

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.~~

37.19. -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.

38.20. The HIV-1 vaccine composition of claim **1937**, 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.~~

40.21. A pharmaceutical composition comprising a therapeutically effective amount of the HIV-1 vaccine composition of claim **37.19** for the treatment or prevention of HIV-1 infection in the subject.

41.22. 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.