

comprising: (i) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 43; (ii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 44; (iii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 45; (iv) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 46; (v) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 47; (vi) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 48; (vii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 49; (viii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 51; (ix) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 52; (x) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 53; (xi) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 54; (xii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 55; (xiii) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 56; or (xiv) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 104. In some embodimentexamples, the CDR1, CDR2 or CDR3 are determined according to the Kabat numbering scheme, the IMGT numbering scheme, the AbM numbering scheme, the Chothia numbering scheme, the Contact numbering scheme, or a combination thereof.

[0008] In some embodimentexamples, the anti-CD19 sdAb provided herein further comprises one or more FR regions as set forth in SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, and/or SEQ ID NO: 104.

[0009] In some embodimentexamples, the anti-CD19 sdAb provided herein comprises the amino acid sequence of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56 or SEQ ID NO: 104. In certain embodimentexamples, the anti-CD19 sdAb provided herein comprises or consists of an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more sequence identity with the sequence of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID

NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56 or SEQ ID NO: 104.

[0010] In some [embodimentexamples](#), the anti-CD19 sdAb provided herein is a llama or camelid sdAb. In other [embodimentexamples](#), the anti-CD19 sdAb provided herein is a humanized sdAb. In certain [embodimentexamples](#), the anti-CD19 sdAb is genetically fused or chemically conjugated to an agent.

[0011] In another aspect, provided herein is a chimeric antigen receptor (CAR), comprising: (a) an extracellular antigen binding domain comprising the anti-CD19 sdAb provided herein; (b) a transmembrane domain; and (c) an intracellular signaling domain. In some [embodimentexamples](#), the extracellular antigen binding domain further comprises one or more additional antigen binding domain(s). In some [embodimentexamples](#), the extracellular antigen binding domain further comprises one additional antigen binding domain. In some [embodimentexamples](#), the extracellular antigen binding domain further comprises two additional antigen binding domains. In some [embodimentexamples](#), the one or more additional antigen binding domain(s) bind to one or more antigen(s) selected from a group consisting of CD20, CD22, CD33, CD38, BCMA, CS1, ROR1, GPC3, CD123, IL-13R, CD138, c-Met, EGFRvIII, GD-2, NY-ESO-1, MAGE A3, and glycolipid F77.

[0012] In some [embodimentexamples](#), the transmembrane domain is derived from a molecule selected from a group consisting of CD8 α , CD4, CD28, CD137, CD80, CD86, CD152, and PD1. In some specific [embodimentexamples](#), the transmembrane domain is derived from CD8 α .

[0013] In some [embodimentexamples](#), the intracellular signaling domain comprises a primary intracellular signaling domain of an immune effector cell. In some [embodimentexamples](#), the primary intracellular signaling domain is derived from CD3 ζ .

[0014] In some [embodimentexamples](#), the intracellular signaling domain further comprises a co-stimulatory signaling domain. In some [embodimentexamples](#), the co-stimulatory signaling domain is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, CD137, OX40, CD30, CD40, CD3, LFA-1, CD2, CD7, LIGHT, NKG2C, B7-H3, ligands of CD83 and combinations thereof. In some specific [embodimentexamples](#), the co-stimulatory signaling domain is derived from CD137.

[0015] In some [embodimentexamples](#), the CAR provided herein further comprises a hinge domain located between the C-terminus of the extracellular antigen binding domain and the N-terminus of the transmembrane domain. In some specific [embodimentexamples](#), the hinge domain is derived from CD8 α .

[0016] In some [embodimentexamples](#), the CAR provided herein further comprises a signal peptide located at the N-terminus of the polypeptide. In some specific [embodimentexamples](#), the signal peptide is derived from CD8 α .

[0017] In another aspect, provided herein is a chimeric antigen receptor (CAR), comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 57, SEQ ID NO: 58,

SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, and SEQ ID NO: 105. In another aspect, provided herein is an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD19 sdAb provided herein.

[0018] In another example aspect, provided herein is a vector comprising an isolated nucleic acid comprising a nucleic acid sequence encoding the anti-CD19 sdAb provided herein. In yet another aspect, provided herein is an isolated nucleic acid comprising a nucleic acid sequence encoding the CAR provided herein. In yet another example aspect, provided herein is a vector comprising an isolated nucleic acid comprising a nucleic acid sequence encoding the CAR provided herein.

[0018a] In one aspect, provided herein is a vector comprising the isolated nucleic acid as disclosed herein.

[0019] In yet another example aspect, provided herein is an engineered immune effector cell, comprising the CAR, the isolated nucleic acid, or the vector provided herein. In one aspect, provided herein is an engineered immune effector cell, comprising the CAR as disclosed herein, the isolated nucleic acid as disclosed herein, or the vector as disclosed herein. In some embodiment examples, the immune effector cell is a T cell or a B cell.

[0020] In yet another example aspect, provided herein is a pharmaceutical composition, comprising the anti-CD19 sdAb, the engineered immune effector cell, or the vector provided herein, and a pharmaceutically acceptable excipient. In one aspect, provided herein is a pharmaceutical composition, comprising the anti-CD19 sdAb as disclosed herein, the engineered immune effector cell as disclosed herein, or the vector as disclosed herein, and a pharmaceutically acceptable excipient.

[0021] In yet another example aspect, provided herein is a method of treating a disease or disorder in a subject, comprising administering to the subject an effective amount of the anti-CD19 sdAb, the engineered immune effector cell, or the pharmaceutical composition provided herein. In one aspect, provided herein is use of the anti-CD19 sdAb as disclosed herein, the engineered immune effector cell as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject. In some embodiment examples, the disease or disorder is CD19 associated disease or disorder. In some embodiment examples, the disease or disorder is a B cell associated disease or disorder. In some embodiment examples, the disease or disorder is cancer. In some embodiment examples, the disease or disorder is a B cell malignancy. In some embodiment examples, the B cell malignancy is a B cell leukemia or B cell lymphoma. In some embodiment examples, the disease or disorder is selected from a group consisting of marginal zone lymphoma (e.g., splenic marginal zone lymphoma), diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), primary central nervous system (CNS) lymphoma, primary mediastinal B cell lymphoma (PMBL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), follicular lymphoma (FL), burkitt lymphoma, primary intraocular lymphoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia (HCL), precursor B lymphoblastic leukemia, non-hodgkin lymphoma (NHL), high-grade B-cell lymphoma (HGBL), and multiple myeloma (MM). In other embodiment examples, the disease or disorder is an autoimmune and/or inflammatory disease. In some embodiment examples, the autoimmune and/or inflammatory disease is associated with inappropriate or enhanced B cell numbers and/or activation.

4. BRIEF DESCRIPTION OF THE FIGURES

[0022] FIGs.1A-1C show the transduction efficiency of VHH-based CAR-T cells (FIGs.1A and 1B) and scFv-based CAR-T cells (FIG.1C). UnT refers to T cells un-transduced with CAR.

[0023] FIGs.2A-2G show *in vitro* cytotoxicity of exemplary VHH-based CAR-T cells compared