

CLAIMS

WHAT IS CLAIMED IS:

1. A nucleic acid comprising a polynucleotide encoding a chimeric polypeptide comprising: (i) a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a CD2 signaling domain but does not comprise a CD3-zeta domain; and at least one of: (ii) an antigen binding domain; or (iii) a transmembrane domain.
2. The nucleic acid of claim 1, wherein the cytoplasmic signaling domain further comprises a co-stimulating domain.
3. The nucleic acid of claim 2, wherein the co-stimulating domain comprises at least one of: a 4-1BB signaling domain, a CD27 signaling domain, an OX40 signaling domain, a CD28 signaling domain, a CD278 signaling domain, a CD40 signaling domain, a CD40L signaling domain, a toll-like receptor signaling domain, or any combination thereof.
4. The nucleic acid of any one of claims 1-3, wherein the cytoplasmic signaling domain comprises an amino acid sequence that is at least 80% homologous to the amino acid sequence of SEQ ID NO: 8.
5. The nucleic acid of any one of claims 1-3, wherein the cytoplasmic domain consists of SEQ ID NO: 8.
6. The nucleic acid of any one of claims 1-5, wherein the chimeric polypeptide comprises an amino acid sequence that is at least about 80% homologous to an amino acid sequence selected from the group consisting of: SEQ ID NOs: 20 to 29 and 92-112.
7. The nucleic acid of any one of claims 1-6, comprising the polynucleotide encoding the chimeric polypeptide, wherein the chimeric polypeptide comprises (ii) the antigen binding domain.
8. The nucleic acid of claim 7, wherein the antigen binding domain comprises an antibody or an antigen binding fragment thereof.
9. The nucleic acid of claim 7, wherein the antigen binding domain comprises an scFv, an sdAb, an Fab, a bispecific antibody or an antigen binding fragment thereof, a trispecific

antibody or an antigen binding fragment thereof, a bispecific diabody, a trispecific traibody, an scFv-Fc, a minibody, a VhH domain, an hclgG domain, a V-NAR domain, or any combination thereof.

10. The nucleic acid of any one of claims 7-9, wherein the antigen binding domain is specific for a B cell surface antigen.
11. The nucleic acid of claim 10, wherein the B cell surface antigen is selected from the group consisting of HLA-DR, CD20, CD32b, CD37, CD38, CD52, CD81, CD79A, CD79B, CD138, CSI, GPRC5D, a BAFF receptor, APRIL, BCMA, and TACI.
12. The nucleic acid of any one of claims 7-9, wherein the antigen binding domain is specific for a tumor associated antigen.
13. The nucleic acid of claim 12, wherein the tumor associated antigen is selected from the group consisting of HLA-DR, CD20, CD32b, CD37, CD38, CD52, CD81, CD79A, CD79B, CD138, CSI, GPRC5D, a BAFF receptor, APRIL, BCMA, TACI, glioma-associated antigen, carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin, alpha-fetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut HSP70-2, M-CSF, prostate-specific antigen (PSA), PAP, NY-ESO-1, LAGE-1a, p53, prostein, PSMA, HER2, survivin and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrinB2, , insulin growth factor (IGF)-I, IGF-II, IGF-I receptor, GD2, GD3, B7-H3, GPC2, L1CAM, EGFR, mesothelin, MART-1, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, p53, Ras, HER-2, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, EBVA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp72, α -fetoprotein, β -HCG, BCA225, BTAA, CA125, BCMA, CA195, CA242, CA-50, CAM43, CD68/P1, CO-029, FGF-5, G250, Ga733/EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS CD19, CD20, CD22, ROR1, and GD2.

14. The nucleic acid of any one of claims 1-13, comprising the polynucleotide encoding the chimeric polypeptide, wherein the chimeric polypeptide comprises (iii) the transmembrane domain.
15. The nucleic acid of claim 14, wherein the transmembrane domain is selected from the group consisting of all or part of the transmembrane domain of CD3 ζ , CD2, CD8 α , CD28, CD40, CTLA4, OX40, PD-1, 4-1BB (CD137), FcERI γ , ICOS (CD278), ILRB (CD122), and IL-2RG (CD132).
16. A nucleic acid comprising a polynucleotide encoding a chimeric polypeptide comprising a sequence that is at least about 80% homologous to a sequence selected from the group consisting of SEQ ID NOs: 20 to 29 and 92-112.
17. A nucleic acid composition comprising a nucleic acid comprising a polynucleotide encoding a chimeric polypeptide according to any one of claims 1-16, and further, a nucleic acid comprising a polynucleotide encoding an additional polypeptide.
18. The nucleic acid composition of claim 17, wherein the additional polypeptide comprises a chimeric antigen receptor (CAR), a T cell receptor (TCR), or a TCR-CAR.
19. The nucleic acid composition of claim 18, wherein the CAR comprises a first generation CAR, second generation CAR, or a third generation CAR.
20. The nucleic acid composition of claim 18 or 19, wherein the additional polypeptide comprises a CAR comprising a CD3-zeta domain.
21. The nucleic acid composition of any one of claims 18-20, wherein the additional polypeptide comprises a CAR comprising an antigen binding domain.
22. The nucleic acid composition of claim 21, wherein the antigen binding domain comprises an antibody or an antigen binding fragment thereof.
23. The nucleic acid composition of claim 21, wherein the antigen binding domain comprises an scFv, an sdAb, an Fab, a bispecific antibody or an antigen binding fragment thereof, a trispecific antibody or an antigen binding fragment thereof, a bispecific diabody, a trispecific traibody, an scFv-Fc, a minibody, a VhH domain, an hIgG domain, a V-NAR domain, or any combination thereof.

24. The nucleic acid composition of any one of claims 17-23, wherein the antigen binding domain is specific for a B cell surface antigen.
25. The nucleic acid composition of claim 24, wherein the B cell surface antigen is selected from the group consisting of HLA-DR, CD20, CD32b, CD37, CD38, CD52, CD81, CD79A, CD79B, CD138, CSI, GPRC5D, a BAFF receptor, APRIL, BCMA, and TACI.
26. The nucleic acid composition of any one of claims 21-23, wherein the antigen binding domain is specific for a tumor associated antigen.
27. The nucleic acid composition of claim 24, wherein the tumor associated antigen is selected from the group consisting of glioma-associated antigen, carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin, alpha-fetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut HSP70-2, M-CSF, prostate-specific antigen (PSA), PAP, NY-ESO-1, LAGE-1a, p53, prostein, PSMA, HER2, survivin and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrinB2, insulin growth factor (IGF)-I, IGF-II, IGF-I receptor, GD2, GD3, B7-H3, GPC2, L1CAM, EGFR, mesothelin, MART-1, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, p53, Ras, HER-2, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, EBVA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp72, α -fetoprotein, β -HCG, BCA225, BTAA, CA125, BCAA, CA195, CA242, CA-50, CAM43, CD68/P1, CO-029, FGF-5, G250, Ga733/EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS CD19, CD20, CD22, ROR1, and GD2.
28. The nucleic acid composition of any one of claims 17-27, wherein the additional polypeptide further comprises a co-stimulating domain.
29. The nucleic acid composition of claim 28, wherein the co-stimulating domain comprises at least one of: a 4-1BB signaling domain, a CD27 signaling domain, an

OX40 signaling domain, a CD28 signaling domain, a CD278 signaling domain, a CD40 signaling domain, a CD40L signaling domain, a toll-like receptor signaling domain, or any combination thereof.

30. The nucleic acid composition of any one of claims 17-29, wherein the additional polypeptide further comprises the transmembrane domain.
31. The nucleic acid composition of claim 30, wherein the transmembrane domain is selected from the group consisting of all or part of the transmembrane domain of CD3 ζ , CD2, CD8 α , CD28, CD40, CTLA4, OX40, PD-1, 4-1BB (CD137), FcERI γ , ICOS (CD278), ILRB (CD122), and IL-2RG (CD132).
32. A vector comprising a nucleic acid according to any one of claims 1-16 or a nucleic acid composition according to any one of claims 17-31.
33. A cell comprising a vector according to claim 32.
34. The cell of claim 33, wherein the cell is an immune cell, a stem cell, a mammalian cell, a primate cell, or a human cell.
35. The cell of claim 33 or 34, wherein the cell is autologous or allogeneic.
36. The cell of any of claims 33-35, wherein the cell is a T cell, a CD8-positive T cell, a CD4-positive T cell, a regulatory T cell, a cytotoxic T cell, or a tumor infiltrating lymphocyte.
37. A method treating of a subject having a hyperproliferative disorder, the method comprising: administering to the subject a composition comprising a therapeutically effective number of a cell according to any one of claims 33-36.
38. A method treating of a subject having a hyperproliferative disorder characterized by proliferation of a target cell that (i) lacks expression of CD58; (ii) expresses a reduced level of CD58; or (iii) expresses a form of CD58 that has reduced ability to activate a CD2, the method comprising: administering to the subject a composition comprising a therapeutically effective number of a cell according to any one of claims 33-36.

39. A chimeric polypeptide comprising: (i) an antigen binding domain; (ii) a transmembrane domain; (iii) a cytoplasmic signaling domain comprising a CD2 signaling domain and a co-stimulatory domain, wherein
- (i) the antigen binding domain comprises an amino acid sequence that is at least about 80% homologous to a sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, and 4;
 - (ii) the transmembrane domain comprises an amino acid sequence that is at least about 80% homologous to the sequence selected from the group consisting of SEQ ID NOs: 5, 6, and 7;
 - (iii) the CD2 signaling domain comprises an amino acid sequence that is at least about 80% homologous to the sequence of SEQ ID NO: 8 and the co-stimulatory domain comprises an amino acid sequence that is at least about 80% homologous to a sequence selected from the group consisting of: SEQ ID NOs: 10 and 11.
40. The chimeric polypeptide of claim 39, wherein the cytoplasmic signaling domain does not comprise a CD3-zeta activating domain.
41. The chimeric polypeptide of claim 39, wherein the cytoplasmic signaling domain comprises an activating domain, wherein the activating domain comprises an amino acid sequence that is at least about 80% homologous to the sequence of SEQ ID NO: 9.
42. A chimeric antigen receptor (CAR), comprising in order from N-terminal to C-terminal: a first antigen binding domain specific for a selected antigen; a spacer domain; a transmembrane domain; and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a CD2 signaling domain, a co-stimulating signaling domain, and a CD3 zeta chain (CD3ζ) activating domain, wherein the co-stimulating signaling domain is not a CD28 signaling domain.
43. The CAR of claim 42, wherein the co-stimulating signaling domain comprises a 4-1BB signaling domain, a CD27 signaling domain, or an OX40 signaling domain.
44. The CAR of claim 42 or 43, wherein the co-stimulating signaling domain comprises a 4-1BB signaling domain.

45. The CAR of any one of claims 42 to 44, wherein the CAR further comprises a second antigen binding domain.
46. The CAR of any one of claims 42 to 45, wherein the first antigen binding domain and the second antigen binding domain are specific for different antigens.
47. The CAR of any one of claims 42 to 45, wherein the first antigen binding domain and the second antigen binding domain are specific for different epitopes of the same antigen.
48. The CAR of any one of claims 42 to 47, wherein the spacer domain is selected from the group consisting of a CD8 α hinge domain, a CD28 hinge domain, a CTLA-4 hinge domain, an IgG1 hinge domain, and an IgG4 hinge domain.
49. The CAR of claim 48, wherein the spacer domain comprises a CD28 hinge domain.
50. The CAR of any one of claims 42 to 46, wherein the spacer domain is a synthetic polypeptide spacer having from about 10 to about 50 amino acids.
51. The CAR of claim 50, wherein the synthetic polypeptide spacer is a (GGS)_n, (SGG)_n, (GGGS)_n, (SGGG)_n, or (GGGGS)_n, where n is about 1 to about 15 (SEQ ID NOs: 87-91).
52. The CAR of any one of claims 42 to 51, wherein the transmembrane domain is selected from the group consisting of all or part of the transmembrane domain of CD3 ζ , CD2, CD8 α , CD28, CD40, CTLA4, OX40, PD-1, 4-1BB (CD137), Fc ϵ RI γ , ICOS (CD278), ILRB (CD122), and IL-2RG (CD132).
53. The CAR of claim 52 wherein the transmembrane domain comprises a CD8 α transmembrane domain.
54. The CAR of claim 52, wherein the transmembrane domain comprises a CD28 transmembrane domain.
55. The CAR of claim 42, wherein the CAR has an amino acid sequence that is at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, or about 100% identical to any one of the sequences SEQ ID NOs: 12 to 29, 114-134.
56. The CAR of any one of claims 42 to 54, wherein the first antigen binding domain specifically binds a tumor-specific antigen or a tumor-associated antigen.

57. The CAR of claim 56, wherein the tumor-specific antigen or tumor-associated antigen is selected from the group glioma-associated antigen, carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin, alpha-fetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut HSP70-2, M-CSF, prostate-specific antigen (PSA), PAP, NY-ESO-1, LAGE-1a, p53, prostein, PSMA, HER2, survivin and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrinB2, insulin growth factor (IGF)-I, IGF-II, IGF-I receptor, GD2, GD3, B7-H3, GPC2, L1CAM, EGFR, mesothelin, MART-1, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, p53, Ras, HER-2, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, EBVA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp72, α -fetoprotein, β -HCG, BCA225, BTAA, CA125, BCAA, CA195, CA242, CA-50, CAM43, CD68/P1, CO-029, FGF-5, G250, Ga733/EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS CD19, CD20, CD22, ROR1, or GD2.
58. The CAR of any one of claims 42-57, wherein CD2 signaling is enhanced with a transgenic T-cell receptor (TCR).
59. The CAR of claim 58, wherein the transgenic TCR comprises a second antigen binding domain specific for a second antigen.
60. The CAR of any one of claims 58-59, the transgenic TCR comprises at least a TCR V α chain CDR3 and/or at least a TCR V β chain CDR3.
61. The CAR of claim 60, wherein the transgenic TCR further comprises a transmembrane domain.
62. The CAR of claim 61, wherein the transmembrane domain is selected from the group consisting of CD3 ζ , CD2, CD8 α , CD28, CD40, CTLA4, OX40, PD-1, 4-1BB (CD137), FcER1 γ , ICOS (CD278), ILRB (CD122), and IL-2RG (CD132).

63. The CAR of any one of claims 58-62, wherein the transgenic TCR further comprises a cytoplasmic signaling domain.
64. The CAR of claim 63, wherein the cytoplasmic signaling domain is a CD2 signaling domain.
65. The CAR of any one of claims 58-64, wherein the second antigen of the transgenic TCR is a tumor-specific antigen or a tumor-associated antigen presented by MHC class I or MHC class II.
66. The CAR of claim 65, wherein the second antigen is selected from the group consisting of glioma-associated antigen, carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin, alpha-fetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut HSP70-2, M-CSF, prostate-specific antigen (PSA), PAP, NY-ESO-1, LAGE-1a, p53, prostein, PSMA, HER2, survivin and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrinB2, insulin growth factor (IGF)-I, IGF-II, IGF-I receptor, GD2, GD3, B7-H3, GPC2, L1CAM, EGFR, mesothelin, MART-1, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, p53, Ras, HER-2, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, EBVA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp72, α -fetoprotein, β -HCG, BCA225, BTAA, CA125, BCAA, CA195, CA242, CA-50, CAM43, CD68/P1, CO-029, FGF-5, G250, Ga733/EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS CD19, CD20, CD22, ROR1, and GD2.
67. A chimeric polypeptide for co-stimulating an immune receptor, wherein the immune receptor is a CAR and/or a transgenic TCR, wherein the CAR has a first antigen binding domain specific for a first antigen and the transgenic TCR has a second antigen binding domain, wherein the chimeric polypeptide comprises in order from N-terminal to C-terminal:

a third antigen binding domain specific for a third antigen;
 a transmembrane domain; and
 a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises
 a CD2 signaling domain, and does not comprise a CD3 ζ activating domain, and
 wherein the third antigen is not CD58.

68. The chimeric polypeptide of claim 67, wherein the third antigen is a tumor-specific antigen, or a tumor-associated antigen.
69. The chimeric polypeptide of claim 68, wherein the third antigen is selected from the group consisting of glioma-associated antigen, carcinoembryonic antigen (CEA), beta-human chorionic gonadotropin, alpha-fetoprotein (AFP), lectin-reactive AFP, thyroglobulin, RAGE-1, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut HSP70-2, M-CSF, prostate-specific antigen (PSA), PAP, NY-ESO-1, LAGE-1a, p53, prostein, PSMA, HER2, survivin and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), MAGE, ELF2M, neutrophil elastase, ephrinB2, insulin growth factor (IGF)-I, IGF-II, IGF-I receptor, GD2, GD3, B7-H3, GPC2, L1CAM, EGFR, mesothelin, MART-1, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15, p53, Ras, HER-2, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, EBVA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, β -Catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp72, α -fetoprotein, β -HCG, BCA225, BTAA, CA125, BCAA, CA195, CA242, CA-50, CAM43, CD68/P1, CO-029, FGF-5, G250, Ga733/EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS CD19, CD20, CD22, ROR1, and GD2.
70. The chimeric polypeptide of claim 69, wherein the third antigen is selected from the group consisting of B7H3, BAFF-R, CD19, CD20, CD22, GD2, GD3, GPC2, IL13R α 2, and ROR1.

71. The chimeric polypeptide of any one of claims 67 to 70, wherein the cytoplasmic signaling domain of the chimeric polypeptide comprises an additional co-stimulating signaling domain.
72. The chimeric polypeptide of claim 71, wherein the additional co-stimulating signaling domain comprises a 4-1BB signaling domain, a CD27 signaling domain, a CD28 signaling domain, or an OX40 signaling domain.
73. The chimeric polypeptide of claim 71 or 72, wherein the additional co-stimulating signaling domain comprises a 4-1BB signaling domain, a CD27 signaling domain, or an OX40 signaling domain.
74. The chimeric polypeptide of claim 67, wherein the CAR has an amino acid sequence that is at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, or about 100% identical to any one of the sequences SEQ ID NOs: 20 to 29 and 114-134.
75. The chimeric polypeptide of any one of claims 67 to 74, wherein the transmembrane domain of the chimeric polypeptide is derived from CD8 α , CD2, or CD28.
76. The chimeric polypeptide of claim 75, wherein the transmembrane domain is derived from CD28.
77. A nucleic acid that encodes the CAR of any one of claims 42 to 66, or the chimeric polypeptide of any one of claims 67 to 76, or both.
78. The nucleic acid of claim 77, further encoding the transgenic TCR of any one of claims 58 to 66.
79. The nucleic acid of claim 77, wherein the nucleic acid encodes a polypeptide that has a sequence that is at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, or about 100% identical to any one of sequences SEQ ID NOs: 41-58 and 92-112.
80. The nucleic acid of claim 77 that encodes the chimeric polypeptide of any one of claims 67 to 76.
81. The nucleic acid of claim 80, wherein the nucleic acid encodes a polypeptide that has a sequence that is at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, or about 100% identical to any one of sequences SEQ ID NOs: 49-58 and 92-112.
82. The nucleic acid of claim 80, which further encodes a CAR.

83. The nucleic acid of claim 82, wherein the nucleic acid encodes a polypeptide that has a sequence that is at least 70%, 80%, 90%, 95%, 97%, 98%, 99%, or about 100% identical to any one of sequences SEQ ID NOs: 73, 75, 77, 79, 81, 83, 85, and 114-134.
84. The nucleic acid of claim 80, which further encodes a transgenic TCR.
85. The nucleic acid of any one of claims 82-84, wherein the CAR antigen binding domain, the transgenic TCR antigen binding domain, and the chimeric polypeptide antigen binding domain are specific for different antigens.
86. The nucleic acid of any one of claims 82-84, wherein the CAR antigen binding domain, the transgenic TCR antigen binding domain, and the chimeric polypeptide binding domain are specific for the same antigen.
87. The nucleic acid of any one of claims 82-84, wherein the first antigen binding domain, the second antigen binding domain, and the third antigen binding domain are specific for different epitopes of the same antigen.
88. The nucleic acid of any one of claims 82-84, wherein the nucleic acid encoding the chimeric polypeptide, the nucleic acid encoding the CAR, and the nucleic acid encoding the TCR each have an individual promoter.
89. The nucleic acid of any one of claims 82 to 88, wherein the CAR transmembrane domain, the transgenic TCR transmembrane, and the chimeric polypeptide transmembrane domain are different.
90. The nucleic acid of any one of claims 82-89, wherein the nucleic acid encoding the chimeric polypeptide, the nucleic acid encoding the CAR, and the nucleic acid encoding the TCR are separated by a ribosomal re-entry site.
91. The nucleic acid of claim 82, wherein the chimeric polypeptide and the CAR are encoded as a single polypeptide, where the chimeric polypeptide and the CAR are separated by a self-cleaving peptide.
92. The nucleic acid of claim 91, wherein the self-cleaving peptide is a 2A peptide.
93. The nucleic acid of any one of claims 77 to 92, wherein the nucleic acid comprises DNA.

94. The nucleic acid of any one of claims 77 to 92, wherein the nucleic acid comprises RNA.
95. The nucleic acid of claim 82, wherein the chimeric polypeptide and the CAR are encoded as a separate polypeptide for co-transduction.
96. A vector comprising the nucleic acid of any one of claims 77 to 93 and 95, operably linked to a promoter.
97. The vector of claim 96, wherein the vector is a lentiviral vector.
98. An engineered cell, comprising the CAR of any one of claims 42 to 57, the transgenic TCR of any one of claims 58 to 66, and/or the chimeric polypeptide of any one of claims 67 to 76, the nucleic acid of any one of claims 77 to 92, and/or the vector of claim 95 or 97.
99. The engineered cell of claim 98, wherein the cell expresses a CAR of any one of claims 42 to 66.
100. The engineered cell of claim 98 or 99, wherein the cell expresses a chimeric polypeptide of any one of claims 67 to 76.
101. The engineered cell of claim 100, wherein the engineered cell further comprises one or more CAR.
102. The engineered cell of claim 101, wherein the first antigen, the second antigen, and the third antigen are different from each other.
103. The engineered cell of claim 101, wherein at least two of the first antigen, the second antigen, and third are the same.
104. The engineered cell of claim 101, wherein the first binding domain, the second binding domain, and the third antigen binding domain are specific for different epitopes of the same antigen.
105. The engineered cell of any one of claims 101 to 104, wherein the CAR transmembrane domain is different from the chimeric polypeptide transmembrane domain.
106. A method for making the engineered cell of any one of claims 98 to 105, comprising:
 - a) providing an immune cell; and
 - b) transducing the immune cell with the nucleic acid of any one of claims 77 to 95.

107. The method of claim 106, wherein the immune cell is a T cell, NK cell, NKT cell, a macrophage, or a tumor-infiltrating lymphocyte (TIL).
108. The method of claim 106, wherein the immune cell is a precursor cell of a T cell, NK cell, NKT cell, a macrophage, or a tumor-infiltrating lymphocyte (TIL).
109. The method of any one of claims 106 to 108, further comprising transducing the immune cell with a nucleic acid that encodes an immune receptor, wherein the immune receptor is a CAR and/or a transgenic TCR.
110. The method of any one of claims 106 to 109, wherein the nucleic acid encodes the CAR and/or the transgenic TCR.
111. A method for making a CAR-T cell having improved functional characteristics, the method comprising:
 - a) providing an immune cell; and
 - b) transducing the immune cell with a nucleic acid that encodes a CAR, and a nucleic acid that encodes the chimeric polypeptide of any one of claims 67 to 76, to produce a CAR-T cell having a CAR specific for a target cell having a first antigen, the CAR-T cell further comprising a chimeric polypeptide of any one of claims 67 to 76 and/or a transgenic TCR of any one of claims 58 to 66; wherein the functional characteristic is
 - i. efficacy against target cells that downregulate expression of or do not substantially express CD58;
 - ii. efficacy against target cells that downregulate or the selected antigen, or express a mutated form of the selected antigen;
 - iii. improved selectivity for the target cell; or
 - iv. rescue a loss of a CAR target antigen.
112. The method of claim 111, wherein the chimeric polypeptide comprises an antigen binding domain specific for an antigen expressed by the target cell.
113. The method of claim 111, wherein the transgenic TCR comprises an antigen binding domain specific for an antigen expressed by the target cell.
114. The method of claim 111, wherein the CAR target antigen is CD19.

115. A method for aiding in the treatment of a subject having a hyperproliferative disorder characterized by the proliferation of a target cell having at least a first antigen, the method comprising:
- a) providing:
 - i) the engineered cell of claim 99, wherein the engineered cell expresses a CAR that is specific for the first antigen and/or a transgenic TCR that is specific for the second antigen; or
 - ii) the engineered cell of claim 101, wherein the engineered cell expresses a CAR that is specific for the first antigen and/or a transgenic TCR that is specific for the second antigen; and
 - b) administering a therapeutically effective number of the engineered cells, wherein the engineered cells aid in the treatment of the subject.
116. The method of claim 115, wherein:
- a) the engineered cell of claim 101 comprises a CAR having at least two co-stimulatory domains; or
 - b) the engineered cell of claim 99 comprises a CAR having at least two co-stimulatory domains in addition to the CD2 co-stimulatory domain.
117. The method of claim 115 or 116, further comprising determining the degree of CD58 expression by the target cell.
118. The method of claim 115, further comprising providing a determination of CD58 expression by the target cell prior to administering the engineered cell, and administering a therapeutically effective number of the engineered cells if the determination of CD58 expression indicates that the target cell expresses mutated CD58, or expresses CD58 at a level below a threshold level.
119. The method of claim 118, wherein the threshold level is about 50,000, 45,000, 40,000, 35,000, 30,000, 25,000, 20,000, 15,000, 14,000, 13,000, 12,000, 11,000, 10,000, 9,000, 8,000, 7,000, 6,000, 5,000, 4,000, 3,000, 2,000, 1,000, or 500 CD58 molecules per target cell.
120. The method of any one of claims 115-119, further providing an antibody or an antigen binding fragment thereof.
121. The method of claim 120, wherein the antibody or the antigen binding fragment thereof is capable of stimulating CD2 signaling in the target cell microenvironment.

122. The method of any one of claims 120-121, wherein the antibody is a multispecific antibody.
123. The method of claims 122, wherein the multispecific antibody is specific for an anti-tumor antigen, CD2, and CD3.
124. The method of any one of claims 120-121, wherein the antibody binding fragment is selected from the group consisting of scFv, scFv-Fc, Fab, Fab', (Fab)₂, (Fab')₂, minibody, diabody, triabody, and dAb.
125. The method of claim 124, wherein the antibody binding fragment is specific for an anti-tumor antigen, CD2, and CD3.
126. The method of any one of claims 115-119, further providing a therapeutic agent capable of crosslinking native CD2 in response to a tumor specific antigen expressed in the target cell microenvironment.
127. The method of claim 126, wherein the therapeutic agent is secreted or cell-surface expressed.
128. The method of claim 127, wherein the therapeutic agent is anti-CD2 scFv, an antibody, a Fab, DARPIN, a ligand, or an antigen binding domain.
129. A method for aiding in the treatment of a subject having a hyperproliferative disorder characterized by the proliferation of a target cell having at least a first antigen, and wherein the target cells express a reduced level of CD58 and/or express a form of CD58 that has reduced ability to activate CD2, the method comprising
 - a. providing an engineered cell, wherein the engineered cell expresses a CAR that comprises:
 - i. a first antigen binding domain capable of specifically binding the first antigen;
 - ii. a spacer domain;
 - iii. a transmembrane domain; and
 - iv. a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a CD2 signaling domain, and a CD3ζ activating domain;
 - b. determining the expression level of functional CD58 in a sample obtained from the subject, wherein the sample contains a tumor cell; and

- c. administering a therapeutically effective number of engineered cells if the expression level of functional CD58 is less than a predetermined threshold level.
- 130. The method of claim 129, wherein the cytoplasmic signaling domain comprises an additional co-stimulatory domain.
- 131. The method of claim 129 or 130, wherein the additional signaling domain comprises a 4-1BB signaling domain, a CD27 signaling domain, a CD28 signaling domain, or an OX40 signaling domain.
- 132. The method of any one of claims 129 to 131, wherein the threshold level is about 50,000, 45,000, 40,000, 35,000, 30,000, 25,000, 20,000, 15,000, 14,000, 13,000, 12,000, 11,000, 10,000, 9,000, 8,000, 7,000, 6,000, 5,000, 4,000, 3,000, 2,000, 1,000, or 500 functional CD58 molecules per target cell.
- 133. The method of any one of claims 129-132, wherein the engineered cell further comprises a transgenic TCR comprising a second antigen binding domain specific for a second antigen and/or a chimeric polypeptide comprising a third antigen binding domain specific for a third antigen, a transmembrane domain, and a cytoplasmic signaling domain.
- 134. The method of any one of claims 129-133, further providing an antibody or an antigen binding fragment thereof.
- 135. The method of claim 134, wherein the antibody or the antigen binding fragment thereof is capable of stimulating CD2 signaling in the target cell microenvironment.
- 136. The method of any one of claims 134-135, wherein the antibody is a multispecific antibody.
- 137. The method of claims 136, wherein the multispecific antibody is specific for an anti-tumor antigen, CD2, and CD3.
- 138. The method of any one of claims 134-135, wherein the antibody binding fragment is selected from the group consisting of scFv, scFv-Fc, Fab, Fab', (Fab)₂, (Fab')₂, minibody, diabody, triabody, and dAb.
- 139. The method of claim 138, wherein the antibody binding fragment is specific for an anti-tumor antigen, CD2, and CD3.

140. The method of any one of claims 129-139, further providing a therapeutic agent capable of crosslinking native CD2 in response to a tumor specific antigen expressed in the target cell microenvironment.
141. The method of claim 140, wherein the therapeutic agent is secreted or cell-surface expressed.
142. A system for aiding in the treatment of a subject having a hyperproliferative disorder characterized by the proliferation of a target cell having at least a first antigen, the system comprising:
the engineered cell of claim 98 or claim 101, wherein the engineered cell expresses a CAR that is specific for the first antigen; and
a labeled binding agent specific for CD58.
143. The system of claim 142, wherein the CAR comprises a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a 4-1BB signaling domain, a CD2 signaling domain, and a CD3 ζ activating domain.
144. The system of claim 142, wherein the CAR comprises a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a co-signaling domain and a CD3 ζ activating domain, and the engineered cell further comprises a chimeric polypeptide of any one of claims 67 to 76.
145. The system of any one of claims 142 to 144, wherein the labeled binding agent comprises an anti-CD58 antibody or antibody derivative.
146. The system of any one of claims 142-145, the engineered cell further comprises a transgenic TCR comprising a second antigen binding domain specific for a second antigen and/or a chimeric polypeptide comprising a third antigen binding domain specific for a third antigen, a transmembrane domain, and a cytoplasmic signaling domain.
147. A therapeutic composition, comprising:
a. a nucleic acid of any one of claims 77 to 94;
b. a vector of claim 95 or 97; and/or
c. an engineered cell of any one of claims 98 to 104; and
d. a pharmaceutically acceptable carrier.
148. A use for the treatment of disease in a subject of:

- a. a CAR of any one of claims 42 to 66;
 - b. a chimeric polypeptide of any one of claims 67 to 76;
 - c. a transgenic TCR of any one of claims 58 to 66;
 - d. a nucleic acid of any one of claims 77 to 94;
 - e. a vector of any one of claims 95 to 97;
 - f. an engineered cell of any one of claims 98 to 104;
 - g. a system of any one of claims 142 to 145; and/or
 - h. a therapeutic composition of claim 147.
149. A use for the manufacture of a medicament for the treatment of disease in a subject of:
- a. a CAR of any one of claims 42 to 66;
 - b. a chimeric polypeptide of any one of claims 67 to 76;
 - c. a transgenic TCR of any one of claims 58 to 66;
 - d. a nucleic acid of any one of claims 77 to 94;
 - e. a vector of any one of claims 95 to 97;
 - f. an engineered cell of any one of claims 98 to 104;
 - g. a system of any one of claims 142 to 145; and/or
 - h. a therapeutic composition of claim 147.
150. The use of claim 148 or 149, wherein the subject is human.
151. The use of claim 148 or 149, wherein the use is combined with one or more selected from the group consisting of a vaccine, an oncolytic virus, a checkpoint inhibitor, a T cell agonist antibody, chemotherapy, and a bispecific antibody.