

1989, J. Virol. 63:2941-50; Garcia-Barreno *et al.*, 1989, J. Virol. 63:925-32; Taylor *et al.*, 1984, Immunology 52: 137-142; Walsh *et al.*, 1984, Infection and Immunity 43:756-758; and U.S. Pat. Nos. 5,842,307 and 6,818,216. Neutralizing epitopes on the F glycoprotein were originally mapped by identifying amino acids that were altered in antibody escape variants and by
5 assessing antibody binding to RSV F-derived peptides. These studies demonstrated neutralizing antibodies are often targeted to two distinct linear epitopes. See Graham *et al.*, 2015, Curr Opin Immunol 35:30-38 for a review of the antigenic sites for the pre-fusion and post-fusion F forms. Antigenic site II (also called site A) includes residues 255 to 275 and is the target of palivizumab (SYNAGIS[®], AstraZeneca). This epitope was predicted to be conformationally dependent, and
10 the structure of a more potent derivative of palivizumab in complex with this epitope revealed that the linear epitope adopts a helix-loop-helix conformation. Antigenic site IV (also called site C) includes residues 422 to 438 and is the target of antibodies MAb19 and 101F. This epitope is C-terminal to the cysteine-rich region and is part of domain II, which in homologous paramyxovirus F glycoproteins remains structurally unchanged between pre- and post-fusion
15 conformations. 5C4, AM22 and D25 delineate an epitope designated as site 0 which is only present on the pre-fusion F protein and were 50 times as potent as palivizumab. See McLellan *et al.*, 2013, Science 340:1113-1117; International Patent Application No. WO 2008/147196 and U.S. Pat. No. 8,568,726. Other hRSV antibodies are described in International Patent Application Nos. WO94/06448 and WO92/04381 and U.S. Pat. No. 8,221,759.

20 An RSV vaccine for active immunization, if available, could not be utilized for the treatment of newborn babies with immature immune systems or patients who are immunosuppressed. In patients where prophylactic passive immunotherapy is required, as a result of a more chronic form of disease, current therapy is mediated via periodic intravenous inoculation of human IgG prepared from pooled plasma. This type of therapy, due to the low
25 titers of neutralizing anti-RSV antibodies, involves a large quantity of globulin (*e.g.*, 0.75 gm per kg) and consequently requires administration intravenously, in a clinic or hospital, over a lengthy period (2 to 4 hours), on a monthly basis during the high risk months (fall, winter and early spring).

SUMMARY

30 The disclosure provides anti-RSV F-protein antibodies and antigen binding fragments thereof comprising the structural and functional features specified below.

In one aspect, there is provided an isolated nucleic acid molecule encoding an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7, an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, or encoding both an antibody heavy chain variable region comprising the amino acid sequence of
5 SEQ ID NO: 7 and an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

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

In another aspect, there is provided a host cell comprising the expression vector as
10 defined herein.

In another aspect, there is provided an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 24, and SEQ ID NO: 26.

In another aspect, there is provided a method of producing an antibody or antigen
15 binding fragment comprising:

(a) culturing a host cell comprising a polynucleotide encoding an antibody heavy chain variable region and a polynucleotide encoding an antibody light chain variable region under conditions favorable to expression of the polynucleotide; and

(b) recovering the antibody or antigen binding fragment from the host cell and/or
20 culture medium;

wherein the antibody heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7 and the antibody light chain variable region comprises the amino acid sequence of SEQ ID NO: 8.

In another aspect, there is provided use of an antibody or antigen binding
25 fragment that binds to human RSV F protein, in the manufacture of a medicament for the prevention or treatment of an RSV infection in a human subject, wherein the antibody or antigen binding fragment comprises a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain variable region CDR3 comprising the amino acid
30 sequence of SEQ ID NO: 3, a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain variable region CDR2 comprising the amino acid

sequence of SEQ ID NO: 5, and a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

In another aspect, there is provided use of an antibody or antigen binding fragment that binds to human RSV F protein, in the manufacture of a medicament for the prevention or treatment of transplantation related RSV infections in a human subject, wherein the antibody or antigen binding fragment comprises a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

CLAIMS

1. An isolated nucleic acid molecule encoding an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7, an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8, or encoding both an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

2. An expression vector comprising the nucleic acid molecule of claim 1.

3. A host cell comprising the expression vector of claim 2.

4. The host cell of claim 3, wherein the host cell is a *Pichia* cell or a Chinese hamster ovary cell.

5. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule encodes an antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 23, an antibody light chain comprising the amino acid sequence of SEQ ID NO: 25, or encoding both an antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 23 and an antibody light chain comprising the amino acid sequence of SEQ ID NO: 25.

6. The isolated nucleic acid molecule of claim 5, wherein the isolated nucleic acid molecule encoding the antibody heavy chain has the nucleic acid sequence set forth in SEQ ID NO: 24 and the nucleic acid molecule encoding the antibody light chain has the nucleic acid sequence set forth in SEQ ID NO: 26.

7. An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 24, and SEQ ID NO: 26.

8. A method of producing an antibody or antigen binding fragment comprising:

(a) culturing a host cell comprising a polynucleotide encoding an antibody heavy chain variable region and a polynucleotide encoding an antibody light chain variable region under conditions favorable to expression of the polynucleotide; and

(b) recovering the antibody or antigen binding fragment from the host cell and/or culture medium;

wherein the antibody heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 7 and the antibody light chain variable region comprises the amino acid sequence of SEQ ID NO: 8.

9. The method of claim 8, wherein the host cell comprises an expression vector having the polynucleotide encoding the antibody heavy chain variable region and an expression vector having the polynucleotide encoding the antibody light chain variable region.

10. The method of claim 8, wherein the host cell comprises an expression vector having both the polynucleotide encoding the antibody heavy chain variable region and the polynucleotide encoding the antibody light chain variable region.

11. The method of any one of claims 8 to 10, wherein the host cell is a *Pichia* cell or a Chinese hamster ovary cell.

12. The method of any one of claims 8 to 11, wherein the polynucleotide encoding the antibody heavy chain variable region encodes an antibody heavy chain comprising the amino acid sequence of SEQ ID NO: 23 and the polynucleotide encoding the antibody light chain encodes an antibody light chain comprising the amino acid sequence of SEQ ID NO: 25.

13. The method of claim 12, wherein the polynucleotide encoding the antibody heavy chain comprises the nucleotide sequence set forth in SEQ ID NO: 24 and the polynucleotide encoding the antibody light chain has the nucleic acid sequence set forth in SEQ ID NO: 26.

14. The method of any one of claims 8 to 11, wherein the polynucleotide encoding the antibody heavy chain variable region comprises the nucleotide sequence of SEQ ID NO: 15 or SEQ ID NO: 17 and the polynucleotide encoding the antibody light chain comprises the nucleotide sequence of SEQ ID NO: 16 or SEQ ID NO: 18.

15. Use of an antibody or antigen binding fragment that binds to human RSV F protein, in the manufacture of a medicament for the prevention or treatment of an RSV infection in a human subject, wherein the antibody or antigen binding fragment comprises a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

16. Use of an antibody or antigen binding fragment that binds to human RSV F protein, in the manufacture of a medicament for the prevention or treatment of transplantation related RSV infections in a human subject, wherein the antibody or antigen binding fragment comprises a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 3, a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

16. The use of claim 14 or 15, wherein the antibody or antigen binding fragment comprises a heavy chain variable domain having the amino acid sequence of SEQ ID NO:7 and a light chain variable domain having the amino acid sequence of SEQ ID NO:8.

17. The use of claim 14 or 15, wherein the antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO:23 and a light chain having the amino acid sequence of SEQ ID NO:25.

5 18. The use of any one of claims 14 to 17, further comprising an antibody or an antigen binding fragment thereof against a respiratory pathogen selected from influenza, human cytomegalovirus (hCMV), human metapneumovirus (hMPV), human parainfluenza (hPIV), human rhinovirus (hRV), mycoplasma pneumonia, streptococcus pneumoniae, adenovirus, bocavirus, enterovirus, norovirus, or BK virus.

10 19. The use of claim 18, wherein the respiratory pathogen is influenza, hCMV, hMPV, hPIV, norovirus, or BK virus.

15 20. The use of any one of claims 14 to 19, wherein the antibody or antigen binding fragment that binds to human RSV F protein is provided in an immunogenic composition comprising an antigen selected from RSV F protein and RSV G protein and fragments thereof.

20 21. The use of any one of claims 14 to 20, wherein the human subject is a human infant.