

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, 130, and 131, 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 at least 90% identical to SEQ ID NO:128 or 147, and the VL comprises an amino acid sequence at least 90% identical to SEQ ID NO:129 or 148.
3. The antigen-binding site of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO:128 or 147, and the VL comprises the amino acid sequence of SEQ ID NO:129 or 148.
4. The antigen-binding site of claim 1, wherein the VH and the VL comprise the amino acid sequences of SEQ ID NOs: 128 and 129; 128 and 148; 147 and 129; or 147 and 148, respectively.
5. 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.
6. The antigen-binding site of claim 5, 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.

7. The antigen-binding site of claim 5 or 6, 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.
8. The antigen-binding site of any one of claims 5-7, 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.
9. The antigen-binding site of claim 5 or 6, 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.
10. 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.
11. The antigen-binding site of claim 10, wherein
 - (a) 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;
 - (b) 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; or
 - (c) 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.
12. The antigen-binding site of claim 10 or 11, 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.

13. The antigen-binding site of claim 12, 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.

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, 33, and 89, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 106, 92, and 46, respectively;

(b) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 72, 33, and 107, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 111, 105, and 46, respectively;

(c) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 87, 102, and 89, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 18, 92, and 46, respectively;

(d) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 26, 37, and 50, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 53, 55, and 56, respectively;

(e) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 64, 68, and 73, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 77, 78, and 80, respectively;

(f) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 86, 88, and 127, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 90, 91, and 93, respectively; or

(g) a VH comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 96, 97, and 98, respectively; and a VL comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 99, 100, and 101, respectively.

15. An antigen-binding site that competes with the antigen-binding site of any one of claims 1-14.

16. The antigen-binding site of any one of claims 1-14, wherein the antigen-binding site binds human CLEC12A:
- (a) with a dissociation constant (K_D) smaller than or equal to:
 - (i) 20 nM as measured by surface plasmon resonance (SPR); or
 - (ii) 1 nM as measured by SPR;
 - (b) in a glycosylation independent manner; and/or
 - (c) comprising a K244Q mutation.
17. The antigen-binding site of any one of claims 1-16, wherein the antigen-binding site is present as a single-chain fragment variable (scFv).
18. The antigen-binding site of any one of claims 5-16, wherein the antigen-binding site is present as a single-chain fragment variable (scFv) and 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, 138, and 139.
19. The antigen-binding site of any one of claims 1-4, wherein the antigen-binding site is present as a single-chain fragment variable (scFv) and comprises an amino acid sequence selected from SEQ ID NOs: 132 or 133.
20. An antigen-binding site that binds CLEC12A in a glycosylation independent manner.
21. A protein comprising the antigen-binding site of any one of the claims 1-20.
22. The protein of claim 21, further comprising an antibody heavy chain constant region.
23. The protein of claim 22, wherein the antibody heavy chain constant region is a human IgG heavy chain constant region.
24. The protein of claim 23, wherein
- (a) each polypeptide chain of the antibody heavy chain constant region comprises an amino acid sequence at least 90% identical to SEQ ID NO:21;
 - (b) 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;

(c) 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; or

(d) 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.

25. The protein of claim 24, wherein one polypeptide chain of the antibody heavy chain constant region comprises:

(a) 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; and/or

(b) 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.

26. An antibody-drug conjugate comprising the protein of any one of claims 21-25 and a drug moiety.

27. The antibody-drug conjugate of claim 26, wherein the drug moiety is selected from the group consisting of auristatin, N-acetyl- γ calicheamicin, maytansinoid, pyrrolobenzodiazepine, and SN-38.
28. An immunocytokine comprising the antigen-binding site of any one of claims 1-20 and a cytokine.
29. The immunocytokine of claim 28, wherein the cytokine is selected from the group consisting of IL-2, IL-4, IL-10, IL-12, IL-15, TNF, and IFN α .
30. A bispecific T-cell engager comprising the antigen-binding site of any one of claims 1-20 and an antigen-binding site that binds CD3.
31. A chimeric antigen receptor (CAR) comprising:
(a) the antigen-binding site of any one of claims 1-20;
(b) a transmembrane domain; and
(c) an intracellular signaling domain.
32. The CAR of claim 31, wherein
(i) 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;
(ii) 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; and/or
(iii) the intracellular signaling domain further comprises a costimulatory signaling domain comprising a functional signaling domain of a costimulatory receptor.
33. The CAR of claim 32, 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.

34. An isolated nucleic acid encoding the CAR of any one of claims 31-33.
35. An expression vector comprising the isolated nucleic acid of claim 34.
36. An immune effector cell
- (i) comprising the nucleic acid of claim 34 or the expression vector of claim 35; or
 - (ii) expressing the CAR of any one of claims 31-33.
37. The immune effector cell of claim 36, wherein the immune effector cell is a T cell, or an NK cell.
38. The immune effector cell of claim 37, wherein the T cell is a CD8⁺ T cell, a CD4⁺ T cell, or an NKT cell.
39. A pharmaceutical composition comprising the protein of any one of claims 21-25, the antibody-drug conjugate of claim 26 or 27, the immunocytokine of claim 28 or 29, the bispecific T-cell engager of claim 30, or the immune effector cell of any one of claims 36-38; and a pharmaceutically acceptable carrier.
40. Use of a protein of any one of claims 21-25, the antibody-drug conjugate of claim 26 or 27, the immunocytokine of claim 28 or 29, the bispecific T-cell engager of claim 30, the immune effector cell of any one of claims 36-38, or the pharmaceutical composition of claim 39 in the manufacture of a medicament for treating a cancer.
41. The use of claim 40, wherein the cancer is a hematologic malignancy.
42. The use of claim 41, 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.
43. The use of claim 42, wherein
- (a) the AML is:

- (i) 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);
- (ii) characterized by expression of CLEC12A on the AML leukemia stem cells (LSCs);
- (iii) a minimal residual disease (MRD);
- (b) the LSCs further express a membrane marker selected from CD34, CD38, CD123, TIM3, CD25, CD32, and CD96;
- (c) 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));
- (d) the MDS is:
 - (i) 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);
 - (ii) a primary MDS or a secondary MDS;
- (e) the ALL is selected from B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL);
- (f) the MPN is selected from polycythaemia vera, essential thrombocythemia (ET), and myelofibrosis.
- (g) the non-Hodgkin lymphoma is selected from B-cell lymphoma and T-cell lymphoma; or
- (h) 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.

44. The use of any one of claims 40-43, wherein the cancer expresses CLEC12A.
45. The protein of any one of claims 21-25, the antibody-drug conjugate of claim 26 or 27, the immunocytokine of claim 28 or 29, the bispecific T-cell engager of claim 30, the immune effector of any one of claims 36-38, or the pharmaceutical composition of claim 39 for use in therapy.