

WHAT IS CLAIMED IS:

1. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a heavy chain variable domain (VH) comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity-determining region 3 (CDR3) comprising the amino acid sequences of SEQ ID NOs: 11, 4, and 5, respectively; and
 - (b) a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively.
2. The antigen-binding site of claim 1, wherein the VH comprises an amino acid sequence of SEQ ID NO:49, and the VL comprises an amino acid sequence of SEQ ID NO:17.
3. The antigen-binding site of claim 1 or 2, wherein the VH comprises an amino acid sequence at least 90% identical to SEQ ID NO:45, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO:140.
4. The antigen-binding site of any one of claims 1-3, wherein the VH comprises the amino acid sequence of SEQ ID NO:45, and the VL comprises the amino acid sequence of SEQ ID NO:140.
5. The antigen-binding site of claim 1 or 2, wherein the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 9 and 10; 13 and 10; 110 and 10; 45 and 10; 122 and 10; 9 and 30; 9 and 34; 9 and 38; or 41 and 42, respectively.
6. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 117, 63, and 112, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 65, 66, and 67, respectively.
7. The antigen-binding site of claim 6, wherein the VH comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 59, 63, and 79, respectively; and the VL comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 65, 66, and 67, respectively.

8. The antigen-binding site of claim 6, wherein the VH comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 59, 63, and 54, respectively, and the VL comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 65, 66, and 67, respectively.
9. The antigen-binding site of claim 6, wherein the VH comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 62, 63, and 54, respectively, and the VL comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 65, 66, and 67, respectively.
10. The antigen-binding site of any one of claims 6-9, wherein the VH comprises the amino acid sequence of SEQ ID NO:115, and the VL comprises the amino acid sequence of SEQ ID NO:116.
11. The antigen-binding site of claim 10, wherein the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 29 and 69; 14 and 69; 76 and 69; 29 and 84; 14 and 84; or 76 and 84, respectively.
12. An antigen-binding site that binds CLEC12A, comprising:
- (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 87, 33, and 89, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 106, 92, and 46, respectively.
13. An antigen-binding site that binds CLEC12A, comprising:
- (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 72, 33, and 107, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 111, 105, and 46, respectively.
14. An antigen-binding site that binds CLEC12A, comprising:
- (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 87, 102, and 89, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 18, 92, and 46, respectively.

15. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 26, 37, and 50, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 53, 55, and 56, respectively.
16. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 64, 68, and 73, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 77, 78, and 80, respectively.
17. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 86, 88, and 127, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 90, 91, and 93, respectively.
18. An antigen-binding site that binds CLEC12A, comprising:
 - (a) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 96, 97, and 98, respectively; and
 - (b) a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 99, 100, and 101, respectively.
19. An antigen-binding site that competes with the antigen-binding site of any one of claims 13-17.
20. The antigen-binding site of any one of claims 1-11, 14-15, and 17, wherein the antigen-binding site binds human CLEC12A with a dissociation constant (K_D) smaller than or equal to 20 nM as measured by surface plasmon resonance (SPR).
21. The antigen-binding site of any one of claims 1-4, wherein the antigen-binding site binds human CLEC12A with a K_D smaller than or equal to 1 nM as measured by SPR.

22. The antigen-binding site of any one of claims 1-11, wherein the antigen-binding site binds CLEC12A in a glycosylation independent manner.
23. The antigen-binding site of any one of claims 1-5 and 20-22, wherein the antigen-binding site binds human CLEC12A comprising a K244Q mutation.
24. The antigen-binding site of any one of claims 1-23, wherein the antigen-binding site is present as a single-chain fragment variable (scFv).
25. The antigen-binding site of claim 24, wherein the scFv comprises an amino acid sequence selected from SEQ ID NOs: 3, 12, 15, 16, 19, 20, 23, 24, 27, 28, 31, 32, 35, 36, 39, 40, 43, 44, 47, 48, 51, 52, 70, 71, 74, 75, 81, 82, 118, 119, 120, 121, 132, 133, 138, and 139.
26. An antigen-binding site that binds CLEC12A in a glycosylation independent manner.
27. A protein comprising the antigen-binding site of any one of the claims 1-26.
28. The protein of claim 27, further comprising an antibody heavy chain constant region.
29. The protein of claim 28, wherein the antibody heavy chain constant region is a human IgG heavy chain constant region.
30. The protein of claim 29, wherein the antibody heavy chain constant region is a human IgG1 heavy chain constant region.
31. The protein of claim 29 or 30, wherein each polypeptide chain of the antibody heavy chain constant region comprises an amino acid sequence at least 90% identical to SEQ ID NO:21.
32. The protein of any one of claims 29-31, wherein at least one polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:21, at one or more positions selected from Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, and K439, numbered according to the EU numbering system.

33. The protein of any one of claims 29-32, wherein at least one polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:21, selected from Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, L351K, L351D, L351Y, S354C, E356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E, T394F, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I, Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E, numbered according to the EU numbering system.

34. The protein of any one of claims 29-33, wherein one polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:21, at one or more positions selected from Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and K439; and the other polypeptide chain of the antibody heavy chain constant region comprises one or more mutations, relative to SEQ ID NO:21, at one or more positions selected from Q347, Y349, L351, S354, E356, E357, S364, T366, L368, K370, N390, K392, T394, D399, D401, F405, Y407, K409, T411, and K439, numbered according to the EU numbering system.

35. The protein of claim 34, wherein one polypeptide chain of the antibody heavy chain constant region comprises K360E and K409W substitutions relative to SEQ ID NO:21; and the other polypeptide chain of the antibody heavy chain constant region comprises Q347R, D399V and F405T substitutions relative to SEQ ID NO:21, numbered according to the EU numbering system.

36. The protein of claim 34 or 35, wherein one polypeptide chain of the antibody heavy chain constant region comprises a Y349C substitution relative to SEQ ID NO:21; and the other polypeptide chain of the antibody heavy chain constant region comprises an S354C substitution relative to SEQ ID NO:21, numbered according to the EU numbering system.

37. An antibody-drug conjugate comprising the protein of any one of claims 27-36 and a drug moiety.

38. The antibody-drug conjugate of claim 37, wherein the drug moiety is selected from the group consisting of auristatin, N-acetyl- γ calicheamicin, maytansinoid, pyrrolobenzodiazepine, and SN-38.
39. An immunocytokine comprising the antigen-binding site of any one of claims 1-26 and a cytokine.
40. The immunocytokine of claim 39, wherein the cytokine is selected from the group consisting of IL-2, IL-4, IL-10, IL-12, IL-15, TNF, and IFN α .
41. A bispecific T-cell engager comprising the antigen-binding site of any one of claims 1-26 and an antigen-binding site that binds CD3.
42. A chimeric antigen receptor (CAR) comprising:
(a) the antigen-binding site of any one of claims 1-26;
(b) a transmembrane domain; and
(c) an intracellular signaling domain.
43. The CAR of claim 42, wherein the transmembrane domain is selected from the transmembrane regions of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CLEC12A, CD37, CD64, CD80, CD86, CD134, CD137, CD152, and CD154.
44. The CAR of claim 42 or 43, wherein the intracellular signaling domain comprises a primary signaling domain comprising a functional signaling domain of CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and DAP12.
45. The CAR of any one of claims 42-44, wherein the intracellular signaling domain further comprises a costimulatory signaling domain comprising a functional signaling domain of a costimulatory receptor.
46. The CAR of claim 45, wherein the costimulatory receptor is selected from the group consisting of OX40, CD27, CD28, CD30, CD40, PD-1, CD2, CD7, CD258, NKG2C, B7-H3, a

ligand that binds to CD83, ICAM-1, LFA-1 (CD11a/CD18), ICOS and 4-1BB (CD137), or any combination thereof.

47. An isolated nucleic acid encoding the CAR of any one of claims 42-46.
48. An expression vector comprising the isolated nucleic acid of claim 47.
49. An immune effector cell comprising the nucleic acid of claim 47 or the expression vector of claim 48.
50. An immune effector cell expressing the CAR of any one of claims 42-46.
51. The immune effector cell of claim 49 or 50, wherein the immune effector cell is a T cell.
52. The immune effector cell of claim 51, wherein the T cell is a CD8⁺ T cell, a CD4⁺ T cell, or an NKT cell.
53. The immune effector cell of claim 49 or 50, wherein the immune effector cell is an NK cell.
54. A pharmaceutical composition comprising the protein of any one of claims 27-36, the antibody-drug conjugate of claim 37 or 38, the immunocytokine of claim 39 or 40, the bispecific T-cell engager of claim 41, or the immune effector cell of any one of claims 49-53; and a pharmaceutically acceptable carrier.
55. A method of treating cancer, the method comprising administering to a subject in need thereof an effective amount of the protein of any one of claims 27-36, the antibody-drug conjugate of claim 37 or 38, the immunocytokine of claim 39 or 40, the bispecific T-cell engager of claim 41, the immune effector cell of any one of claims 49-53, or the pharmaceutical composition of claim 54.
56. The method of claim 55, wherein the cancer is a hematologic malignancy.
57. The method of claim 56, wherein the hematologic malignancy is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute

lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPNs), lymphoma, non-Hodgkin lymphomas, and classical Hodgkin lymphoma.

58. The method of claim 57, wherein the AML is selected from undifferentiated acute myeloblastic leukemia, acute myeloblastic leukemia with minimal maturation, acute myeloblastic leukemia with maturation, acute promyelocytic leukemia (APL), acute myelomonocytic leukemia, acute myelomonocytic leukemia with eosinophilia, acute monocytic leukemia, acute erythroid leukemia, acute megakaryoblastic leukemia (AMKL), acute basophilic leukemia, acute panmyelosis with fibrosis, and blastic plasmacytoid dendritic cell neoplasm (BPDCN).

59. The method of claim 57 or 58, wherein the AML is characterized by expression of CLEC12A on the AML leukemia stem cells (LSCs).

60. The method of claim 59, wherein the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96.

61. The method of any one of claims 57-60, wherein the AML is a minimal residual disease (MRD).

62. The method of claim 61, wherein the MRD is characterized by the presence or absence of a mutation selected from *FLT3-ITD* ((Fms-like tyrosine kinase 3)-internal tandem duplications (ITD)), *NPM1* (Nucleophosmin 1), *DNMT3A* (DNA methyltransferase gene *DNMT3A*), and *IDH* (Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2)).

63. The method of claim 57, wherein the MDS is selected from MDS with multilineage dysplasia (MDS-MLD), MDS with single lineage dysplasia (MDS-SLD), MDS with ring sideroblasts (MDS-RS), MDS with excess blasts (MDS-EB), MDS with isolated del(5q), and MDS, unclassified (MDS-U).

64. The method of claim 57, wherein the MDS is a primary MDS or a secondary MDS.

65. The method of claim 57, wherein the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL).

66. The method of claim 57, wherein the MPN is selected from polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis.
67. The method of claim 57, wherein the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma.
68. The method of claim 57, wherein the lymphoma is selected from chronic lymphocytic leukemia (CLL), lymphoblastic lymphoma (LPL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary mediastinal large B-cell lymphoma (PMBL), follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, plasma cell myeloma (PCM) or multiple myeloma (MM), mature T/NK neoplasms, and histiocytic neoplasms.
69. The method of any one of claims 55-68, wherein the cancer expresses CLEC12A.