

CLAIMS

1. A multimeric influenza hemagglutinin stem domain polypeptide, wherein the multimeric influenza hemagglutinin stem domain polypeptide comprises at least a first and a second influenza hemagglutinin stem domain monomer, said first and second monomer each comprising: (a) an influenza hemagglutinin HA1 domain that comprises an HA1 amino (N)-terminal stem segment, wherein said HA1 N-terminal segment comprises the amino acids 1-52 of HA1, preferably the amino acids 18-52 of HA1, covalently linked by a linking sequence of less than 10 residues to an HA1 carboxy (C)-terminal stem segment, comprising the amino acids from position 321 to the C-terminal amino acid of HA1, wherein said HA1 C-terminal segment is linked to (b) an influenza hemagglutinin HA2 domain, and
 - (c) wherein the polypeptide comprises no protease cleavage site at the junction between the HA1 and HA2 domains; and
 - (d) wherein the first monomer is linked to said second monomer by a disulfide bridge between the amino acid on position 411 of the first monomer and the amino acid on position 419 of the second monomer, and wherein in each influenza hemagglutinin stem domain monomer the region comprising the amino acid residues 402-418 comprises the amino acid sequence $X_1NTQX_2TAX_3GKEX_4N(H/K)X_5E(K/R)$ (SEQ ID NO: 8), wherein X_1 is M, X_2 is Y, X_3 is I, X_4 is Y and X_5 is S; and wherein in each influenza hemagglutinin stem domain monomer the amino acid sequence CMKQIEDKIEEIESK (SEQ ID NO: 193) has been introduced at positions 419-433; and wherein the amino acid residue on position 337 is K; the amino acid residue on position 340 is K, the amino acid residue on position 352 is F and the amino acid residue on position 353 is T; wherein the HA1 and HA2 domains are derived from an influenza A virus subtype derived from phylogenetic group 1, preferably from an influenza A virus subtype comprising HA of the H1 subtype, and wherein the numbering of the amino acid positions is in relation to SEQ ID NO: 1.
2. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein the multimeric polypeptide is trimeric.

3. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein the HA2 domain of each influenza hemagglutinin stem domain monomer has been truncated.
4. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 3, wherein the C-terminal part of the HA2 domain from position 519 to the C-terminal amino acid has been deleted.
5. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 3, wherein the C-terminal part of the HA2 domain from position 530 to the C-terminal amino acid has been deleted.
6. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 3, wherein the C-terminal part of the HA2 domain has been replaced by the amino acid sequence GYIPEAPRDGQAYVRKDGEWVLLSTFL (SEQ ID NO: 3), optionally connected through a linker.
7. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein the C-terminal amino acid residue of the HA1 C-terminal stem segment of each influenza hemagglutinin stem domain monomer is any amino acid other than arginine (R) or lysine (K), preferably glutamine (Q).
8. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein the polypeptide comprises one or more further mutations in the HA1 domain and/or the HA2 domains.
9. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein the polypeptide selectively binds to the antibodies CR6261 and/or CR9114.
10. A nucleic acid molecule encoding the polypeptide of claim 1.

11. A vector comprising the nucleic acid molecule of claim 10.
12. A composition comprising the polypeptide according to claim 1 and a pharmaceutically acceptable carrier.
13. A composition comprising the nucleic acid molecule according to claim 10 and a pharmaceutically acceptable carrier.
14. The polypeptide according to claim 1 for use in inducing an immune response against influenza virus in a subject in need thereof, wherein the polypeptide is to be administered to the subject.
15. Use of the polypeptide according to claim 1 in the manufacture of a medicament for inducing an immune response against influenza virus in a subject in need thereof, wherein the medicament is to be administered to the subject.
16. The nucleic acid molecule according to claim 10 for use in inducing an immune response against influenza virus in a subject in need thereof, wherein the nucleic acid molecule is to be administered to the subject.
17. Use of the nucleic acid molecule according to claim 10 in the manufacture of a medicament for inducing an immune response against influenza virus in a subject in need thereof, wherein the medicament is to be administered to the subject.
18. The vector according to claim 11 for use in inducing an immune response against influenza virus in a subject in need thereof, wherein the medicament is to be administered to the subject.
19. Use of the vector according to claim 11 in the manufacture of a medicament for inducing an immune response against influenza virus in a subject in need thereof, wherein the medicament is to be administered to the subject.

20. A composition comprising the vector according to claim 11 and a pharmaceutically acceptable carrier.
21. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein each polypeptide monomer comprises the amino acid sequence:
 DTICIGYHANNSTDVDTVLEKNVTVTTHSVNLLENG GGGGKYVCSAKLRMVTGL
 RNX₁PSX₂QSQGLFGAIAGX₃X₄EGGWTGMVDGWYGYHHQNEQSGSYAADQKS
 TQNAINGITNKVNSVIEKX₅NTQX₆TAX₇GCEX₈NKX₉ERCMKQIEDKIEEIESKIWC
 YNAELLVLLNERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDE
 CMESVKNGTYDYPKYSEESKLNREKIDG (SEQ ID NO: 146), wherein X₁ is K, X₂ is K, X₃ is F, X₄ is T, X₅ is M, X₆ is Y, X₇ is I, X₈ is Y and X₉ is S.
22. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein each polypeptide monomer comprises the amino acid sequence:
 DTICIGYHANNSTDVDTVLEKNVTVTTHSVNLLENG GGGGKYVCSAKLRMVTGL
 RNX₁PSX₂QSQGLFGAIAGX₃X₄EGGWTGMVDGWYGYHHQNEQSGSYAADQKS
 TQNAINGITNKVNSVIEKX₅NTQX₆TAX₇GCEX₈NKX₉ERCMKQIEDKIEEIESKIWC
 YNAELLVLLNERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDE
 CMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQIEG (SEQ ID NO: 147),
 wherein X₁ is K, X₂ is K, X₃ is F, X₄ is T, X₅ is M, X₆ is Y, X₇ is I, X₈ is Y and X₉ is S.
23. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein each polypeptide monomer comprises the amino acid sequence:
 DTICIGYHANNSTDVDTVLEKNVTVTTHSVNLLENG GGGGKYVCSAKLRMVTGL
 RNX₁PSX₂QSQGLFGAIAGX₃X₄EGGWTGMVDGWYGYHHQNEQSGSYAADQKS
 TQNAINGITNKVNSVIEKX₅NTQX₆TAX₇GCEX₈NKX₉ERCMKQIEDKIEEIESKIWC
 YNAELLVLLNERTLDFHDSNVKNLYEKVKSQLKNNAKEIGNGCFEFYHKCNDE
 CMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVASSLVLLVS
 LGAISFWMCSNGSLQCRICI (SEQ ID NO: 148), wherein X₁ is K, X₂ is K, X₃ is F, X₄ is T, X₅ is M, X₆ is Y, X₇ is I, X₈ is Y and X₉ is S.

24. The multimeric influenza hemagglutinin stem domain polypeptide according to claim 1, wherein each polypeptide monomer comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 164, 186, 202, 203, 207-216, 218-226, and 254-258.