CLAIMS

1. An isolated human binding molecule capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, and having cross-neutralizing activity against at least an influenza virus comprising HA of the H7 subtype, and/or an influenza virus comprising HA of the H10 subtype.

2. An isolated binding molecule according to claim 1, capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, characterized in that said binding molecule has at least neutralizing activity against one or more of the H3N2 strains selected from the group consisting of A/Wisconsin/67/2005, A/Hiroshima/52/2005, A/Panama/2007/99, and A/Johannesburg/33/94.

3. A binding molecule according to claim 2, wherein said binding molecule further has neutralizing activity against the H3N2 strain A/Hong Kong/1/68.

4. A binding molecule according to claim 2 or 3, wherein said said binding molecule has neutralizing activity against all naturally occurring isolates of influenza virus H3N2 known before January 20, 2010.

5. A binding molecule according to any of the claims 1-4, wherein said binding molecule binds to an epitope comprising the amino acid at position 19, 25, 27, 33 and/or 34 of the HA2 polypeptide of the H3 HA protein.

6. A binding molecule according to claim 5, wherein the binding molecule binds to said epitope on HA2, when the amino acid on position 19 is aspartic acid (D), the amino acid on position 25 is glutamine (Q), the amino acid on position 27 is glycine (G), the amino acid at position 33 is glycine (G) and/or the amino acid at position 34 is glutamine.

7. A binding molecule according to claim 6, wherein the binding molecule does not bind to said epitope on HA2 when one or more of said amino acids have changed.

8. A binding molecule according to any one of claims 1-7, wherein the binding molecule is capable of preventing *in vitro* the trypsin cleavage of the H3 HA precursor molecule HA0 in HA1 and HA2.

9. A binding molecule according to any one of claims 1-8, wherein the binding molecule is capable of preventing the conformational change of the H3 HA protein required for fusion of the viral membrane with the endosomal membrane of an infected cell.

10. A binding molecule according to any one of claims 1-9, wherein the binding molecule is not capable of binding to and neutralizing influenza virus A comprising HA of the H1 subtype, such as H1N1.

11. A binding molecule according to any one of claims 1-10, wherein said binding molecule has cross-neutralizing activity against at least an influenza virus comprising HA of the H7 subtype, and/or an influenza virus comprising HA of the H10 subtype.

12. A binding molecule according to any one of the preceding claims 1-11, wherein said binding molecule has cross-neutralizing activity against all influenza virus subtypes of phylogenetic group 2.

13. A binding molecule according to any of the preceding claims 1-12, wherein the binding molecule is selected from the group consisting of:

a) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:81, a heavy chain CDR2 region of SEQ ID NO:82, and a heavy chain CDR3 region of SEQ ID NO:83,

b) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:87, a heavy chain CDR2 region of SEQ ID NO:88, and a heavy chain CDR3 region of SEQ ID NO:89,

c) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:103, a heavy chain CDR2 region of SEQ ID NO:104, and a heavy chain CDR3 region of SEQ ID NO:105,

d) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:109, a heavy chain CDR2 region of SEQ ID NO:110, and a heavy chain CDR3 region of SEQ ID NO:111,

e) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:115, a heavy chain CDR2 region of SEQ ID NO:116, and a heavy chain CDR3 region of SEQ ID NO:117,

f) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:121, a heavy chain CDR2 region of SEQ ID NO:122, and a heavy chain CDR3 region of SEQ ID NO:123,

g) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:126, a heavy chain CDR2 region of SEQ ID NO:127, and a heavy chain CDR3 region of SEQ ID NO:128,

h) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:132, a heavy chain CDR2 region of SEQ ID NO:133, and a heavy chain CDR3 region of SEQ ID NO:134,

i) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:138, a heavy chain CDR2 region of SEQ ID NO:139, and a heavy chain CDR3 region of SEQ ID NO:140,

j) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:144, a heavy chain CDR2 region of SEQ ID NO:145, and a heavy chain CDR3 region of SEQ ID NO:146,

k) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:150, a heavy chain CDR2 region of SEQ ID NO:151, and a heavy chain CDR3 region of SEQ ID NO:152,

l) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:156, a heavy chain CDR2 region of SEQ ID NO:157, and a heavy chain CDR3 region of SEQ ID NO:158,

m) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:162, a heavy chain CDR2 region of SEQ ID NO:163, and a heavy chain CDR3 region of SEQ ID NO:164,

n) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:168, a heavy chain CDR2 region of SEQ ID NO:169, and a heavy chain CDR3 region of SEQ ID NO:170,

o) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:173, a heavy chain CDR2 region of SEQ ID NO:174, and a heavy chain CDR3 region of SEQ ID NO:175, and

p) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:179, a heavy chain CDR2 region of SEQ ID NO:180, and a heavy chain CDR3 region of SEQ ID NO:181.

14. A binding molecule according to any of the claims 1-13, wherein the binding molecule is selected from the group consisting of:

a) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:81, a heavy chain CDR2 region of SEQ ID NO:82, and a heavy chain CDR3 region of SEQ ID NO:83,

b) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:109, a heavy chain CDR2 region of SEQ ID NO:110, and a heavy chain CDR3 region of SEQ ID NO:111,

c) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:138, a heavy chain CDR2 region of SEQ ID NO:139, and a heavy chain CDR3 region of SEQ ID NO:140,

d) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:144, a heavy chain CDR2 region of SEQ ID NO:145, and a heavy chain CDR3 region of SEQ ID NO:146, and

e) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:173, a heavy chain CDR2 region of SEQ ID NO:174, and a heavy chain CDR3 region of SEQ ID NO:175.

15. A binding molecule according to any one of claims 1-14, wherein said binding molecule is a human monoclonal antibody.

16. A binding molecule according to any one of claims 1-15 for use as a medicament.

17. A binding molecule according to any one of claims 1-16 for use as a medicament in the diagnostic, therapeutic and/or prophylactic treatment of influenza infection caused by influenza virus comprising HA of the H3 subtype, such as H3N2.

18. A functional variant of a binding molecule according to any one of claims 1-17, characterized in that the functional variant has neutralizing activity against an influenza virus comprising HA of the H3 subtype, such as H3N2.

19. An immunoconjugate comprising a binding molecule according to any one of the claims 1-17, or a functional variant according to claim 18, the immunoconjugate further comprising at least one tag.

20. A pharmaceutical composition comprising a binding molecule according to any one of claims 1–17, and/or a functional variant according to claim 18, and/or an immunoconjugate according to claim 19, and a pharmaceutically acceptable excipient.

21. Use of a binding molecule according to any one of claims 1–17, and/or a functional variant according to claim 18, and/or an immunoconjugate according to claim 19 in the preparation of a medicament for the diagnosis, prophylaxis, and/or treatment of an influenza virus infection.

22. Use according to claim 21, characterized in that of influenza infection is caused by influenza virus comprising HA of the H3 subtype H3, such as H3N2.

23. A pharmaceutical composition according to claim 20 comprising at least one additional binding molecule.

24. A pharmaceutical composition according to claim 23, characterized in that the additional binding molecule is capable of neutralizing influenza virus comprising HA of the H1 and H5 subtype, such as H1N1 and H5N1, or a functional variant thereof.

25. A pharmaceutical composition comprising at least two influenza virus neutralizing binding molecules, characterized in that at least one binding molecules is capable of neutralizing one or more influenza virus subtypes of phylogenetic group 1 and in that at least one binding molecules is capable of neutralizing one or more influenza virus subtypes of phylogenetic group 2.

26. A pharmaceutical composition comprising at least two influenza virus neutralizing binding molecules, characterized in that at least one binding molecules is capable of neutralizing influenza viruses comprising HA of the H1 and/or H5 subtype, and in that at least one

binding molecule is capable of neutralizing influenza viruses comprising HA of the H3, H7 and/or H10 subtype.

27. A nucleic acid molecule encoding a binding molecule according to any one of the claims 1-17 or a functional variant according to claims 18.

28. A vector comprising at least one nucleic acid molecule according to claim 27.

29. A host comprising at least one vector according to claim 28.

30. A host according to claim 29, wherein the host is a human cell.

31. A method of producing a binding molecule according to any one of claims 1-17 or a functional variant according to claim 18, wherein the method comprises the steps of:

a) culturing a host according to claim 29 or 30 under conditions conducive to the expression of the binding molecule or functional variant, and optionally,

b) recovering the expressed binding molecule or functional variant.

CLAIMS

1. An isolated human binding molecule capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, and having cross-neutralizing activity against at least an influenza virus comprising HA of the H7 subtype, and/or an influenza virus comprising HA of the H10 subtype.

2. An isolated binding molecule according to claim 1, capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, characterized in that said binding molecule has at least neutralizing activity against one or more of the H3N2 strains selected from the group consisting of A/Wisconsin/67/2005, A/Hiroshima/52/2005, A/Panama/2007/99, and A/Johannesburg/33/94.

3. A binding molecule according to claim 2, wherein said binding molecule further has neutralizing activity against the H3N2 strain A/Hong Kong/1/68.

4. A binding molecule according to any of the claims 1-3, wherein said binding molecule binds to an epitope comprising the amino acid at position 19, 25, 27, 33 and/or 34 of the HA2 polypeptide of the H3 HA protein.

5. A binding molecule according to claim 4, wherein the binding molecule binds to said epitope on HA2, when the amino acid on position 19 is aspartic acid (D), the amino acid on position 25 is glutamine (Q), the amino acid on position 27 is glycine (G), the amino acid at position 33 is glycine (G) and/or the amino acid at position 34 is glutamine.

6. A binding molecule according to claim 5, wherein the binding molecule does not bind to said epitope on HA2 when one or more of said amino acids have changed.

7. A binding molecule according to any one of claims 1-6, wherein the binding molecule is capable of preventing *in vitro* the trypsin cleavage of the H3 HA precursor molecule HA0 in HA1 and HA2.

8. A binding molecule according to any one of claims 1-7, wherein the binding molecule is capable of preventing the conformational change of the H3 HA protein required for fusion of the viral membrane with the endosomal membrane of an infected cell.

9. A binding molecule according to any one of claims 1-8, wherein the binding molecule is not capable of binding to and neutralizing influenza virus A comprising HA of the H1 subtype, such as H1N1.

10. A binding molecule according to any of the claims 1-9, wherein the binding molecule is selected from the group consisting of:
    a. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:109, a heavy chain CDR2 region of SEQ ID NO:110, and a heavy chain CDR3 region of SEQ ID NO:111; and a light chain CDR1 region of SEQ ID NO: 112, a light chain CDR2 region of SEQ ID NO: 113 and a light chain CDR3 region of 114,
    b. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:138, a heavy chain CDR2 region of SEQ ID NO:139, and a heavy chain CDR3 region of SEQ ID NO:140, and a light chain CDR1 region of SEQ ID NO: 141, a light chain CDR2 region of SEQ ID NO: 142 and a light chain CDR3 region of 143,
    c. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:144, a heavy chain CDR2 region of SEQ ID NO:145, and a heavy chain CDR3 region of SEQ ID NO:146; and a light chain CDR1 region of SEQ ID NO: 147, a light chain CDR2 region of SEQ ID NO: 148 and a light chain CDR3 region of 149.

11. A binding molecule according to any one of claims 1-10, wherein said binding molecule is a human monoclonal antibody.

12. A binding molecule according to any one of claims 1-11 for use as a medicament.

13. A binding molecule according to any one of claims 1- 12 for use as a medicament in the diagnostic, therapeutic and/or prophylactic treatment of influenza infection caused by influenza virus comprising HA of the H3 subtype, such as H3N2.

14. A functional variant of a binding molecule according to any one of claims 1-13, characterized in that the functional variant has neutralizing activity against an influenza virus comprising HA of the H3 subtype, such as H3N2.

15. An immunoconjugate comprising a binding molecule according to any one of the claims 1-13, or a functional variant according to claim 14, the immunoconjugate further comprising at least one tag.

16. A pharmaceutical composition comprising a binding molecule according to any one of claims 1-13, and/or a functional variant according to claim 14, and/or an immunoconjugate according to claim 15 and a pharmaceutically acceptable excipient.

17. Use of a binding molecule according to any one of claims 1-13, and/or a functional variant according to claim 14, and/or an immunoconjugate according to claim 15 in the preparation of a medicament for the diagnosis, prophylaxis, and/or treatment of an influenza virus infection.

18. Use according to claim ~~21~~ 17 characterized in that of influenza infection is caused by influenza virus comprising HA of the H3 subtype H3, such as H3N2.

19. A pharmaceutical composition according to claim 16 comprising at least one additional binding molecule.

20. A pharmaceutical composition according to claim 19 characterized in that the additional binding molecule is capable of neutralizing influenza virus comprising HA of the H1 and H5 subtype, such as H1N1 and H5N1, or a functional variant thereof.

21. A pharmaceutical composition comprising at least two influenza virus neutralizing binding molecules, characterized in that at least one binding molecules is capable of neutralizing one or more influenza virus subtypes of phylogenetic group 1 and in that at least one binding molecules is capable of neutralizing one or more influenza virus subtypes of phylogenetic group 2.

22. A pharmaceutical composition comprising at least two influenza virus neutralizing binding molecules, characterized in that at least one binding molecules is capable of neutralizing influenza viruses comprising HA of the H1 and/or H5 subtype, and in that at least one binding molecule is capable of neutralizing influenza viruses comprising HA of the H3, H7 and/or H10 subtype.

23. A nucleic acid molecule encoding a binding molecule according to any one of the claims 1-13 or a functional variant according to claim 14.

24. A vector comprising at least one nucleic acid molecule according to claim 23.

25. A host comprising at least one vector according to claim 24.

26. A host according to claim 25, wherein the host is a human cell.

27. A method of producing a binding molecule according to any one of claims 1-13 or a functional variant according to claim 14, wherein the method comprises the steps of: culturing a host according to claim 25 or 26 under conditions conducive to the expression of the binding molecule or functional variant, and optionally, recovering the expressed binding molecule or functional variant.

CLAIMS

1. An isolated human binding molecule capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, and having cross-neutralizing activity against at least an influenza virus comprising HA of the H7 subtype, and/or an influenza virus comprising HA of the H10 subtype, wherein the binding molecule binds to an epitope comprising the amino acid at position 19, 25, 27, 33 and/or 34 of the HA2 polypeptide of the H3 HA protein.

2. An isolated binding molecule according to claim 1, capable of specifically recognizing and binding to an epitope in influenza haemagglutinin protein (HA), having neutralizing activity against influenza viruses comprising HA of the H3 subtype, such as H3N2, characterized in that said binding molecule has at least neutralizing activity against one or more of the H3N2 strains selected from the group consisting of A/Wisconsin/67/2005, A/Hiroshima/52/2005, A/Panama/2007/99, and A/Johannesburg/33/94.

3. A binding molecule according to claim 2, wherein said binding molecule further has neutralizing activity against the H3N2 strain A/Hong Kong/1/68.

4. A binding molecule according to any one of claims 1-3, wherein the binding molecule is capable of preventing *in vitro* the trypsin cleavage of the H3 HA precursor molecule HA0 in HA1 and HA2.

5. A binding molecule according to any one of claims 1-4, wherein the binding molecule is capable of preventing the conformational change of the H3 HA protein required for fusion of the viral membrane with the endosomal membrane of an infected cell.

6. A binding molecule according to any one of claims 1-5, wherein the binding molecule is not capable of binding to and neutralizing influenza virus A comprising HA of the H1 subtype, such as H1N1.

7. A binding molecule according to any of the claims 1-6, wherein the binding molecule is selected from the group consisting of:
    a. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:109, a heavy chain CDR2 region of SEQ ID NO:110, and a heavy chain CDR3 region of SEQ ID NO:111; and a light chain CDR1 region of SEQ ID NO: 112, a light chain CDR2 region of SEQ ID NO: 113 and a light chain CDR3 region of 114,
    b. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:138, a heavy chain CDR2 region of SEQ ID NO:139, and a heavy chain CDR3 region of SEQ ID NO:140, and a light chain CDR1 region of SEQ ID NO: 141, a light chain CDR2 region of SEQ ID NO: 142 and a light chain CDR3 region of 143,
    c. a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:144, a heavy chain CDR2 region of SEQ ID NO:145, and a heavy chain CDR3 region of SEQ ID NO:146; and a light chain CDR1 region of SEQ ID NO: 147, a light chain CDR2 region of SEQ ID NO: 148 and a light chain CDR3 region of 149.

8. A binding molecule according to any one of claims 1-7, wherein said binding molecule is a human monoclonal antibody.

9. A binding molecule according to any one of claims 1-8 for use as a medicament.

10. A binding molecule according to any one of claims 1-9 for use as a medicament in the diagnostic, therapeutic and/or prophylactic treatment of influenza infection caused by influenza virus comprising HA of the H3 subtype, such as H3N2.

11. A functional variant of a binding molecule according to any one of claims 1-10, characterized in that the functional variant has neutralizing activity against an influenza virus comprising HA of the H3 subtype, such as H3N2.

12. An immunoconjugate comprising a binding molecule according to any one of the claims 1-10, or a functional variant according to claim 11, the immunoconjugate further comprising at least one tag.

13. A pharmaceutical composition comprising a binding molecule according to any one of claims 1-10, and/or a functional variant according to claim 11, and/or an immunoconjugate according to claim 12 and a pharmaceutically acceptable excipient.

14. Use of a binding molecule according to any one of claims 1-10, and/or a functional variant according to claim 11, and/or an immunoconjugate according to claim 12 in the preparation of a medicament for the diagnosis, prophylaxis, and/or treatment of an influenza virus infection.

15. Use according to claim 14 characterized in that of influenza infection is caused by influenza virus comprising HA of the H3 subtype H3, such as H3N2.

16. A pharmaceutical composition according to claim 13 comprising at least one additional binding molecule.

17. A pharmaceutical composition according to claim 16 characterized in that the additional binding molecule is capable of neutralizing influenza virus comprising HA of the H1 and H5 subtype, such as H1N1 and H5N1, or a functional variant thereof.

18. A nucleic acid molecule encoding a binding molecule according to any one of the claims 1-10 or a functional variant according to claim 11.

19. A vector comprising at least one nucleic acid molecule according to claim 18.

20. A host comprising at least one vector according to claim 19.

21. A host according to claim 20, wherein the host is a human cell.

22. A method of producing a binding molecule according to any one of claims 1-10 or a functional variant according to claim 11, wherein the method comprises the steps of: culturing a host according to claim 20 or 21 under conditions conducive to the expression of the binding molecule or functional variant, and optionally, recovering the expressed binding molecule or functional variant.