

Claims

1. An antibody or an antigen-binding fragment thereof that binds to human immunodeficiency virus-1 (HIV-1) Envelope glycoprotein gp120, the antibody or antigen-binding fragment thereof comprising (i) a heavy chain variable region (VH) comprising VH complementary determining regions 1-3 (CDRs 1-3) and (ii) a light chain variable region (VL) comprising VL CDRs 1-3, wherein the VH CDRs 1-3 and VL CDRs 1-3 have the sequences set forth in:

- (i) SEQ ID NOs.: 159, 138, 139, 140, 141, and 142, respectively;
- (ii) SEQ ID NOs.: 137, 160, 139, 140, 141, and 142, respectively;
- (iii) SEQ ID NOs.: 137, 161, 139, 140, 141, and 142, respectively;
- (iv) SEQ ID NOs.: 137, 162, 139, 140, 141, and 142, respectively;
- (v) SEQ ID NOs.: 137, 163, 139, 140, 141, and 142, respectively;
- (vi) SEQ ID NOs.: 137, 138, 164, 140, 141, and 142, respectively;
- (vii) SEQ ID NOs.: 159, 138, 164, 140, 141, and 142, respectively;
- (viii) SEQ ID NOs.: 137, 138, 139, 140, 165, and 142, respectively;
- (ix) SEQ ID NOs.: 137, 138, 139, 140, 166, and 142, respectively;
- (x) SEQ ID NOs.: 137, 138, 139, 140, 167, and 142, respectively;
- (xi) SEQ ID NOs.: 137, 138, 139, 140, 168, and 142, respectively;
- (xii) SEQ ID NOs.: 137, 138, 154, 140, 141, and 142, respectively; or

(xiii) SEQ ID NOs.: 137, 138, 139, 140, 141, and 142, respectively; and wherein the antibody or antigen-binding fragment thereof includes in framework region 3 (FR3) of the VH at position corresponding to 74a, 74b, 74c, and 74d (Kabat numbering) the amino acid sequence set forth in SEQ ID NO: 627.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises one or more of the following amino acids at the indicated positions (position numbering according to Kabat): valine at position 5, glutamic acid at position 10, lysine at position 12, lysine at position 23, asparagine at position 28, arginine at position 30, tyrosine at position 32, threonine at position 68, methionine at position 69, histidine at position 72, phenylalanine at position 76, alanine at position 78, serine at position 82a, arginine at position 82b, threonine at position 89, tyrosine at position 99, glutamine at position 105, or methionine at position 108.

3. The antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the FR3 of the VH comprising the following amino acid sequence:
RVSLTRHASFDFDTFSFYMDLKALRSDDTAVYFCAR (SEQ ID NO: 629).

4. The antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein the VL comprises one or more of the following amino acids at the indicated positions (position numbering according to Kabat): arginine at position 18, alanine at position 19, serine at position 65, threonine or histidine at position 72, lysine at position 74, serine at position 76, serine at position 77, phenylalanine at position 98, or glycine at position 99.

5. The antibody or antigen-binding fragment thereof of any one of claims 1 to 4, comprising a human IgG1 Fc region.

6. The antibody or antigen-binding fragment thereof of claim 5, wherein the human IgG1 Fc region is IgG1m17 (SEQ ID NO: 348).

7. The antibody or antigen-binding fragment thereof of any one of claims 1 to 6, comprising a human IgG1 Fc region comprising (position numbered according to EU numbering):

(i) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330;

(ii) aspartic acid at position 239, glutamic acid at position 332, leucine at position 428, and serine at position 434;

(iii) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 428, and serine at position 434;

(iv) aspartic acid at position 239, glutamic acid at position 332, leucine at position 330, leucine at position 428, and serine at position 434;

(v) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330, leucine at position 428, and serine at position 434; or

(vi) leucine at position 243, proline at position 292, leucine at position 300, isoleucine at position 305, leucine at position 396, leucine at position 428, and serine at position 434.

8. The antibody or antigen-binding fragment thereof of any one of claims 1 to 5, comprising a human kappa light chain constant region.

9. The antibody or antigen-binding fragment thereof of claim 8, wherein the human kappa light chain constant region is Km3 (SEQ ID NO:351).

10. The antibody or antigen-binding fragment thereof of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment has a serum half-life in a human of at least about 3 days.

11. The antibody of claim 1, the antibody comprising (i) a heavy chain variable region (VH) comprising VH complementary determining regions 1-3 (CDRs 1-3) and (ii) a light chain variable region (VL) comprising VL CDRs 1-3, wherein the VH CDRs 1-3 and VL CDRs 1-3 have the sequences set forth in:

(i) SEQ ID NOs.: 137, 138, 139, 140, 141, and 142, respectively; or

(ii) SEQ ID NOs.: 153, 138, 154, 140, 141, and 142, respectively,

wherein the antibody comprises a human IgG1 Fc region comprising (position numbered according to EU numbering):

(i) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330;

(ii) aspartic acid at position 239, glutamic acid at position 332, leucine at position 428, and serine at position 434;

(iii) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 428, and serine at position 434;

(iv) aspartic acid at position 239, glutamic acid at position 332, leucine at position 330, leucine at position 428, and serine at position 434;

(v) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330, leucine at position 428, and serine at position 434; or

(vi) leucine at position 243, proline at position 292, leucine at position 300, isoleucine at position 305, leucine at position 396, leucine at position 428, and serine at position 434, and wherein the antibody comprises in framework region 3 (FR3) of the VH at positions corresponding to 74a, 74b, 74c, and 74d (Kabat numbering) the amino acid sequence set forth in SEQ ID NO: 627.

12. The antibody of claim 11, wherein the antibody comprises a light chain comprising an alanine at position 19 (Kabat numbering).

13. The antibody of claim 11, wherein the FR3 of the VH comprising the following amino acid sequence: RVSLTRHASFDFTFSFYMDLKALRSDDTAVYFCAR (SEQ ID NO: 629).

14. The antibody of any one of claims 11 to 13, wherein the human IgG1 Fc region is IgG1m17 (SEQ ID NO:348).

15. The antibody of any one of claims 11 to 14, wherein the antibody comprises a human kappa light chain constant region.

16. The antibody of claim 15, wherein the human kappa light chain constant region is Km3 (SEQ ID NO:351).

17. The antibody or antigen-binding fragment thereof of any one of claims 11 to 160, wherein the antibody or antigen-binding fragment has a serum half-life in a human of at least about 3 days.

18. The antibody or an antigen-binding fragment thereof of claim 1, the antibody or antigen-binding fragment thereof comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the amino acid sequences set forth, respectively, below:

- (i) SEQ ID NOs.: 477 and 223;
- (ii) SEQ ID NOs.: 477 and 278;
- (iii) SEQ ID NOs.: 477 and 292; or
- (iv) SEQ ID NOs.: 478 and 276.

19. The antibody or antigen-binding fragment of claim 18, wherein the VH and VL comprise the amino acid sequence set forth in SEQ ID NOs.: 477 and 278, respectively.

20. The antibody or antigen-binding fragment thereof of any one of claims 1 to 19, comprising a VH that is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 465-478 and a VL that is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 222-311, 479-516 and 569.

21. The antibody or antigen-binding fragment thereof of any one of claims 18 to 20, comprising a human IgG1 Fc region.

22. The antibody or antigen-binding fragment thereof of claim 21, wherein the human IgG1 Fc region is IgG1m17 (SEQ ID NO:348).

23. The antibody or antigen-binding fragment thereof of any one of claims 18 to 22, comprising a human IgG1 Fc region comprising (position numbered according to EU numbering):

(i) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330;

(ii) aspartic acid at position 239, glutamic acid at position 332, leucine at position 428, and serine at position 434;

(iii) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 428, and serine at position 434;

(iv) aspartic acid at position 239, glutamic acid at position 332, leucine at position 330, leucine at position 428, and serine at position 434;

(v) aspartic acid at position 239, glutamic acid at position 332, alanine at position 236, leucine at position 330, leucine at position 428, and serine at position 434; or

(vi) leucine at position 243, proline at position 292, leucine at position 300, isoleucine at position 305, leucine at position 396, leucine at position 428, and serine at position 434.

24. The antibody or antigen-binding fragment thereof of any one of claims 18 to 23, wherein the antibody comprises a human kappa light chain constant region.

25. The antibody or antigen-binding fragment thereof of claim 24, wherein the human kappa light chain constant region is Km3 (SEQ ID NO:351).

26. The antibody or antigen-binding fragment thereof of any one of claims 18 to 25, wherein the antibody or antigen-binding fragment has a serum half-life in a human of at least about 3 days.

27. An antigen-binding fragment of any one of claims 1 to 26, comprising a scFv, sc(Fv)₂, Fab, F(ab)₂, Fab', F(ab')₂, Facb or Fv fragment.

28. The antibody of claim 1, the antibody comprising a heavy chain and a light chain, wherein the heavy chain and the light chain comprise the amino acid sequences set forth, respectively, below:

(i) SEQ ID NOs.: 529 and 49;

(ii) SEQ ID NOs.: 529 and 103;

(iii) SEQ ID NOs.: 529 and 117; or

(iv) SEQ ID NOs.: 530 and 101.

29. The antibody of claim 28, wherein the heavy chain and light have the amino acid sequence set forth in SEQ ID NOs.: 529 and 103, respectively.

30. The antibody or antigen-binding fragment thereof of any one of claims 1 to 297, comprising a heavy chain (HC) that is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 529-530 and a light chain (LC) that is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-136 and 531-567.

31. The antibody or antigen-binding fragment thereof of any one of claims 1 to 30, wherein at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, or more, N-linked glycosylation sites in the VL are sialylated.

32. The antibody or antigen-binding fragment of claim 1, wherein the asparagine at VL amino acid position 72 according to Kabat numbering (N72) is sialylated.

33. The antibody or antigen-binding fragment of claim 31 or 32, wherein the sialylated N-linked glycosylation sites in the VL comprise from 1 to 5 sialic acid residues.

34. The antibody or antigen-binding fragment thereof of any one of claims 31 to 33, wherein the VL are sialylated with N-acetylneuraminic acid (NANA).

35. The antibody or antigen-binding fragment thereof of any one of claims 31 to 34, wherein the sialic acid residues are present in biantennary structures.

36. The antibody or antigen-binding fragment thereof of any one of claims 31 to 35, wherein the sialic acid residues are present in complex N-linked glycan structures.

37. The antibody or antigen-binding fragment thereof of any one of claims 31 to 35, wherein the sialic acid residues are present in hybrid N-linked glycan structures.

38. The antibody or antigen-binding fragment thereof of any one of claims 31 to 37, wherein the glycans are terminally sialylated.

39. A bispecific antibody comprising:
a first antigen binding arm that binds to gp120, the first antigen binding arm comprising:

the VH and the VL of claim 18; and

a second antigen binding arm binding to a second antigen.

40. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-39, and a pharmaceutically acceptable carrier.

41. The pharmaceutical composition of claim 40, further comprising a second agent for treating an HIV infection.

42. The pharmaceutical composition of claim 41, further comprising a second antibody or antigen-binding fragment thereof that binds, inhibits, and/or neutralizes HIV, wherein the second antibody or antigen-binding fragment thereof does not compete with the antibody or antigen-binding fragment of f claim **Error! Reference source not found.** for binding to gp120.

43. A chimeric antigen receptor (CAR) comprising an antigen-binding fragment according to claim 27.

44. A CAR T-cell comprising the CAR of claim 43.