

maintenance of B cell populations in the marginal zone, optimal B cell antigen receptor-induced proliferation and B cell turnover, *etc.* Majority of B-cell malignancies express CD22, making it a promising target in cancer treatments. In addition, selective modulation of B cell activity through targeting CD22 has been proposed for treating autoimmune diseases (*see, e.g.,* Steinfeld and Youinou, *Expert. Opin. Biol.Ther.*, 6: 943-949 (2006)).

[0007] Chimeric antigen receptor T (CAR-T) cell therapy is an emerging and effective cancer immunotherapy, especially in hematological malignancies. However, the application of CAR-T cells is hampered by adverse effects, such as cytokines release syndrome and on-target off-tumor toxicity (Yu *et al.*, *Molecular Cancer* 18 (1): 125 (2019)).

[0008] Improved binding molecules and engineered cells are needed. For example, there is a need to develop stable and therapeutically effective CD20, CD19 and/or CD22 binding molecules for use in more effective or efficient CAR-T therapies.

3. SUMMARY

[0009] In one aspect, provided herein is a chimeric antigen receptor (CAR), comprising: (a) an extracellular antigen binding domain comprising an anti-CD20 single domain antibody (sdAb), an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain, wherein the anti-CD20 sdAb is closer to the transmembrane domain than the anti-CD19 sdAb or the anti-CD22 sdAb to the transmembrane domain. In some [embodimentexamples](#), the anti-CD19 sdAb is at the N-terminus of the anti-CD22 sdAb. In other [embodimentexamples](#), the anti-CD19 sdAb is at the C-terminus of the anti-CD22 sdAb.

[0010] In another aspect, provided herein is a [chimeric antigen receptor \(CAR\)](#), comprising: (a) an extracellular antigen binding domain comprising an anti-CD20 [single domain antibody \(sdAb\)](#), an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain, wherein the anti-CD19 sdAb is closer to the transmembrane domain than the anti-CD20 sdAb or the anti-CD22 sdAb to the transmembrane domain. In some [embodimentexamples](#), the anti-CD20 sdAb is at the N-terminus of the anti-CD22 sdAb. In other [embodimentexamples](#), the anti-CD20 sdAb is at the C-terminus of the anti-CD22 sdAb.

[0011] In yet another aspect, provided herein is a [chimeric antigen receptor \(CAR\)](#), comprising: (a) an extracellular antigen binding domain comprising an anti-CD20 [single domain antibody \(sdAb\)](#), an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain, wherein the anti-CD22 sdAb is closer to the transmembrane domain than the anti-CD19 sdAb or the anti-CD20 sdAb to the transmembrane domain. In some [embodimentexamples](#), the anti-CD19 sdAb is at the N-terminus of the anti-CD20 sdAb. In other [embodimentexamples](#), the anti-CD19 sdAb is at the C-terminus of the anti-CD20 sdAb.

[0012] In some [embodimentexamples](#), the anti-CD20 sdAb, the anti-CD19 sdAb and the anti-CD22 sdAb

are fused to each other directly or via one or more peptide linker(s); and wherein the one or more peptide linker(s) comprises no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 amino acids. In some embodimentexamples, the one or more peptide linker(s) is (GGGGS)_n, n is 1, 2, 3, or 4.

[0013] In yet another aspect, provided herein is a chimeric antigen receptor (CAR), comprising: (a) an extracellular antigen binding domain comprising an anti-CD20 single domain antibody (sdAb), an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain; wherein the anti-CD20 sdAb, the anti-CD19 sdAb and the anti-CD22 sdAb are fused to each other directly or via one or more peptide linker(s); and wherein the one or more peptide linker(s) comprises no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 amino acids. In some embodimentexamples, the one or more peptide linker(s) is (GGGGS)_n, n is 1, 2, 3, or 4.

[0014] In some embodimentexamples, the anti-CD20 sdAb comprises: (i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 2; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; (ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 5; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6; (iii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 7; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8; (iv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10; (v) a CDR1 comprising the amino acid sequence of SEQ ID NO: 11 or 311; a CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8; (vi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 13; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10; (vii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 14 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 15; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16; (viii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 17; a CDR2 comprising the amino acid sequence of SEQ ID NO: 18; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19; (ix) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 21; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16; (x) a CDR1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR2 comprising the amino acid sequence of SEQ ID NO: 23; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19; (xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24 or 313; a CDR2 comprising the amino acid sequence of SEQ ID NO: 25; and a

comprising the amino acid sequence of SEQ ID NO: 119; (x) a CDR1 comprising the amino acid sequence of SEQ ID NO: 120; a CDR2 comprising the amino acid sequence of SEQ ID NO: 121; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 122; (xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 123 or 323; a CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 125; or (xii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 126; a CDR2 comprising the amino acid sequence of SEQ ID NO: 127; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 128.

[0015] In yet another ~~aspect~~example, provided herein is a CAR, comprising: (a) an extracellular antigen binding domain comprising at least two of an anti-CD20 sdAb, an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain, wherein the anti-CD20 sdAb comprises: (i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 2; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3; (ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 5; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6; (iii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 7; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8; (iv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10; (v) a CDR1 comprising the amino acid sequence of SEQ ID NO: 11 or 311; a CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8; (vi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 13; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10; (vii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 14 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 15; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16; (viii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 17; a CDR2 comprising the amino acid sequence of SEQ ID NO: 18; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19; (ix) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 21; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16; (x) a CDR1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR2 comprising the amino acid sequence of SEQ ID NO: 23; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19; (xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24 or 313; a CDR2 comprising the amino acid sequence of SEQ ID NO: 25; and a CDR3 comprising the amino acid

acid sequence of SEQ ID NO: 122; (xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 123 or 323; a CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 125; or (xii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 126; a CDR2 comprising the amino acid sequence of SEQ ID NO: 127; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 128.

[0015a] In yet another aspect, provided herein is chimeric antigen receptor (CAR), comprising:

(a) an extracellular antigen binding domain comprising at least two of an anti-CD20 single domain antibody (sdAb), an anti-CD19 sdAb and an anti-CD22 sdAb;

(b) a transmembrane domain; and

(c) an intracellular signaling domain,

wherein:

(I) the anti-CD20 sdAb comprises:

(i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 2; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3;

(ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 5; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6;

(iii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 7; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(iv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10;

(v) a CDR1 comprising the amino acid sequence of SEQ ID NO: 11 or 311; a CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(vi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 13; a CDR2 comprising the amino acid sequence of SEQ ID NO: 9; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 10;

(vii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 14 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 15; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(viii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 17; a CDR2 comprising the amino acid sequence of SEQ ID NO: 18; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19;

(ix) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 21; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(x) a CDR1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR2 comprising the amino acid sequence of SEQ ID NO: 23; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19;

(xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24 or 313; a CDR2 comprising the amino acid sequence of SEQ ID NO: 25; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 26;

(xii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR2 comprising the amino acid sequence of SEQ ID NO: 28; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 29;

(xiii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 14 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 30; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(xiv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 17; a CDR2 comprising the amino acid sequence of SEQ ID NO: 31; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19;

(xv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 or 310; a CDR2 comprising the amino acid sequence of SEQ ID NO: 32; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3;

(xvi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR2 comprising the amino acid sequence of SEQ ID NO: 33; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6;

(xvii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 34; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(xviii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR2 comprising the amino acid sequence of SEQ ID NO: 35; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 19;

(xix) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 36; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(xx) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 37; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(xxi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 20 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 38; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

- (xxii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 283 or 314; a CDR2 comprising the amino acid sequence of SEQ ID NO: 284; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 285;
- (xx) a CDR1 comprising the amino acid sequence of SEQ ID NO: 286; a CDR2 comprising the amino acid sequence of SEQ ID NO: 287; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 288;
- (xxi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 289 or 315; a CDR2 comprising the amino acid sequence of SEQ ID NO: 290; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 291;
- (xxii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 292; a CDR2 comprising the amino acid sequence of SEQ ID NO: 293; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 294;
- (xxiii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 295 or 312; a CDR2 comprising the amino acid sequence of SEQ ID NO: 296; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 297; or
- (xxiv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 298; a CDR2 comprising the amino acid sequence of SEQ ID NO: 299; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 300;
- (II) the anti-CD19 sdAb comprises:
- (i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 73 or 316; a CDR2 comprising the amino acid sequence of SEQ ID NO: 74; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 75;
- (ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 76; a CDR2 comprising the amino acid sequence of SEQ ID NO: 77; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 78;
- (iii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 79 or 317; a CDR2 comprising the amino acid sequence of SEQ ID NO: 80; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 81;
- (iv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 82; a CDR2 comprising the amino acid sequence of SEQ ID NO: 83; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 84;
- (v) a CDR1 comprising the amino acid sequence of SEQ ID NO: 73 or 316; a CDR2 comprising the amino acid sequence of SEQ ID NO: 307; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or
- (vi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 76; a CDR2 comprising the amino acid sequence of SEQ ID NO: 77; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 78;
- (III) the anti-CD22 sdAb comprises:
- (i) a CDR1 comprising the amino acid sequence of SEQ ID NO: 93 or 318; a CDR2 comprising the amino acid sequence of SEQ ID NO: 94; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 95;
- (ii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 96; a CDR2 comprising the amino acid sequence of SEQ ID NO: 97; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 98;

- (iii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 99 or 319; a CDR2 comprising the amino acid sequence of SEQ ID NO: 100; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 101;
- (iv) a CDR1 comprising the amino acid sequence of SEQ ID NO: 102; a CDR2 comprising the amino acid sequence of SEQ ID NO: 103; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 104;
- (v) a CDR1 comprising the amino acid sequence of SEQ ID NO: 105 or 320; a CDR2 comprising the amino acid sequence of SEQ ID NO: 106; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 107;
- (vi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 108; a CDR2 comprising the amino acid sequence of SEQ ID NO: 109; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 110;
- (vii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 111 or 321; a CDR2 comprising the amino acid sequence of SEQ ID NO: 112; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 113;
- (viii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 114; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 116;
- (ix) a CDR1 comprising the amino acid sequence of SEQ ID NO: 117 or 322; a CDR2 comprising the amino acid sequence of SEQ ID NO: 118; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 119;
- (x) a CDR1 comprising the amino acid sequence of SEQ ID NO: 120; a CDR2 comprising the amino acid sequence of SEQ ID NO: 121; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 122;
- (xi) a CDR1 comprising the amino acid sequence of SEQ ID NO: 123 or 323; a CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 125; or
- (xii) a CDR1 comprising the amino acid sequence of SEQ ID NO: 126; a CDR2 comprising the amino acid sequence of SEQ ID NO: 127; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 128.

[0016] In yet another aspect example, provided herein is a CAR, comprising: (a) an extracellular antigen binding domain comprising at least two of an anti-CD20 sdAb, an anti-CD19 sdAb and an anti-CD22 sdAb; (b) a transmembrane domain; and (c) an intracellular signaling domain, wherein the anti-CD20 sdAb comprises (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: 39; (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: 40; (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: 41; (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: 42; (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: 43; (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: 44; (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: 45; (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: 46; (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: 47; (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: 48; (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: 49; (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: 50; (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: 51; (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: 52; (xv) 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; (xvi) 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; (xvii) 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; (xviii) 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: 301; (xix) 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: 302; or (xx) 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: 303; the anti-CD19 sdAb comprises: (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: 85; (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: 86; (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: 87; or (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: 88; or (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: 308; and the anti-CD22 sdAb comprises: (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: 129; (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: 130; (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: 131; (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: 132; (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: 133; (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: 134; or (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: 135. In some ~~embodiment~~examples, 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.

[0016a] In yet another aspect, provided herein is chimeric antigen receptor (CAR), comprising:

(a) an extracellular antigen binding domain comprising at least two of an anti-CD20 single domain antibody (sdAb), an anti-CD19 sdAb and an anti-CD22 sdAb;

(b) a transmembrane domain; and

(c) an intracellular signaling domain,

wherein:

(I) the anti-CD20 sdAb comprises:

(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: 39;

(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: 40;

(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: 41;

(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: 42;

(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: 43;

(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: 44;

(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: 45;

(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: 46;

(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: 47;

(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: 48;

(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: 49;

(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: 50;

(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: 51;

(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: 52;

- (xv) 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;
- (xvi) 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;
- (xvii) 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;
- (xviii) 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: 301;
- (xix) 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: 302; or
- (xx) 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: 303;
- (II) the anti-CD19 sdAb comprises:
 - (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: 85;
 - (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: 86;
 - (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: 87;
 - (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: 88; or
 - (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: 308; and
- (III) the anti-CD22 sdAb comprises:
 - (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: 129;
 - (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: 130;
 - (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: 131;
 - (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: 132;
 - (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: 133;

(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: 134; or

(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: 135.

[0017] In some embodimentexamples, the CAR comprises: (1) the anti-CD20 sdAb and the anti-CD19 sdAb; (2) the anti-CD20 sdAb and the anti-CD22 sdAb; (3) the anti-CD19 sdAb and the anti-CD22 sdAb; or (4) the anti-CD20 sdAb, the anti-CD19 sdAb, and the anti-CD22 sdAb.

[0018] In some embodimentexamples, the anti-CD20 sdAb, the anti-CD19 sdAb, and the anti-CD22 sdAb are each independently a camelid sdAb or a humanized sdAb.

[0019] In some embodimentexamples, the anti-CD20 sdAb comprises an amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, 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: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 301, SEQ ID NO: 302, or SEQ ID NO: 303; the anti-CD19 sdAb comprises an amino acid sequence of SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88 or SEQ ID NO: 308; and the anti-CD22 sdAb comprises an amino acid sequence of SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, or SEQ ID NO: 135.

[0020] In other [embodimentexamples](#), the anti-CD20 sdAb comprises 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: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, 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: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 301, SEQ ID NO: 302, or SEQ ID NO: 303; the anti-CD19 sdAb comprises 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: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88 or SEQ ID NO: 308; and the anti-CD22 sdAb comprises 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: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, or SEQ ID NO: 135.

[0021] 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 [embodimentexamples](#), the transmembrane domain is derived from CD8 α .

[0022] 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 .

[0023] 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 [embodimentexamples](#), the co-stimulatory signaling domain is derived from CD137.

[0024] 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 [embodimentexample](#), the hinge domain is derived from CD8 α .

[0025] In some embodimentexamples, the CAR provided herein further comprises a signal peptide located at the N-terminus of the polypeptide. In some embodimentexamples, the signal peptide is derived from CD8 α .

[0026] In another aspect, provided herein is a chimeric antigen receptor (CAR), comprising (i) an amino acid sequence selected from the group consisting of SEQ ID NOs:174-226; or (ii) an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more sequence identity with the sequence selected from a group consisting of SEQ ID NOs: 174-226.

[0027] In yet another aspect, provided herein is an isolated nucleic acid comprising a nucleic acid sequence encoding the CAR provided herein. In another aspect, provided herein is vector comprising the isolated nucleic acid provided herein. ~~In another aspect, provided herein is a vector comprising a nucleic acid encoding the CAR provided herein.~~

[0028] In yet another aspect, provided herein is an engineered immune effector cell, comprising the CAR, the isolated nucleic acid, or the vector provided herein. In some embodimentexamples, the engineered immune effector cell is a T cell or B cell.

[0029] In another aspect, provided herein is a pharmaceutical composition, comprising the engineered immune effector cell, or the vector provided herein, and a pharmaceutically acceptable excipient.

[0030] In yet another aspect, provided herein is use of the engineered immune effector cell, or the pharmaceutical composition provided herein, in the manufacture of a medicament for treating a disease or disorder in a subject. ~~In yet another 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 engineered immune effector cell, or the pharmaceutical composition provided herein.~~ In some embodimentexamples, the disease or disorder is a B cell associated disease or disorder, a CD19 associated disease or disorder, a CD20 associated disease or disorder and/or a CD22 associated disease or disorder. In some embodimentexamples, the disease or disorder is cancer. In other embodimentexamples, the disease or disorder is a B cell malignancy. In some embodimentexamples, the B cell malignancy is a B cell leukemia or B cell lymphoma. In some embodimentexamples, 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~~ urkitt 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 embodimentexamples, the disease or disorder is an autoimmune and/or inflammatory disease. In some embodimentexamples, the autoimmune and/or inflammatory disease is associated with inappropriate or enhanced B cell numbers and/or activation.

[0031] In some embodimentexamples, the use or method provided herein further comprises detecting and/or

measuring the levels of CD19, CD20, and/or CD22 expressed on a cancer cell obtained from the subject prior to administering to the subject an effective amount of the engineered immune effector cell. In some embodiment examples, the levels of CD19, CD20, and/or CD22 expressed on the cancer cell obtained from the subject determines the selection of an engineered immune effector cell expressing a CAR that is suitable for treating the cancer.

4. BRIEF DESCRIPTION OF THE FIGURES

[0032] FIGs.1A-1B show the transduction efficiency of exemplary mono-specific VHH CAR-T cells (**FIG.1A**) and trispecific VHH CAR-T cells (**FIG.1B**). UnT refers to T cells un-transduced with CAR.

[0033] FIGs.2A-2I show *in vitro* cytotoxicity of trispecific VHH CAR-T cells compared to that of mono-specific VHH CAR-T cells or mono-specific scFv CAR-T cells against cell lines Raji.Luc (**FIGs.2A, 2G and 2J**), Nalm.6.Luc (**FIGs.2B, 2I and 2K**), K562-CD19.Luc (**FIG.2C**), K562-CD20.Luc (**FIG.2D**), K562-CD22.Luc (**FIG.2E**), K562.Luc (**FIG.2F**) and Daudi.Luc (**FIG.2H**).

[0034] FIGs.3A-3B show IFN- γ release level and cytotoxicity of trispecific VHH CAR-T cells compared to that of mono-specific VHH CAR-T cells after co-cultured with Raji.Luc or K562.Luc cells at different E:T ratios for 24 hours. P value was analyzed using T test.

[0035] FIGs.4A-4G show *in vivo* anti-tumor efficacy of trispecific VHH CAR-T cells in a Raji xenograft NCG mouse model. Mice treated with different doses of trispecific VHH CAR-T cells were assessed on a regular basis to monitor tumor growth by bioluminescence imaging (**FIGs.4A-4F**), and body weight (**FIG.4G**).

[0036] FIGs.5A-5B show the transduction efficiency of exemplary mono-specific humanized VHH CAR-T cells (**FIG.5A**) and trispecific humanized VHH CAR-T cells (**FIG.5B**). UnT refers to T cells un-transduced with CAR.

[0037] FIGs.6A-6F show *in vitro* cytotoxicity of trispecific humanized VHH CAR-T cells against tri-positive antigens expressing lymphoma cell line - Raji.Luc (**FIG.6A, FIG.6C and FIG.6E**) and dual-positive antigens expressing leukemia cell line - Nalm.6.Luc (**FIG.6B, FIG.6D and FIG.6F**).

[0038] FIGs.7A-7F show *in vitro* cytotoxicity of trispecific humanized VHH CAR-T cells against single-antigen expressing cell lines - K562-CD19.Luc (**FIG.7A and FIG.7D**), K562-CD20.Luc (**FIG.7B and FIG.7E**) and K562-CD22.Luc (**FIG.7C and FIG.7F**).

[0039] FIG.8 shows IFN- γ release level of trispecific humanized VHH CAR-T cells compared to that of mono-specific scFv CAR-T cells after co-culture with Raji.Luc or K562.Luc cells at different E:T ratios for 24 hours.