66, 86, 106, 126, 146, 166, 186, 206, 226, 246, 266, 286, 306, 326, 346, 366, 386, 406, 426, 446, 466, 486, 506, 526, 546, 566, 586, 606, 626, 646, 666, 686, 706, 726, 746, 766, 786, 806, 826, 846, 866, 886, 906, 926, 946, 966, 986, 1006, 1026, 1046, 1066, 1086, 1106, 1126, 1146, 1166, 1186, 1206, 1226, 1246, 1266, and 1286;

and

a light chain with an amino acid sequence selected from the group consisting of SEQ ID NO: 28, 48, 68, 88, 108, 128, 148, 168, 188, 208, 228, 248, 268, 288, 308, 328, 348, 368, 388, 408,

Claims

1. A humanized or a human therapeutic monoclonal antibody or antigen-binding fragment, or a substantially similar variant thereof that binds specifically to SARS-CoV-2 glycoprotein S with the amino acid sequence of SEQ ID NO: 02 and neutralizes the infectious activity of SARS-CoV-2.
2. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to claim 1, wherein the neutralization of the infectious activity of SARS-CoV-2 results in confluence score of at least 95% as measured with an infectious SARS-CoV-2 VERO E6 neutralizing assay.
3. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any of claims 1 or 2, wherein the antibody or antigen-binding fragment binds specifically to an epitope within the receptor binding domain (RBD) of the S1 domain of SARS-CoV-2 glycoprotein (SEQ ID NO: 06) and binds specifically to at least one of the escape-mutations of the S1 domain of SARS-CoV-2 glycoprotein selected from the list consisting of S1-V367F, S1-N439K, S1-G476S, S1-V483A, S1-E484K, S1-G485R, S1-F486V, S1-7PM-mutant (SEQ ID NO: 1730), and any combination thereof.
4. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to claim 3, wherein said antibody or antigen-binding fragment thereof binds specifically both to an epitope comprising the amino acids 400-FVIR-GDEV RQIAPQTGKIADDYN-422 within the RBD (SEQ ID NO: 06) as well as to the S1-7PM-mutant (SEQ ID NO: 1730).
5. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any of claims 1 or 2, wherein said antibody or antigen-binding fragment thereof competes for binding to an epitope within the RBD (SEQ ID NO: 06) with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 1305; and a light chain variable region of the amino acid sequence in SEQ ID NO: 1309 or with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 926 and a light chain variable region of the amino acid sequence in SEQ ID NO: 928; and wherein the contamination ratio is less than 0.2.
6. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any of claims 1 or 2, wherein said antibody or antigen-binding fragment thereof competes for binding to the epitope 165-AKRVNCYFPLQSYGFQ-180

within the S1-7PM-mutant (SEQ ID NO: 1730) with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 1305; and a light chain variable region of the amino acid sequence in SEQ ID NO: 1309 or with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 926 and a light chain variable region of the amino acid sequence in SEQ ID NO: 928.

7. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any of the previous claims, comprising

a heavy chain CDR1 (H-CDR1) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1306, 910, 350, and 390;

a heavy chain CDR2 (H-CDR2) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1307, 912, 352, and 392;

a heavy chain CDR3 (H-CDR3) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1308, 914, 354, and 394;

and

a light chain CDR1 (L-CDR1) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1310, 916, 356, and 396;

a light chain CDR2 (L-CDR2) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1311, 918, 358, and 398;

a light chain CDR3 (L-CDR3) domain with an amino acid sequence selected from the group consisting of SEQ ID NO: 1312, 920, 360, and 400.

8. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any one of the previous claims, selected from the group of antibodies comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 1305 and a light chain variable region of the amino acid sequence in SEQ ID NO: 1309; a heavy chain variable region of the amino acid sequence in SEQ ID NO: 926 and a light chain variable region of the amino acid sequence in SEQ ID NO: 928; a heavy chain variable region of the amino acid sequence in SEQ ID NO: 366 and a light chain variable region of the amino acid sequence in SEQ ID NO: 368; and/or a heavy chain variable region of the amino acid sequence in SEQ ID NO: 406 and a light chain variable region of the amino acid sequence in SEQ ID NO: 408; and/or any combinations thereof.

9. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any one of the previous claims, comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 1305 and a light chain variable region of the amino acid sequence in SEQ ID NO: 1309.
10. The therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any of the previous claims, characterized by one or more of the following:
 - capable of binding specifically to the RBD of SARS-CoV-2 Glycoprotein S with an affinity (K_D) of 6.5×10^{-8} M or less, preferably 10×10^{-9} M or less,
 - capable of reducing or preventing an antibody-dependent enhancement (ADE) reaction in a patient,
 - capable of preventing, reducing or healing a viral infection with SARS-CoV-2,
 - capable of reducing or preventing the cytokine storm syndrome (CSS) in a patient,
 - capable of reducing the load of viral particles in the sputum of a patient by at least 50% for at least 48 hours after administration of the therapeutic antibody or antigen-binding fragment thereof,
 - having a specific binding specifically to the S1-7PM-mutant (SEQ ID. 1730) with a K_D of 10×10^{-9} M or less,
 - having an IC_{50} of less than 0.036 $\mu\text{g/ml}$, preferably of 0.026 $\mu\text{g/ml}$ or less.
11. An isolated nucleic acid molecule encoding the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any one of the previous claims.
12. An expression vector comprising the nucleic acid molecule according to claim 11.
13. A method of producing the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any one of the previous claims comprising the steps of
 - introducing the expression vector according to claim 12 into an isolated host cell,
 - growing the cell under conditions permitting production of the antibody or antigen-

binding fragment thereof ,

recovering the antibody or fragment so produced.

14. A pharmaceutical composition comprising the therapeutic antibody or antigen-binding fragment or a substantially similar variant thereof according to any one of claims 1 to 10, and a pharmaceutically acceptable carrier.
15. A therapeutic antibody or antigen-binding fragment according to any one of claims 1 to 10 for the use in the prevention and/or treatment of a SARS-CoV-2-related disease or condition in a patient.
16. Use of a therapeutic antibody or antigen-binding fragment according to any one of claims 1 to 10 in the manufacture of a medicament for preventing and/or treating a SARS-CoV-2-related disease or condition in a patient.