

CLAIMS

1. A composition comprising a chimeric polypeptide comprising, in an order from N-terminal to C-terminal:
an antigen binding domain;
a transmembrane domain; and
a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises or consists of a CD2 signaling domain, wherein the cytoplasmic signaling domain lacks a CD3-zeta activating domain.
2. The composition of claim 1, wherein
 - (a) the CD2 signaling domain comprises an amino acid sequence with at least 80% identity to the amino acid sequence of SEQ ID NO: 8, or consists of the amino acid sequence of SEQ ID NO: 8; and/or
 - (b) the cytoplasmic signaling domain further comprises a co-stimulating domain, 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; and/or
 - (c) the antigen binding domain is specific for a B cell surface antigen or a tumor associated antigen, wherein optionally the antigen binding domain is specific for CD19, CD20, or CD22, wherein optionally the antigen binding domain is a scFv, wherein optionally the antigen binding domain comprises an amino acid sequence with at least 80% identity to a sequence of SEQ ID NO: 1, 2, 3 or 4; and/or
 - (d) 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), wherein optionally the transmembrane domain comprises an amino acid sequence with at least 95% identity to a sequence of SEQ ID NO: 5, 6, or 7.

3. The composition of claim 1 or 2, wherein the chimeric polypeptide comprises an amino acid sequence with at least 80% identity to any one of the sequences of SEQ ID NOs: 20-29 and 123-132.
4. The composition of any one of claims 1-3, wherein the antigen binding domain is specific for CD19, CD20, or CD22, and wherein the transmembrane domain is a CD28 transmembrane domain, CD2 transmembrane domain, or a CD8 transmembrane domain.
5. The composition of any one of claims 1-4, further comprising an additional polypeptide, wherein the additional polypeptide comprises
 - (a) a chimeric antigen receptor (CAR), wherein optionally the CAR comprises a CD3-zeta domain; or
 - (b) a T cell receptor (TCR); or
 - (c) a TCR-CAR.
6. The composition of any one of claim 1-5, wherein the additional polypeptide comprises an antigen binding domain and wherein the antigen binding domain is specific for a B cell surface antigen or a tumor associated antigen.
7. The composition of claim 6, wherein the antigen binding domain of the additional polypeptide and the antigen binding domain of the chimeric polypeptide are specific for different antigens.
8. The composition of claim 7, wherein the antigen binding domain of the additional polypeptide or the antigen binding domain of the chimeric polypeptide is specific for CD19, CD20, or CD22.
9. The composition of claim 7, wherein the composition comprises the CAR, wherein the antigen binding domain of the CAR is specific for CD22, and wherein the antigen binding domain of the chimeric polypeptide is specific for CD19.

10. The composition of claim 9, wherein the antigen binding domain of the CAR comprises a scFv specific for CD22, and wherein the scFv specific for CD22 comprises an amino acid sequence with at least 80% identity to a sequence of SEQ ID NO: 2; and wherein the antigen binding domain of the chimeric polypeptide comprises a scFv specific for CD19, and wherein the scFv specific for CD19 comprises an amino acid sequence with at least 80% identity to a sequence of SEQ ID NO: 1.
11. A nucleic acid comprising a sequence encoding the chimeric polypeptide of the composition of any one of claims 1-10.
12. A vector comprising the nucleic acid of claim 11, optionally operably linked to a promoter, wherein optionally the vector is a lentiviral vector.
13. An engineered cell comprising the nucleic acid of claim 11 or the vector of claim 12, wherein optionally the engineered cell is an immune cell, a stem cell, a mammalian cell, a primate cell, a human cell, 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, wherein optionally the cell is autologous or allogeneic.
14. The composition of any one of claims 1-10, the nucleic acid of claim 11, the vector of claim 12, or the engineered cell of claim 13 for use in treating a hyperproliferative disorder in a subject.
15. The composition, the nucleic acid, the vector, or the engineered cell of claim 14, wherein the hyperproliferative disorder is characterized by the proliferation of a target cell that (i) lacks expression of CD58; (ii) expresses a reduced level of CD58 and/or (iii) expresses a form of CD58 that has reduced ability to activate CD2.
16. A chimeric antigen receptor (CAR), comprising:
an antigen binding domain;
a transmembrane domain; and

a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a CD2 signaling domain, an activating domain, and a co-stimulating signaling domain; wherein the co-stimulating signaling domain is not a CD28 signaling domain.

17. The CAR of claim 16, wherein
 - (a) the activating domain comprises a CD3 zeta activating domain; and/or
 - (b) the co-stimulating signaling domain comprises a 4-1BB signaling domain, a CD27 signaling domain, or an OX40 signaling domain; and/or
 - (c) 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); and/or
 - (d) the antigen binding domain is specific for a B cell surface antigen or a tumor associated antigen, wherein optionally the antigen binding domain is specific for CD19, CD20, or CD22, wherein optionally the antigen binding domain comprises an amino acid sequence with at least 80% identity to a sequence of SEQ ID NO: 1, 2, 3 or 4.
18. The CAR of claim 16 or 17, further comprising a spacer domain, wherein optionally the spacer domain is a CD8 α hinge domain, a CD28 hinge domain, a CTLA-4 hinge domain, an IgG1 hinge domain, an IgG4 hinge domain, or a synthetic polypeptide spacer having from about 10 to about 50 amino acids.
19. The CAR of any one of claims 16-18, comprising an amino acid sequence at least 80% identity to any one of the sequences of SEQ ID NOs: 12-19, 114-122 and 133-134.
20. A transgenic T cell receptor (TCR), comprising an antigen binding domain and a transmembrane domain, a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a CD2 signaling domain.