CLAIMS

1. An influenza hemagglutinin (HA) stem domain polypeptide comprising (a) an influenza hemagglutinin HA1 domain that comprises an HAl N-terminal stem segment, comprising the amino acids from position 1 to position x, preferably from position p to position x, of the HA1 domain, covalently linked by a linking sequence of 0-50 amino acid residues to an HA1 C- terminal stem segment, comprising the amino acids from position y to and including the C-terminal amino acid of the HA1 domain and (b) an influenza hemagglutinin HA2 domain, wherein the hemagglutinin stem domain polypeptide is resistant to protease cleavage at the junction between HA1 and HA2, and wherein one or more amino acids at positions 337, 340, 352, 353, 402, 406, 409, 413 and/or 416 have been mutated as compared to the corresponding positions in wild-type influenza HA.

2. Influenza HA stem domain polypeptide according to claim 1, wherein the HA1 and HA2 domain are derived from A/Brisbane/59/2007 (SEQ ID NO: 1).

3. Influenza HA stem domain polypeptide according to claim 1 or 2, wherein x is 52, y=321 and p=18.

4. Influenza HA stem domain polypeptide according to any of the preceding claims 1-3, wherein the amino acid sequence from position (or the equivalent of) 519, 520, 521, 522, 523, 524, 525, 526, 527, 526, 528, 529, or 530 of the HA2 domain to the C-terminus of the HA2 domain has been removed.

5. Influenza HA stem domain polypeptide according to any of the preceding claims, wherein
the mutated amino acid on position 337 is an amino acid selected from the group consisting of E, I, K, V, A, and T;
the mutated amino acid on position 340 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

the mutated amino acid on position 352 is an amino acid selected from the group consisting of D, V, Y, A, I, N, S, and T;

the mutated amino acid on position 353 is an amino acid selected from the group consisting of K, R, T, E, G and V;

the mutated amino acid on position 402 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

the mutated amino acid on position 406 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

the mutated amino acid on position 409 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

the mutated amino acid on position 413 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, and V; and

the mutated amino acid on position 416 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

6. Influenza HA stem domain polypeptide according to any of the preceding claims, wherein the polypeptides comprise the amino acid sequence:

DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGL
RNX_1PSX_2QSQGLFGAIAGX_3X_4EGGWTGMVDGWYGYHHQNEQGSGYAADQKS
TQNAINGITNKVNSVIEKX_5NTQX_6TAX_7GKEX_8NX_9ERMKQIEDKIEEIESKQIWC
YNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDE
CMESVKNGTYDYPKYSEESKLNREKIDGVSGRDYKDDDDKLVPRGSPGSGYIPE
APRDGQAYVRKDGEWVLLSTFLGHHHHHH (SEQ ID NO: 53),

wherein X_1 is an amino acid selected from the group consisting of E, I, K, V, A, and T;

X_2 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

X_3 is an amino acid selected from the group consisting of D, F, V, Y, A, I, N, S, and T;

X_4 is an amino acid selected from the group consisting of I, K, R, T, E, G and V;

X_5 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

X_6 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

X_7 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

X_8 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, and V; and

X_9 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

7. Influenza HA stem domain polypeptide according to any of the preceding claims 1-5, wherein the polypeptides comprise the amino acid sequence:

DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGL
RNX_1PSX_2QSQGLFGAIAGX_3X_4EGGWTGMVDGWYGYHHQNEQGSGYAADQKS
TQNAINGITNKVNSVIEKX_5NTQX_6TAX_7GKEX_8NKX_9ERMKQIEDKIEEIESKQIW
CYNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCN
DECMESVKNGTYDYPKYSEESKLNREKIDG (SEQ ID NO: 54),

wherein

X_1 is an amino acid selected from the group consisting of E, I, K, V, A, and T; X_2 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

X_3 is an amino acid selected from the group consisting of D, F, V, Y, A, I, N, S, and T;

X_4 is an amino acid selected from the group consisting of I, K, R, T, E, G and V;

X_5 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

X_6 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

X_7 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

X_8 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, M, and V; and

X_9 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

8. Influenza HA stem domain polypeptide according to any of the preceding claims 1-5, wherein the polypeptides comprise the amino acid sequence:

DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGL
RNX_1PSX_2QSQGLFGAIAGX_3X_4EGGWTGMVDGWYGYHHQNEQGSGYAADQKS
TQNAINGITNKVNSVIEKX_5NTQX_6TAX_7GKEX_8NKX_9ERMKQIEDKIEEIESKQIW
CYNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCN
DECMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQIEG (SEQ ID NO: 70),

wherein

X_1 is an amino acid selected from the group consisting of E, I, K, V, A, and T;

X_2 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

X_3 is an amino acid selected from the group consisting of D, F, V, Y, A, I, N, S, and T;

X_4 is an amino acid selected from the group consisting of I, K, R, T, E, G and V;

X_5 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

X_6 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

X_7 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

X_8 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, M and V; and

X_9 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

9. Influenza HA stem domain polypeptide according to any of the preceding claims 1-5, wherein the polypeptides comprise the amino acid sequence:

DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGL RN**X**$_1$PS**X**$_2$QSQGLFGAIAG**X**$_3$**X**$_4$EGGWTGMVDGWYGYHHQNEQGSGYAADQKS TQNAINGITNKVNSVIEK**X**$_5$NTQ**X**$_6$TA**X**$_7$GKE**X**$_8$NK**X**$_9$ERMKQIEDKIEEIESKQIW CYNAELLVLLENERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCN DECMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVASSLVL LVSLGAISFWMCSNGSLQCRICI (SEQ ID NO: 71),

wherein

X_1 is an amino acid selected from the group consisting of E, I, K, V, A, and T;

X_2 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

X_3 is an amino acid selected from the group consisting of D, F, V, Y, A, I, N, S, and T;

X_4 is an amino acid selected from the group consisting of I, K, R, T, E, G and V;

X_5 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

X_6 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

X_7 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

X_8 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, M and V; and

X_9 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

10. Influenza HA stem domain polypeptide according to any of the preceding claims, wherein the polypeptides comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55-76.

11. Influenza HA stem domain polypeptide according to any of the preceding claims, wherein the polypeptides comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55, SEQ ID NO: 66 and SEQ ID NO: 73.

12. A nucleic acid molecule encoding a polypeptide according to any one of claims 1 to 11.

13. A vector comprising the nucleic acid molecule of claim 12.

14. A composition comprising the polypeptide of any one of claims 1 to 11, and/or a nucleic acid molecule according to claim 12 and/or a vector according to claim 13.

15. Influenza HA stem domain polypeptide according to any of the claims 1-11, a nucleic acid according to claim 12, and/or a composition according to claim 14 for use as a medicament, in particular for use as a vaccine.

16. Influenza HA stem domain polypeptide according to any of the claims 1-11, a nucleic acid molecule according to claim 12 and/or a composition according to claim 14 for use in inducing an immune response against influenza HA protein.

17. Influenza HA stem domain polypeptide according to any of the claims 1-11, a nucleic acid molecule according to claim 12 and/or a composition according to claim 14 for use in the prophylaxis and/or treatment of influenza infection.

CLAIMS

1. An influenza hemagglutinin (HA) stem domain polypeptide comprising (a) an influenza hemagglutinin HA1 domain that comprises an HAl N-terminal stem segment, comprising the amino acids from position 1 to position 52, preferably from position 18 to position 52, of the HA1 domain, covalently linked by a linking sequence of 0-50 amino acid residues to an HA1 C-terminal stem segment, comprising the amino acids from position 321 to and including the C-terminal amino acid of the HA1 domain and (b) an influenza hemagglutinin HA2 domain, wherein the HA1 and HA2 domain are derived from A/Brisbane/59/2007 (SEQ ID NO: 1), wherein the hemagglutinin stem domain polypeptide is resistant to protease cleavage at the junction between HA1 and HA2, and wherein the polypeptide further comprises the mutation R324C in the HA1 domain and T436C in the HA2 domain and wherein the sequence MKQIEDKIEEIESKQ (SEQ ID NO: 5) is introduced at position 419-433, and wherein one or more amino acids at positions 337, 340, 352, 353, 402, 406, 409, 413 and/or 416 have been mutated as compared to the corresponding positions in wild-type influenza HA,
wherein the polypeptide comprises the amino acid sequence:
DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGLRN$\mathbf{X_1}$PS
$\mathbf{X_2}$QSQGLFGAIAG$\mathbf{X_3X_4}$EGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNK
VNSVIEK$\mathbf{X_5}$NTQ$\mathbf{X_6}$TA$\mathbf{X_7}$GKE$\mathbf{X_8}$NK$\mathbf{X_9}$ERMKQIEDKIEEIESKQIWCYNAELLVLLENERTL
DFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDECMESVKNGTYDYPKYSEES
KLNREKIDGVSGRDYKDDDDKLVPRGSPGSGYIPEAPRDGQAYVRKDGEWVLLSTFLG
HHHHHH (SEQ ID NO: 53),
DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGLRN$\mathbf{X_1}$PS
$\mathbf{X_2}$QSQGLFGAIAG$\mathbf{X_3X_4}$EGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNK
VNSVIEK$\mathbf{X_5}$NTQ$\mathbf{X_6}$TA$\mathbf{X_7}$GKE$\mathbf{X_8}$NK$\mathbf{X_9}$ERMKQIEDKIEEIESKQIWCYNAELLVLLENERTL
DFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDECMESVKNGTYDYPKYSEES
KLNREKIDG (SEQ ID NO: 54),
DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGLRN$\mathbf{X_1}$PS
$\mathbf{X_2}$QSQGLFGAIAG$\mathbf{X_3X_4}$EGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNK
VNSVIEK$\mathbf{X_5}$NTQ$\mathbf{X_6}$TA$\mathbf{X_7}$GKE$\mathbf{X_8}$NK$\mathbf{X_9}$ERMKQIEDKIEEIESKQIWCYNAELLVLLENERTL

DFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDECMESVKNGTYDYPKYSEES KLNREKIDGVKLESMGVYQIEG (SEQ ID NO: 70), or

DTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLENGGGGKYVCSAKLRMVTGLRNX_1PS X_2QSQGLFGAIAGX_3X_4EGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNK VNSVIEKX_5NTQX_6TAX_7GKEX_8NKX_9ERMKQIEDKIEEIESKQIWCYNAELLVLLENERTL DFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDECMESVKNGTYDYPKYSEES KLNREKIDGVKLESMGVYQILAIYSTVASSLVLLVSLGAISFWMCSNGSLQCRICI (SEQ ID NO: 71),

wherein

X_1 is an amino acid selected from the group consisting of E, I, K, V, A, and T;

X_2 is an amino acid selected from the group consisting of I, K, R, T, F, N, S and Y;

X_3 is an amino acid selected from the group consisting of D, F, V, Y, A, I, N, S, and T;

X_4 is an amino acid selected from the group consisting of I, K, R, T, E, G and V;

X_5 is an amino acid selected from the group consisting of E, K, M, V, R, and T;

X_6 is an amino acid selected from the group consisting of F, I, N, S, T, Y, H, and L;

X_7 is an amino acid selected from the group consisting of A, G, I, R, T, V, F, and S;

X_8 is an amino acid selected from the group consisting of F, I, N, S, T, Y, G, E, K, M and V; and

X_9 is an amino acid selected from the group consisting of H, I, L, N, R, and S.

2. Influenza HA stem domain polypeptide according to claim 1, wherein the polypeptides comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55-76.

3. Influenza HA stem domain polypeptide according to claim 2, wherein the polypeptides comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55, SEQ ID NO: 66 and SEQ ID NO: 73.

4. A nucleic acid molecule encoding a polypeptide according to any one of claims 1 to 3.

5. A vector comprising the nucleic acid molecule of claim 4.

6. A composition comprising the polypeptide of any one of claims 1 to 3, and/or a nucleic acid molecule according to claim 4 and/or a vector according to claim 5.

7. Influenza HA stem domain polypeptide according to any one of claims 1 to 3, and/or a nucleic acid molecule according to claim 4, and/or a composition according to claim 6 for use as a medicament, in particular for use as a vaccine.

8. Influenza HA stem domain polypeptide according to any of the claims 1 to 3, and/or a nucleic acid molecule according to claim 4, for use in inducing an immune response against influenza HA protein.

9. Influenza HA stem domain polypeptide according to any of the claims 1 to 3, and/or a nucleic acid molecule according to claim 4, for use in the prophylaxis and/or treatment of influenza infection.