CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR) that specifically binds CD33, wherein the CAR comprises a human CD33 binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein said CD33 binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), a heavy chain complementary determining region 3 (HC CDR3), a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 89, 98, 107, 116, 125 and 134, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 274, 283, 292, 301, 310 and 319, respectively;

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 328, 337, 346, 355, 364, and 373, respectively;

(d) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 84, 93, 102, 111, 120 and 129, respectively;

(e) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 269, 278, 287, 296, 305 and 314, respectively;

(f) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 323, 332, 341, 350, 359 and 368, respectively;

(g) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 85, 94, 103, 112, 121 and 130, respectively;

(h) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 270, 279, 288, 297, 306 and 315, respectively;

(i) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 324, 333, 342, 351, 360 and 369, respectively;

(j) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 87, 96, 105, 114, 123 and 132, respectively;

(k) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 272, 281, 290, 299, 308 and 317, respectively;

(l) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 326, 335, 344, 353, 362 and 371, respectively;

(m) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 88, 97, 106, 115, 124, and 133, respectively;

(n) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 273, 282, 291, 300, 309 and 318, respectively;

(o) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 327, 336, 345, 354, 363 and 372, respectively;

(p) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 90, 99, 108, 117, 126 and 135, respectively;

(q) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 275, 284, 293, 302, 311 and 320, respectively;

(r) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 329, 338, 347, 356, 365 and 374, respectively;

(s) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 92, 101, 110, 119, 128 and 137, respectively;

(t) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 277, 286, 295, 304, 313 and 322, respectively; or

(u) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 331, 340, 349, 358, 367 and 376, respectively.

2. The isolated nucleic acid molecule of claim 1, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 89, 98, 107, 116, 125 and 134, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 274, 283, 292, 301, 310 and 319, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 328, 337, 346, 355, 364, and 373, respectively.

3. The isolated nucleic acid molecule of claim 1, wherein:

(d) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 84, 93, 102, 111, 120 and 129, respectively;

(e) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 269, 278, 287, 296, 305 and 314, respectively; or

(f) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 323, 332, 341, 350, 359 and 368, respectively.

4. The isolated nucleic acid molecule of claim 1, wherein:

(g) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 85, 94, 103, 112, 121 and 130, respectively;

(h) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 270, 279, 288, 297, 306 and 315, respectively; or

(i) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 324, 333, 342, 351, 360 and 369, respectively.

5. The isolated nucleic acid molecule of claim 1, wherein:

(j) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 87, 96, 105, 114, 123 and 132, respectively;

(k) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 272, 281, 290, 299, 308 and 317, respectively; or

(l) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 326, 335, 344, 353, 362 and 371, respectively.

6. The isolated nucleic acid molecule of claim 1, wherein:

(m) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 88, 97, 106, 115, 124, and 133, respectively;

(n) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 273, 282, 291, 300, 309 and 318, respectively; or

(o) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 327, 336, 345, 354, 363 and 372, respectively.

7. The isolated nucleic acid molecule of claim 1, wherein:

(p) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 90, 99, 108, 117, 126 and 135, respectively;

(q) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 275, 284, 293, 302, 311 and 320, respectively; or

(r) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 329, 338, 347, 356, 365 and 374, respectively.

8. The isolated nucleic acid molecule of claim 1, wherein:

(s) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 92, 101, 110, 119, 128 and 137, respectively;

(t) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 277, 286, 295, 304, 313 and 322, respectively; or

(u) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 331, 340, 349, 358, 367 and 376, respectively.

9. The isolated nucleic acid molecule of claim 1, which encodes a CAR comprising:

(a) (i) the amino acid sequence of a light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74; and/or

(b) (i) the amino acid sequence of a heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65.

10. The isolated nucleic acid molecule of claim 1 or 2, wherein:

(i) the encoded CD33 binding domain comprises the amino acid sequence selected from a group consisting of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268;

(ii) the encoded CD33 binding domain comprises an amino acid sequence having at least one, two or three modifications to any of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268;

(iii) the encoded CD33 binding domain comprises an amino acid sequence with 95-99% identity to any of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268; or

(iv) the CD33 binding domain comprises a nucleotide sequence selected from a group consisting of SEQ ID NO: 259, 255-258, 260, or 261, or a sequence with 95-99% identity thereto.

11. The isolated nucleic acid molecule of any of the preceding claims, wherein:

(i) the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154, optionally wherein:

(a) the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, an amino acid sequence comprises at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6; or

(b) the nucleic acid sequence encoding the transmembrane domain comprises a sequence of SEQ ID NO:17, or a sequence with 95-99% identity thereto; and/or

(ii) the encoded CD33 binding domain is connected to the transmembrane domain by a hinge region, optionally wherein:

(a) the encoded hinge region comprises the amino acid sequence of SEQ ID NO:2, or a sequence with 95-99% identity thereto; or

(b) the nucleic acid sequence encoding the hinge region comprises the nucleotide sequence of SEQ ID NO: 13, or a sequence with 95-99% identity thereto.

12. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain comprises a functional

signaling domain obtained from a costimulatory molecule selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83, optionally wherein:

(i) the encoded costimulatory domain comprises the amino acid sequence of SEQ ID NO:7, or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7; or

(ii) the nucleic acid sequence encoding the costimulatory domain comprises the nucleotide sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereto.

13. The isolated nucleic acid molecule of any of the preceding claims, wherein:

(i) the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta;

(ii) intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10;

(iii) the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain;

(iv) the nucleic acid sequence encoding the intracellular signaling domain comprises the sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereto, and/or the sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereto; and/or

(v) the isolated nucleic acid molecule further comprises a leader sequence which encodes the amino acid sequence of SEQ ID NO:1.

14. The isolated nucleic acid molecule of any of the preceding claims, wherein
(a) the isolated nucleic acid molecule encodes a CAR comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 53, 48, 49, 51, 52, 54, or 56;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NOs: 53, 48, 49, 51, 52, 54, or 56; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 53, 48, 49, 51, 52, 54, or 56; and/or

(b) the isolated nucleic acid molecule of any of the preceding claims, comprising the nucleotide sequence of any of SEQ ID NOs: 80, 75, 76, 78, 79, 81 or 83, or a nucleotide sequence with 95-99% identity to any of SEQ ID NOs: 80, 75, 76, 78, 79, 81 or 83.

15. An isolated chimeric antigen receptor (CAR) polypeptide that specifically binds to CD33, wherein the CAR comprises an antibody or antibody fragment which includes a human CD33 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain, and wherein said CD33 binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3), a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3), wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 89, 98, 107, 116, 125 and 134, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 274, 283, 292, 301, 310 and 319, respectively;

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 328, 337, 346, 355, 364, and 373, respectively;

(d) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 84, 93, 102, 111, 120 and 129, respectively;

(e) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 269, 278, 287, 296, 305 and 314, respectively;

(f) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 323, 332, 341, 350, 359 and 368, respectively;

(g) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 85, 94, 103, 112, 121 and 130, respectively;

(h) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 270, 279, 288, 297, 306 and 315, respectively;

(i) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 324, 333, 342, 351, 360 and 369, respectively;

(j) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 87, 96, 105, 114, 123 and 132, respectively;

(k) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 272, 281, 290, 299, 308 and 317, respectively;

(l) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 326, 335, 344, 353, 362 and 371, respectively;

(m)said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 88, 97, 106, 115, 124, and 133, respectively;

(n) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 273, 282, 291, 300, 309 and 318, respectively;

(o) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 327, 336, 345, 354, 363 and 372, respectively;

(p) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 90, 99, 108, 117, 126 and 135, respectively;

(q) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 275, 284, 293, 302, 311 and 320, respectively;

(r) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 329, 338, 347, 356, 365 and 374, respectively;

(s) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 92, 101, 110, 119, 128 and 137, respectively;

(t) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 277, 286, 295, 304, 313 and 322, respectively; or

(u) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 331, 340, 349, 358, 367 and 376, respectively.

16. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 89, 98, 107, 116, 125 and 134, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 274, 283, 292, 301, 310 and 319, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 328, 337, 346, 355, 364, and 373, respectively.

17. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 84, 93, 102, 111, 120 and 129, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 269, 278, 287, 296, 305 and 314, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 323, 332, 341, 350, 359 and 368, respectively.

18. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 85, 94, 103, 112, 121 and 130, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 270, 279, 288, 297, 306 and 315, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 324, 333, 342, 351, 360 and 369, respectively.

19. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 87, 96, 105, 114, 123 and 132, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 272, 281, 290, 299, 308 and 317, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 326, 335, 344, 353, 362 and 371, respectively.

20. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 88, 97, 106, 115, 124, and 133, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 273, 282, 291, 300, 309 and 318, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 327, 336, 345, 354, 363 and 372, respectively.

21. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 90, 99, 108, 117, 126 and 135, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 275, 284, 293, 302, 311 and 320, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 329, 338, 347, 356, 365 and 374, respectively.

22. The isolated CAR polypeptide of claim 8, wherein:

(a) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 92, 101, 110, 119, 128 and 137, respectively;

(b) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 277, 286, 295, 304, 313 and 322, respectively; or

(c) said HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 and LC CDR3 sequences comprise the amino acid sequences of SEQ ID NO: 331, 340, 349, 358, 367 and 376, respectively.

23. The isolated CAR polypeptide of claim 8, comprising:

(a) (i) the amino acid sequence of a light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the light chain variable region of SEQ ID NO: 71, 66, 67, 69, 70, 72, or 74; and/or

(b) (i) the amino acid sequence of a heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65;

(ii) an amino acid sequence having at least one, two or three modifications of the amino acid sequence of the heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 62, 57, 58, 60, 61, 63, or 65.

24. The isolated CAR polypeptide of claim 8 or 9, wherein:

(a) the isolated CAR polypeptide comprises:

(i) an amino acid sequence selected from a group consisting of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268;

(ii) an amino acid sequence having at least one, two or three modifications to any of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 44, 266, 39, 40, 42, 43, 45, 47, 57, 58, 60-63, 65, 66, 67, 69-72, 74, 262-265, 267, or 268;

(b) the transmembrane domain comprises a transmembrane domain from a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154;

(c) the transmembrane domain comprises:

(i) the amino acid sequence of SEQ ID NO: 6,

(ii) an amino acid sequence comprises at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or

(iii) a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6; and/or

(d) the CD33 binding domain is connected to the transmembrane domain by a hinge region optionally, wherein the hinge region comprises SEQ ID NO:2, or a sequence with 95-99% identity thereto.

25. The isolated CAR polypeptide of any of claims 8-10, wherein:

(i) the costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83;

(ii) the costimulatory domain comprises the amino acid sequence of SEQ ID NO:7, or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7;

(iii) the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta;

(iv) the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10; or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10;

(v) the intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain; and/or

(vi) the isolated CAR polypeptide further comprises a leader sequence which comprises the amino acid sequence of SEQ ID NO:1.

26. The isolated CAR polypeptide of any of claims 8-11, comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 53, 48, 49, 51,52, 54, or 56;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NOs: 53, 48, 49, 51, 52, 54, or 56; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NOs: 53, 48, 49, 51,52, 54, or 56.

27. A vector comprising a nucleic acid molecule encoding a CAR of any of the preceding claims, wherein the vector is selected from the group consisting of a DNA vector, an RNA vector, a plasmid, a lentivirus vector, adenoviral vector, or a retrovirus vector, optionally wherein the vector further comprises an EF-1 promoter comprising the sequence of SEQ ID NO: 11.

28. A cell, e.g., an immune effector cell, comprising nucleic acid of any of claims 1-7, the CAR polypeptide of any of 8-12, or the vector of claim 13.

29. An *in vitro* or *ex vivo* method of making a cell, e.g., an immune effector cell, comprising transducing an immune effector cell with a vector of claim 13.

30. An *in vitro* or *ex vivo* method of generating a population of RNA-engineered cells, comprising introducing an *in vitro* transcribed RNA or synthetic RNA into a cell, where the RNA comprises a nucleic acid encoding a CAR polypeptide of any of the preceding claims.

31. Use of a cell, e.g., a population of immune effector cells, comprising the CAR nucleic acid of any of claims 1-7, or the CAR polypeptide of any of claims 8-12 in the manufacture of a medicament for providing an anti-tumor immunity in a mammal.

32. The use of the cell according to claim 17, wherein the cell is an autologous T cell or an allogeneic T cell.

33. Use of a cell, e.g., a population of immune effector cells, comprising the CAR nucleic acid of any of claims 1-7, or the CAR polypeptide of any of claims 8-12 in the

manufacture of a medicament for the treatment of a cancer associated with expression of CD33.

34. The use of the cell according to claim 19, wherein the cancer is a hematologic cancer.

35. The use of the cell according to any of claims 19-20, wherein the cancer is an acute leukemia chosen from one or more of acute myeloid leukemia (AML); myelodysplastic syndrome; myeloproliferative neoplasms; chronic myeloid leukemia (CML); or Blastic plasmacytoid dendritic cell neoplasm, or a combination thereof.

36. The use of the cell according to any of claims 19-21, wherein the cell, e.g., the population of immune effector cells, are to be administered in combination with one or more of:

(i) an agent that increases the efficacy of the cell comprising the CAR nucleic acid or CAR polypeptide;

(ii) an agent that ameliorates one or more side effects associated with administration of the cell comprising the CAR nucleic acid or CAR polypeptide; or

(iii) an agent that treats the cancer associated with CD33.

37. The isolated nucleic acid molecule of any of claims 1-7, the isolated CAR polypeptide molecule of any of claims 8-12, the vector of either of claim 13, or the cell of claim 14 for use as a medicament.

38. The isolated nucleic acid molecule of any of claims 1-7, the isolated CAR polypeptide molecule of any of claims 8-12, the vector of either of claim 13, or the cell of claim 14 for use in the treatment of a cancer associated with expression of CD33.

39. A cell, e.g., a population of immune effector cells, of claim 17, further expressing an inhibitory molecule that inhibits T cell function, wherein the molecule comprises a first polypeptide that comprises an inhibitory molecule, wherein the inhibitory molecule is PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, TGFR beta, or a fragment thereof; and

a second polypeptide that comprises an intracellular signaling domain, wherein the intracellular signaling domain comprises a co-stimulatory intracellular signaling domain

derived from 4-1BB, CD27 or CD28, or a primary signaling domain derived from CD3 zeta, or both.

40. The use of the cell according to claim 22, wherein the agent is an mTOR inhibitor and the subject is to be administered a low, immune enhancing, dose of an mTOR inhibitor, e.g., RAD001 or rapamycin.

41. The use of the cell according to claim 26, wherein the mTOR inhibitor is to be administered for an amount of time sufficient to decrease the proportion of PD-1 positive T cells, increase the proportion of PD-1 negative T cells, or increase the ratio of PD-1 negative T cells/ PD-1 positive T cells, in the peripheral blood of the subject, or in a preparation of T cells isolated from the subject.

42. Use of the cell comprising the CAR nucleic acid molecule of any of claims 1-7 or the CAR polypeptide of any of claims 8-12 in the manufacture of a medicament to condition a subject prior to cell transplantation, wherein the conditioning of a subject prior to cell transplantation comprises reduction of the number of CD33-expressing cells in a subject, e.g., CD33-expressing normal cells or CD33-expressing cancer cells.

43. The use of the cell according to claim 28, wherein the cell transplantation is a stem cell transplantation, e.g., a hematopoietic stem cell transplantation, or a bone marrow transplantation.