

WHAT IS CLAIMED IS:

1. A modified HIV-1 envelope gp140 protein, comprising a gp120 polypeptide and a gp41 polypeptide, wherein the N-terminus of heptad 1 region (HR1) of
5 the gp41 polypeptide is replaced with a loop sequence of about 6 to about 14 amino acid residues in length that stabilizes the pre-fusion gp140 structure.
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, which is a trimer.
- 10 4. The modified HIV-1 gp140 protein of claim 1, wherein the gp120 and gp41 polypeptides are from different HIV-1 strains.
5. The modified HIV-1 gp140 protein of claim 1, which is derived from HIV-1 strain BG505.
6. The modified HIV-1 gp140 protein of claim 1, wherein the loop
15 sequence comprises (GS)_n (SEQ ID NO:23), wherein n is any integer between 3 and 7, inclusive.
7. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises (GS)₄ (SEQ ID NO:24).
8. The modified HIV-1 gp140 protein of claim 1, wherein the loop
20 sequence comprises 10 amino acid residues.
9. The modified HIV-1 gp140 protein of claim 8, wherein the loop sequence comprises any one of SEQ ID NOs:1-5.
10. The modified HIV-1 gp140 protein of claim 1, wherein the loop sequence comprises 8 amino acid residues.
- 25 11. The modified HIV-1 gp140 protein of claim 10, wherein the loop sequence comprises any one of SEQ ID NOs:6-10.

12. 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.

13. The modified HIV-1 gp140 protein of claim 12, wherein the linker
5 sequence comprises $(G_4S)_2$ (SEQ ID NO:22) or SGS and substitutes for residues 508-511 at the cleavage site.

14. The modified HIV-1 gp140 protein of claim 12, 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
10 HIV-1 strain BG505. SOSIP.664 gp140.

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

16. The modified HIV-1 gp140 protein of claim 1, further comprising (a) an engineered disulfide bond between gp120 and gp41 and/or (b) a stabilizing mutation in
15 gp41.

17. The modified HIV-1 gp140 protein of claim 16, wherein the engineered disulfide bond is between residues A501C and T605C, and the stabilizing mutation is I559P.

18. The modified HIV-1 gp140 protein of claim 1, comprising a gp140
20 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.

19. The modified HIV-1 gp140 protein of claim 18, further comprising (a)
25 a linker sequence $(G_4S)_2$ (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.

20. An HIV-1 vaccine immunogen, comprising a modified trimeric HIV-1 envelope gp140 protein of claim 1.

21. 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).

22. The HIV-1 vaccine composition of claim 21, wherein the HIV-1
5 Env-derived trimer immunogen is V1V2, gp120 or gp140.

23. The HIV-1 vaccine composition of claim 21, wherein the HIV-1 Env-derived trimer immunogen is a modified gp140 protein comprising a gp120 polypeptide and a gp41_{ECTO} polypeptide, and wherein the N-terminus of heptad 1 region (HR1) of the gp41_{ECTO} polypeptide is replaced with a loop sequence of about 6 to about
10 14 amino acid residues that stabilizes the pre-fusion gp140 structure.

24. The HIV-1 vaccine composition of claim 23, wherein the loop sequence comprises (a) (GS)_n (SEQ ID NO:23), wherein n is any integer between 3 and 7, inclusive or (b) a rationally redesigned sequence via ensemble-based protein design.

25. The HIV-1 vaccine composition of claim 23, wherein the modified
15 gp140 protein is covalently fused to the nanoparticle platform.

26. The HIV-1 vaccine composition of claim 23, wherein the nanoparticle platform comprises a trimeric sequence.

27. The HIV-1 vaccine composition of claim 23, wherein the nanoparticle platform comprises dihydrolipoyl acyltransferase (E2P), ferritin, or
20 lumazine synthase (LS).

28. The HIV-1 vaccine composition of claim 23, wherein the nanoparticle platform has one or more 3-fold axes on the surface with the N-terminus of each monomer subunit being in close proximity to the 3-fold axis, and the spacing of the three N-termini matching the spacing of the C-termini of the modified gp140 protein trimer.

25 29. The HIV-1 vaccine composition of claim 23, wherein the C-terminus of the modified gp140 protein sequence is fused to the N-terminus of the subunit of the nanoparticle platform sequence.

30. The HIV-1 vaccine composition of claim 23, the nanoparticle platform comprises a self-assembling nanoparticle with a diameter of about 20nm or less that is assembled from 12 or 24 subunits.

31. The HIV-1 vaccine composition of claim 23, further comprising an
5 adjuvant.

32. The HIV-1 vaccine composition of claim 23, wherein the gp140 trimer is derived from HIV-1 strain BG505, and the loop sequence has a sequence shown in SEQ ID NO:6.

33. The modified HIV-1 gp140 protein of claim 32, further comprising (a)
10 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.

34. A method of preventing HIV-1 infection in a subject, comprising administering to the subject a therapeutically effective amount of the vaccine immunogen of claim 20, thereby preventing HIV-1 infection in the subject.

15 35. A method of treating HIV-1 infection or eliciting an immune response against HIV-1 in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the vaccine immunogen of claim 20, thereby treating HIV-1 infection or eliciting an immune response against HIV-1 in the subject.

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