

CLAIMS

1. A modified HIV-1 envelope gp140 protein, comprising a gp120 polypeptide and a gp41 polypeptide, wherein amino acid residues 548-568 of the N-terminus of heptad 1 region (HR1) of the gp41 polypeptide is replaced with a loop sequence of 6 to 14 amino acid residues in length that stabilizes the pre-fusion gp140 structure, wherein the numbering of the amino acid residues corresponds to HxB2 nomenclature.
2. The modified HIV-1 gp140 protein of claim 1, wherein the gp41 polypeptide is gp41_{ECTO}.
3. The modified HIV-1 gp140 protein of claim 1, wherein the gp120 and gp41 polypeptides are from different HIV-1 strains.
4. The modified HIV-1 gp140 protein of claim 1, which is derived from HIV-1 strain BG505.
5. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises (GS)_n (SEQ ID NO:23), wherein n is any integer between 3 and 7, inclusive.
6. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises (GS)₄ (SEQ ID NO:24).
7. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises 10 amino acid residues.
8. The modified HIV-1 gp140 protein of claim 7, wherein the loop sequence comprises any one of SEQ ID NOs:1-5.
9. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises 8 amino acid residues.
10. The modified HIV-1 gp140 protein of claim 9, wherein the loop sequence comprises any one of SEQ ID NOs:6-10.
11. The modified HIV-1 gp140 protein of claim 1, further comprising a flexible linker sequence that substitutes for the cleavage site sequence between gp120 and gp41.

12. The modified HIV-1 gp140 protein of claim 11, wherein the linker sequence comprises (G₄S)₂ (SEQ ID NO:22) or SGS and substitutes for residues 508-511 at the cleavage site.

13. The modified HIV-1 gp140 protein of claim 11, wherein the linker sequence comprises 8 amino acid residues and substitutes for residues 501-518 at the cleavage site, and wherein numbering of the amino acid residues corresponds to that of HIV-1 strain BG505.SOSIP.664 gp140.

14. The modified HIV-1 gp140 protein of claim 13, wherein the linker sequence comprises the sequence shown in any one of SEQ ID NOs:16-20.

15. The modified HIV-1 gp140 protein of claim 1, further comprising an engineered disulfide bond between gp120 and gp41.

16. The modified HIV-1 gp140 protein of claim 15, wherein the engineered disulfide bond is between residues A501C and T605C.

17. The modified HIV-1 gp140 protein of claim 1, comprising a gp140 trimer with each monomer comprising a gp120 polypeptide and a gp41_{ECTO} polypeptide, wherein the gp41_{ECTO} polypeptide is derived from HIV-1 strain BG505, and wherein the N-terminus of heptad 1 region (HR1) (SEQ ID NO:28) in the gp41_{ECTO} polypeptide is replaced with a loop sequence shown in SEQ ID NO:6.

18. The modified HIV-1 gp140 protein of claim 17, further comprising (a) a linker sequence (G₄S)₂ (SEQ ID NO:22) that substitutes for residues 508-511 at the cleavage site, and (b) an engineered disulfide bond between residues A501C and T605C.

19. A polynucleotide encoding a monomer of a modified HIV-1 envelope gp140 trimer protein of claim 1.

20. The polynucleotide of claim 19, wherein the gp41 polypeptide is gp41_{ECTO}.

21. The polynucleotide of claim 19, wherein the gp120 and gp41 polypeptides are from different HIV-1 strains.

22. The polynucleotide of claim 19, wherein the modified HIV-1 envelope gp140 protein is derived from HIV-1 strain BG505.

23. The polynucleotide of claim 19, wherein the loop sequence comprises (GS)_n (SEQ ID NO:23), wherein n is any integer between 3 and 7, inclusive.

24. The polynucleotide of claim 19, wherein the loop sequence comprises (GS)₄ (SEQ ID NO:24).

25. The polynucleotide of claim 19, wherein the loop sequence comprises 10 amino acid residues.

26. The polynucleotide of claim 25, wherein the loop sequence comprises any one of SEQ ID NOs:1-5.

27. The polynucleotide of claim 19, wherein the loop sequence comprises 8 amino acid residues.

28. The polynucleotide of claim 27, wherein the loop sequence comprises any one of SEQ ID NOs:6-10.

29. The polynucleotide of claim 19, wherein the modified HIV-1 envelope gp140 protein further comprises a flexible linker sequence that substitutes for the cleavage site sequence between gp120 and gp41.

30. The polynucleotide of claim 29, wherein the linker sequence comprises (G₄S)₂ (SEQ ID NO:22) or SGS and substitutes for residues 508-511 at the cleavage site.

31. The polynucleotide of claim 29, wherein the linker sequence comprises 8 amino acid residues and substitutes for residues 501-518 at the cleavage site, and wherein numbering of the amino acid residues corresponds to that of HIV-1 strain BG505. SOSIP.664 gp140.

32. The polynucleotide of claim 31, wherein the linker sequence comprises the sequence shown in any one of SEQ ID NOs:16-20.

33. The polynucleotide of claim 19, wherein the modified HIV-1 envelope gp140 protein further comprises an engineered disulfide bond between gp120 and gp41.

34. The polynucleotide of claim 33, wherein the engineered disulfide bond is between residues A501C and T605C.

35. The polynucleotide of claim 19, wherein the gp41_{ECTO} polypeptide is derived from HIV-1 strain BG505, and wherein the N-terminus of heptad 1 region (HR1) (SEQ ID NO:28) in the gp41_{ECTO} polypeptide is replaced with a loop sequence shown in SEQ ID NO:6.

36. The polynucleotide of claim 19, wherein the modified HIV-1 envelope gp140 protein further comprises (a) a linker sequence (G₄S)₂ (SEQ ID NO:22) that substitutes for residues 508-511 at the cleavage site, and (b) an engineered disulfide bond between residues A501C and T605C.

37. A HIV-1 vaccine composition, comprising an HIV-1 Env-derived trimer immunogen presented on a self-assembling nanoparticle or a virus-like particle (VLP), wherein the HIV-1 Env-derived trimer immunogen is a modified gp140 protein of claim 1.

38. The HIV-1 vaccine composition of claim 37, wherein the nanoparticle platform comprises dihydrolipoyl acyltransferase (E2P), ferritin, or lumazine synthase (LS).

39. An isolated or recombinant polynucleotide encoding the HIV-1 vaccine composition of claim 37.

40. A pharmaceutical composition comprising a therapeutically effective amount of the HIV-1 vaccine composition of claim 37 for the treatment or prevention of HIV-1 infection in the subject.

41. Use of the modified HIV-1 envelope gp140 protein of claim 1 in the manufacture of a medicament for use in the treatment or prevention of HIV-1 infection.