immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. H1N1 influenza virus is one of the influenza viruses capable of infecting humans following human to human transmission. Antibodies capable of neutralizing H1N1 influenza virus are therefore particularly important for application in humans.

In another preferred embodiment the disclosure provides an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H5N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 3.0 μg/ml, more preferably of less than 2.0 μg/ml, more preferably equal to or less than about 1.3 μg/ml. Said H5N1 influenza A virus preferably comprises a H5N1 A/turkey/Turkey/05 strain. In a particularly preferred embodiment said antibody or functional part or immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. H5N1 influenza virus is one of the influenza viruses capable of infecting humans following human to human transmission. Antibodies capable of neutralizing H5N1 influenza virus are therefore particularly important for application in humans.

The disclosure provides in one aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of binding H3N2 and H7N7 and having an in vitro H3N2 influenza A virus neutralizing activity with an IC50 value of less than 1 μg/ml, comprising: the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 4, 9, 14, 19, 24 and 29, respectively; or the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 3, 8, 13, 18, 23 and 28, respectively; or the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 1, 6, 11, 16, 21 and 26, respectively. Also disclosed is an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of binding H3N2 and H7N7, comprising:

- a heavy chain CDR1 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 1, 3 and 4, and
- a heavy chain CDR2 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 6, 8 and 9, and

- a heavy chain CDR3 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 11, 13 and 14, and
- a light chain CDR1 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 16, 18 and 19, and
- a light chain CDR2 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 21, 23 and 24, and
- a light chain CDR3 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's: 26, 28 and 29.

The disclosure provides in another aspect an nucleic acid molecule comprising a nucleotide sequence which has at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO's: 71, 73 and 74 and/or comprising a sequence which has at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO's: 76, 78, and 79. Also disclosed is an isolated, synthetic or recombinant nucleic acid molecule with a length of at least 15 nucleotides, or a functional equivalent thereof, encoding at least one CDR sequence of an antibody or functional part thereof or immunoglobulin chain or functional equivalent as defined herein.

The disclosure provides in another aspect a vector comprising a nucleic acid molecule or functional equivalent as defined herein.

The disclosure provides in another aspect an isolated or recombinant cell comprising a nucleic acid molecule or functional equivalent as defined herein, and/or a vector as defined herein.

The disclosure provides in another aspect a pharmaceutical composition comprising an antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent or a vector as defined herein and a pharmaceutical acceptable carrier, diluent and/or excipient.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent thereof or a vector as defined herein, for use as a medicament and/or prophylactic agent.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent, or a nucleic acid molecule or functional equivalent, or a vector as defined herein, for use as a medicament and/or

prophylactic agent for at least in part treating and/or preventing an influenza A virus infection.

The disclosure provides in another aspect a method for producing an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein, comprising providing a cell with a nucleic acid molecule or functional equivalent or a vector as defined herein, and allowing said cell to translate said nucleic acid molecule or functional equivalent or vector, thereby producing said antibody or functional part or immunoglobulin chain or functional equivalent as defined herein, preferably further comprising harvesting, purifying and/or isolating said antibody or functional part or immunoglobulin chain or functional equivalent

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein for use in diagnosis of an influenza A virus infection.

The disclosure provides in another aspect a method for determining whether an influenza A virus is present in a sample comprising:

- contacting said sample with an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein,
- allowing said antibody or functional part or immunoglobulin chain or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said antibody or functional part or immunoglobulin chain or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent thereof, capable of binding H3N2 and H7N7, said multimeric antibody or multimeric immunoglobulin or functional equivalent comprising: i) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005; and ii) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005, wherein said antibody selected in i) is different from said antibody selected in ii), and wherein the AT10_001 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 4, 9, 14, 19,

24 and 29, respectively; the AT10_002 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 3, 8, 13, 18, 23 and 28, respectively; the AT10_004 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 1, 6, 11, 16, 21 and 28, respectively, the AT10_005 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 5, 10, 15, 20, 25 and 30, respectively. Also disclosed is a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent thereof, capable of binding H3N2 and H7N7, said multimeric antibody or multimeric immunoglobulin or functional equivalent comprising:

i) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005; and

ii) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005,

wherein said antibody selected in i) is different from said antibody selected in ii).

The disclosure provides in another aspect an isolated or recombinant cell or a pharmaceutical composition comprising a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use as a medicament and/or prophylactic agent.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing and/or alleviating the symptoms of an influenza A infection.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use in diagnosis of an influenza A infection.

The disclosure provides in another aspect use of a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein and/or a cell or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment and/or prevention of an influenza A virus infection.

The disclosure provides in another aspect use of a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein in the manufacture of a medicament for the neutralization of a H1N1 influenza A virus and/or an H3N2 influenza A virus, wherein said H1N1 influenza A virus and/or said H3N2 influenza A virus is to be contacted with a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein, resulting in neutralization of said virus.

The disclosure provides in another aspect a method for determining whether an influenza A virus is present in a sample comprising:

- contacting said sample with a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein,
- allowing said multimeric antibody, multimeric immunoglobulin or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said multimeric antibody, multimeric immunoglobulin or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

Also disclosed is an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with amino acids at positions A21, A324, A325, A327, B12, B14, B15, B16, B17, B18, B19, B25, B26, B30, B31, B32, B33, B34, B35, B36, B38, B146, B150, B153, and B154 of influenza A virus group 2 hemagglutinin (H3/H7).

Also disclosed is an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with amino acids at positions A38, A48, A275, A276, A277, A278, A289, A291, A318, B19, B20, B21, B36, B38, B39, B41, B42, B45, B46, B48, B49, B50, B52, B53, B56, B57, B58, B150 of influenza A virus group 2 hemagglutinin (H3/H7).

A "functional part of an antibody" is defined herein as a part that has at least one shared property as said antibody in kind, not necessarily in amount. Said functional part is capable of binding the same antigen as said antibody, albeit not necessarily to the same extent. A functional part of an antibody preferably comprises a single domain antibody, a single chain antibody, a nanobody, an unibody, a single chain variable fragment (scFv), a Fab fragment or a $F(ab')_2$ fragment.

A functional part of an antibody is also produced by altering an antibody such that at least one property - preferably an antigen-binding property - of the resulting compound is essentially the same in kind, not necessarily in amount. This is done in many ways, for instance through conservative amino acid substitution, whereby an amino acid residue is substituted by another residue with generally

Claims

1. An isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of binding H3N2 and H7N7 and having an in vitro H3N2 influenza A virus neutralizing activity with an IC50 value of less than 1 μg/ml, comprising:

the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 4, 9, 14, 19, 24 and 29, respectively; or

the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 3, 8, 13, 18, 23 and 28, respectively; or

the heavy and light chain CDRs1-3 as defined by SEQ ID NO: 1, 6, 11, 16, 21 and 26, respectively.

2. An isolated, synthetic or recombinant antibody or functional part or immunoglobulin chain or functional equivalent according to claim 1, having an in vitro H3N2 influenza A virus neutralizing activity with an IC50 value of less than 0.7 μg/ml.

3. An antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-2, having a heavy chain sequence selected from the group consisting of SEQ ID NO's:31, 33 and 34 and/or having a light chain sequence selected from the group consisting of SEQ ID NO's:36, 38 and 39.

4. An nucleic acid molecule comprising a nucleotide sequence which has at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO's: 71, 73 and 74 and/or comprising a sequence which has at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NO's: 76, 78, and 79.

5. A nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO's: 71, 73 and 74 and/or comprising a sequence selected from the group consisting of SEQ ID NO's: 76, 78 and 79.

6. A vector comprising a nucleic acid molecule or functional equivalent according to claim 4 or 5.

7. An isolated or recombinant cell comprising a nucleic acid molecule or functional equivalent according to claim 4 or 5, and/or a vector according to claim 6.

8. A pharmaceutical composition comprising an antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent or a vector according to any one of claims 1-6 and a pharmaceutical acceptable carrier, diluent and/or excipient.

9. An antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent thereof or a vector according to any one of claims 1-6, for use as a medicament and/or prophylactic agent.

10. An antibody or functional part or immunoglobulin chain or functional equivalent, or a nucleic acid molecule or functional equivalent, or a vector according to any one of claims 1-6, for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing an influenza A virus infection.

11. A method for producing an antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-3, comprising providing a cell with a nucleic acid molecule or functional equivalent or a vector according to any one of claims 4-6, and allowing said cell to translate said nucleic acid molecule or functional equivalent or vector, thereby producing said antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-3, preferably further comprising harvesting, purifying and/or isolating said antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-3.

12. An antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-3 for use in diagnosis of an influenza A virus infection.

13. A method for determining whether an influenza A virus is present in a sample comprising:

- contacting said sample with an antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 1-3,
- allowing said antibody or functional part or immunoglobulin chain or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said antibody or functional part or immunoglobulin chain or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

14. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent thereof, capable of binding H3N2 and H7N7, said multimeric antibody or multimeric immunoglobulin or functional equivalent comprising:

i) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005; and

ii) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005,

wherein said antibody selected in i) is different from said antibody selected in ii),

and wherein

the AT10_001 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 4, 9, 14, 19, 24 and 29, respectively;

the AT10_002 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 3, 8, 13, 18, 23 and 28, respectively;

the AT10_004 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 1, 6, 11, 16, 21 and 28, respectively,

the AT10_005 heavy and light chain CDRs1-3 are defined by SEQ ID NO: 5, 10, 15, 20, 25 and 30, respectively.

15. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to claim 14, comprising:

i) heavy chain CDR1, CDR2 and CDR3 and light chain CDR1, CDR2 and CDR3 sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005; and

ii) heavy chain CDR1, CDR2 and CDR3 and light chain CDR1, CDR2 and CDR3 sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005,

wherein said antibody selected in i) is different from said antibody selected in ii).

16. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to claim 14 or 15, comprising:

i) the heavy chain sequence and the light chain sequence of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005,; and

ii) the heavy chain sequence and the light chain sequence of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_004 and AT10_005,

wherein said antibody selected in i) is different from said antibody selected in ii),

and wherein

the AT10_001 heavy and light chain sequences are defined by SEQ ID NO: 34 and 39, respectively;

the AT10_002 heavy and light chain sequences are defined by SEQ ID NO: 33 and 38, respectively;

the AT10_004 heavy and light chain sequences are defined by SEQ ID NO:31 and 36, respectively, and

the AT10_005 heavy and light chain sequences are defined by SEQ ID NO: 35 and 40, respectively.

17. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to claim 16, comprising:

i) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of antibody AT10_002; and
ii) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of antibody AT10_005.

18. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to claim 14 or 15, comprising:
i) heavy chain CDR1, CDR2 and CDR3 and light chain CDR1, CDR2 and CDR3 sequences of antibody AT10_002; and
ii) heavy chain CDR1, CDR2 and CDR3 and light chain CDR1, CDR2 and CDR3 sequences of antibody AT10_005.

19. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-18, comprising:
i) the heavy chain sequence and the light chain sequence of antibody AT10_002; and
ii) the heavy chain sequence and the light chain sequence of antibody AT10_005.

20. A multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-19, which is a dimeric antibody.

21. An isolated or recombinant cell or a pharmaceutical composition comprising a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20.

22. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20 for use as a medicament and/or prophylactic agent.

23. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20 for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing and/or alleviating the symptoms of an influenza A infection.

24. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20 for use in diagnosis of an influenza A infection.

25. Use of a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20 and/or a cell or pharmaceutical composition according to claim 21 in the manufacture of a medicament for the treatment and/or prevention of an influenza A virus infection.

26. Use of a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20 in the manufacture of a medicament for the neutralization of a H1N1 influenza A virus and/or an H3N2 influenza A virus, wherein said H1N1 influenza A virus and/or said H3N2 influenza A virus is to be contacted with a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20, resulting in neutralization of said virus, and wherein said multimeric antibody, multimeric immunoglobulin or functional equivalent comprises at least one of antibodies AT10_004 and AT10_005, and at least one of antibodies AT10_001, AT10_002 and AT10_004, or functional equivalents thereof.

27. A method for determining whether an influenza A virus is present in a sample comprising:

- contacting said sample with a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 14-20,
- allowing said multimeric antibody, multimeric immunoglobulin or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said multimeric antibody, multimeric immunoglobulin or functional equivalent, thereby determining whether an influenza A virus is present in said sample.