CLAIMS

1. A pharmaceutical composition comprising a cell and a pharmaceutically or physiologically acceptable carrier, diluent or excipient, wherein the cell comprises an isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises a~~n antibody or antibody fragment~~ scFv which comprises a~~n anti-~~ CD19 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, wherein said ~~anti-~~CD19 binding domain comprises:

(i) a light chain complementarity determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,

(ii) a light chain complementarity determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,

(iii) a light chain complementarity determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,

(iv) a heavy chain complementarity determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,

(v) a heavy chain complementarity determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

(vi) a heavy chain complementarity determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

2. The pharmaceutical composition of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

3. The pharmaceutical composition of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

4. The pharmaceutical composition of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

5. The pharmaceutical composition of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

6. The pharmaceutical composition of claim 1, which encodes any heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

7. The pharmaceutical composition of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42 and any heavy chain variable region listed SEQ ID NOs: 32, 31, or 33-42.

~~8. The pharmaceutical composition of any of the preceding claims, wherein the anti-CD19 binding domain is a scFv.~~

~~9~~8. The pharmaceutical composition of any of ~~the preceding~~ claims 1-4 or 6, wherein the light chain variable region comprises ~~an amino acid sequence having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or~~ an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

~~10~~9. The pharmaceutical composition of any of ~~the preceding~~ claims 1-5, wherein the heavy chain variable region comprises ~~an amino acid sequence having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or~~ an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

~~11~~10. The pharmaceutical composition of any of the preceding claims, wherein the ~~anti-~~CD19 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof.

~~12~~11. The pharmaceutical composition of any of the preceding claims, wherein the nucleic acid sequence encoding the ~~anti-~~CD19 binding domain comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:62, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO: 69,

SEQ ID NO:70, SEQ ID NO:71 and SEQ ID NO:72, or a nucleic acid sequence with at least 95% identity thereof.

~~13~~12. The pharmaceutical composition of any of the preceding claims, wherein the cell comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO: 86, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, or a nucleic acid sequence with at least 95% identity thereof.

~~14~~13. The pharmaceutical composition of any of the preceding claims, wherein the encoded CAR comprises 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 or the encoded CAR comprises a transmembrane domain that comprises a transmembrane domain of the alpha chain of CD8.

~~15~~14. The pharmaceutical composition of any of the preceding claims, wherein the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 15, ~~or comprises an amino acid sequence comprising 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:15,~~ or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:15 or the nucleic acid sequence encoding the transmembrane domain comprises the nucleic acid sequence of SEQ ID NO:56, or a sequence with at least 95% identity thereof.

~~16~~15. The pharmaceutical composition of any of the preceding claims, wherein the encoded ~~anti-~~CD19 binding domain is connected to the transmembrane domain by a hinge region, wherein the hinge region is optionally a CD8 alpha hinge.

~~17~~16. The pharmaceutical composition of claim ~~16~~15, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14, or an amino acid sequence with at least 95% identity thereof or wherein the nucleic acid sequence encoding the hinge region comprises the nucleic acid sequence of SEQ ID NO: 55, or a nucleic acid sequence with at least 95% identity thereof.

~~18~~17. The pharmaceutical composition of any of the preceding claims, wherein the intracellular signaling domain comprises a costimulatory domain.

~~19~~18. The pharmaceutical composition of claim ~~18~~17, wherein the costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137).

~~20~~19. The pharmaceutical composition of claim ~~18 or 19~~17 or 18, wherein the encoded costimulatory domain comprises the amino acid sequence of SEQ ID NO:16~~ 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:16,~~ or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 or the nucleic acid sequence encoding the costimulatory domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof.

~~21~~20. The pharmaceutical composition of any of the preceding claims, wherein the intracellular signaling domain comprises a primary signaling domain.

~~22~~21. The pharmaceutical composition of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

~~23~~22. The pharmaceutical composition of any of the preceding claims, wherein the encoded intracellular signaling domain comprises: (i) the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or (ii) ~~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:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or (iii)~~ an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

~~24~~23. The pharmaceutical composition of any of the preceding claims, wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:16 and the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

~~25~~24. The pharmaceutical composition of any of the preceding claims, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof, and/or the nucleic acid sequence of SEQ ID NO:101 or SEQ ID NO:44, or a nucleic acid sequence with at least 95% identity thereof.

~~26~~25. The pharmaceutical composition of any of the preceding claims, wherein the isolated nucleic acid molecule further comprises a leader sequence.

~~27~~26. The pharmaceutical composition of claim ~~26~~25, wherein the leader sequence encodes the amino acid sequence of SEQ ID NO: 13, or a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 13.

~~28~~27. A pharmaceutical composition comprising a cell and a pharmaceutically or physiologically acceptable carrier, diluent or excipient, wherein the cell comprises an isolated chimeric antigen receptor (CAR) molecule comprising: (i) ~~an antibody or antibody fragment~~ a scFv which comprises a humanized ~~anti-~~CD19 binding domain, (ii) a transmembrane domain, and (iii) an intracellular signaling domain, wherein the humanized ~~anti-~~CD19 binding domain comprises:

(i) a light chain complementarity determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,

(ii) a light chain complementarity determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,

(iii) a light chain complementarity determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,

(iv) a heavy chain complementarity determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,

(v) a heavy chain complementarity determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

(vi) a heavy chain complementarity determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

~~29~~28. The pharmaceutical composition of claim ~~28~~27, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

~~30~~29. The pharmaceutical composition of claim ~~28~~27, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

~~31~~30. The pharmaceutical composition of claim ~~28~~27, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

~~32. The pharmaceutical composition of any of claims 28-31, wherein the anti-CD19 binding domain is a scFv.~~

~~33~~31. The pharmaceutical composition of any of claims ~~28-32~~27-31, wherein the ~~anti-~~CD19 binding domain comprises a light chain and a heavy chain of an amino acid sequence listed in SEQ ID NOs: 32, 31, or 33-42.

~~34~~32. The pharmaceutical composition of any of claims ~~28-33~~28-30, wherein the ~~anti-~~CD19 binding domain comprises: (i) a light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, or (ii) ~~a light chain variable region comprising an amino acid sequence having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii)~~ an amino acid sequence with at least 95% identity with a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

~~35~~33. The pharmaceutical composition of any of claims ~~28-34~~27-30 or 32, wherein the ~~anti-~~CD19 binding domain comprises: (i) a heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, or (ii) ~~a heavy chain variable region comprising an amino acid sequence having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid~~

~~sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii)~~ an amino acid sequence with at least 95% identity to a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

~~36~~34. The pharmaceutical composition of any of claims ~~28-35~~27-33, wherein the ~~anti-~~CD19 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof, or

wherein the ~~anti-~~CD19 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO:32, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, and SEQ ID NO:42, or an amino acid sequence with at least 95% identity thereof.

~~37~~35. The pharmaceutical composition of any of claims ~~28-36~~27-34, wherein the transmembrane domain 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, or

the transmembrane domain comprises a transmembrane domain of the alpha chain of CD8.

~~38~~36. The pharmaceutical composition of claim ~~37~~35, wherein the transmembrane domain comprises: (i) the amino acid sequence of SEQ ID NO: 15, or (ii) ~~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: 15, or (iii)~~ a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 15.

~~39~~37. The pharmaceutical composition of any one of claims ~~28-38~~27-36, wherein the humanized ~~anti-~~CD19 binding domain is connected to the transmembrane domain by a hinge region, wherein optionally the hinge region is a CD8 alpha hinge.

~~40~~38. The pharmaceutical composition of claim ~~39~~37, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14 or SEQ ID NO:102, or a sequence with at least 95% identity thereof.

~~41~~39. The pharmaceutical composition of any of claims ~~28-40~~27-38, wherein the intracellular signaling domain comprises a costimulatory domain.

~~42~~40. The pharmaceutical composition of claim ~~41~~39, wherein the costimulatory domain comprises a functional signaling domain of a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), and 4-1BB (CD137).

~~43~~41. The pharmaceutical composition of claim ~~41 or 42~~39 or 40, wherein the costimulatory domain comprises: (i) the amino acid sequence of SEQ ID NO: 16, or (ii) ~~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: 16, or (iii)~~ an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 16.

~~44~~42. The pharmaceutical composition of any one of claims ~~28-43~~27-41, wherein the intracellular signaling domain comprises a primary signaling domain.

~~45~~43. The pharmaceutical composition of claim ~~44~~42, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

~~46~~44. The pharmaceutical composition of claim ~~44 or 45~~42 or 43 wherein the intracellular signaling domain comprises: (i) the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17, or the amino acid sequence of SEQ ID NO:43, or (ii) ~~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:16 and/or~~ the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

~~47~~45. The pharmaceutical composition of any of claims ~~44-46~~42-44, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 16 and the amino acid sequence of SEQ ID NO: 17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

~~48~~46. The pharmaceutical composition of any of claims ~~28-47~~27-45, wherein the CAR further comprises a leader sequence.

~~49~~47. The pharmaceutical composition of claim ~~48~~46, wherein the leader sequence comprises the amino acid sequence of SEQ ID NO: 13, or a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:13.

~~50~~48. A pharmaceutical composition comprising a cell and a pharmaceutically or physiologically acceptable carrier, diluent or excipient, wherein the cell comprises a scFv comprising a humanized ~~anti-~~ CD19 binding domain comprising:

(i) a light chain complementarity determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,

(ii) a light chain complementarity determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,

(iii) a light chain complementarity determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,

(iv) a heavy chain complementarity determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,

(v) a heavy chain complementarity determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

(vi) a heavy chain complementarity determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

~~51~~49. The pharmaceutical composition of claim ~~50~~48, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

~~52~~50. The pharmaceutical composition of claim ~~50~~48, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

~~53~~51. The pharmaceutical composition of claim ~~50~~48, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

~~54~~52. The pharmaceutical composition of any of claims ~~50-53~~48-51, wherein the humanized ~~anti-~~CD19 binding domain comprises:

(i) ~~a scFv comprising~~ a light chain variable region and a heavy chain variable region of an amino acid sequence of any of SEQ ID NOs: 32, 31, or 33-42;

(ii) a light chain variable region comprising an amino acid sequence ~~having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid sequence of a light chain variable region provided in any of SEQ ID NOs: 32, 31, or 33-42, or a sequence~~ with at least 95% identity to an amino acid sequence of a light chain variable region provided in any of SEQ ID NOs: 32, 31, or 33-42; and/or

(iii) a heavy chain variable region comprising an amino acid sequence ~~having at least one, two, or three modifications but not more than 30, 20, or 10 modifications of an amino acid sequence of a heavy chain variable region provided in any of SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence~~ with at least 95% identity to an amino acid sequence of a heavy chain variable region provided in any of SEQ ID NOs: 32, 31, or 33-42.

~~55~~53. A humanized ~~anti-~~CD19 binding domain comprising:

(i) a light chain complementarity determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,

(ii) a light chain complementarity determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,

(iii) a light chain complementarity determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,

(iv) a heavy chain complementarity determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,

(v) a heavy chain complementarity determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

(vi) a heavy chain complementarity determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24;

wherein the ~~anti-~~CD19 binding domain:

~~(i) is an scFv having a thermal stability greater than 5 degrees Celsius than that of an scFv of SEQ ID NO:59, as assessed by measuring melting temperature (Tm) using differential scanning fluorimetry; and~~

(~~ii~~i) retains the affinity for human CD19 of an scFv having the amino acid sequence of SEQ ID NO:59.

~~56~~54. An isolated chimeric antigen receptor (CAR) molecule comprising a humanized ~~anti-~~CD19 binding domain as defined in claim ~~55~~53, a transmembrane domain, and an intracellular signaling domain.

~~57~~55. An isolated nucleic acid molecule encoding a CD19 binding domain as defined in claim ~~55-~~53 or a CAR molecule as defined in claim ~~56~~54.

~~58~~56. A vector comprising a nucleic acid molecule encoding the CAR molecule as defined in any one of any of claims ~~28-49 or 56~~27-47 or 54.

~~59~~57. The vector of claim ~~58~~56, wherein the vector is selected from the group consisting of a DNA, an RNA, a plasmid, a viral vector, a lentivirus vector, an adenoviral vector, and a retrovirus vector.

~~60~~58. The vector of claim ~~58 or 59~~56 or 57, further comprises a promoter.

~~61~~59. The vector of claim ~~60~~58, wherein the promoter is an EF-1 promoter.

~~62~~60. The vector of claim ~~61~~59, wherein the EF-1 promoter comprises the nucleic acid sequence of SEQ ID NO: 100.

~~63~~61. The vector of any of claims ~~58-62~~56-60, wherein the vector is an in vitro transcribed vector.

~~64~~62. The vector of any of claims ~~58-63~~56-61, wherein the nucleic acid sequence in the vector further comprises a poly(A) tail.

~~65~~63. The vector of any of claims ~~58-64~~56-62, wherein the nucleic acid sequence in the vector further comprises a 3'UTR.

~~66~~64. A cell comprising the vector of any of claims ~~58-65~~56-63.

~~67~~65. A cell comprising the nucleic acid molecule of claim ~~57~~55.

~~68~~66. A cell ~~comprising~~ expressing the CAR molecule of claim ~~56~~54.

~~69~~67. The cell of any of claims ~~66-68~~64-66, wherein the cell is a human T cell.

~~70~~68. The cell of any of claims ~~66-68~~64-66, wherein the cell is a CD8+ T cell.

~~71~~69. The cell of any of claims ~~66-70~~64-68, further expressing an inhibitory ~~molecule~~ polypeptide that comprises a first polypeptide that comprises at least a portion of an inhibitory molecule, associated with a second polypeptide that comprises a positive signal from an intracellular signaling domain.

~~72~~70. The cell of claim ~~71~~69, wherein the inhibitory molecule comprises a first polypeptide that comprises at least a portion of PD1 and a second polypeptide comprising a costimulatory domain and primary signaling domain.

~~73~~71. A method of making a cell comprising transducing a T cell with the vector of any of claims ~~58-65~~54-63 or the nucleic acid molecule of claim ~~57~~55.
~~74~~72. A 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 the CAR molecule of claim ~~57~~55.

~~75~~73. The pharmaceutical composition of any one of claims 1-~~54~~52, the CD19 binding domain of claim ~~55~~53, the CAR molecule of claim ~~56~~54, the nucleic acid molecule of claim ~~57~~55, the vector of any one of claims ~~58-65~~56-63, or the cell of any one of claims ~~66-72~~64-70, for use in providing an anti-tumor immunity.

~~76~~74. Use of the pharmaceutical composition of any one of claims 1-~~54~~52, the CD19 binding domain of claim ~~55~~53, the CAR molecule of claim ~~56~~54, the nucleic acid molecule of claim ~~57~~55, the vector of any one of claims ~~58-65~~56-63, or the cell of any one of claims ~~66-72~~64-70, in the manufacture of a medicament for the provision of an anti-tumor immunity.

~~77~~75. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim ~~75~~73, or the use of claim ~~76~~74, wherein the cell is an autologous T cell.

76~~78~~. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim ~~75~~73, or the use of claim ~~76~~74, wherein the cell is an allogeneic T cell.

~~79~~77. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim ~~75~~76, or the use of claim ~~76~~74, wherein the anti-tumor immunity is provided in a human.

78~~80~~. The pharmaceutical composition of any one of claims 1-~~54~~52, the CD19 binding domain of claim ~~55~~53, the CAR molecule of claim ~~56~~54, the nucleic acid molecule of claim ~~57~~55, the vector of any one of claims ~~58-65~~56-63, or the cell of any one of claims ~~66-72~~64-70, for use in treating a proliferative disease ~~associated with expression of CD19~~.

~~81~~79. Use of the pharmaceutical composition of any one of claims 1-~~54~~52, the CD19 binding domain of claim ~~55~~53, the CAR molecule of claim ~~56~~54, the nucleic acid molecule of claim ~~57~~55, the vector of any one of claims ~~58-65~~56-63, or the cell of any one of claims ~~66-72~~64-70, in the manufacture of a medicament for the treatment of a proliferative disease ~~associated with expression of CD19~~.

~~82. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim 80, or the use of claim 81, wherein the disease associated with expression of CD19 is selected from a cancer, malignancy, precancerous condition, autoimmune disease, or inflammatory disorder.~~

~~83~~80. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim ~~80~~78, or the use of claim ~~81~~79, wherein the ~~disease associated with CD19 expression is selected from a~~ proliferative disease ~~such as~~ is a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19.

~~84~~81. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of claim ~~83~~ 80 or the use of claim ~~83~~80, wherein the disease is a hematologic cancer selected from the group consisting of one or more acute leukemias including B-cell acute ~~lymphoid~~ lymphoblastic leukemia ("BALL"), T-cell acute ~~lymphoid~~ lymphoblastic leukemia ("TALL"), acute ~~lymphoid~~ lymphoblastic leukemia (ALL); one or more chronic leukemias including chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and preleukemia; and combinations thereof.

~~85~~82. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of any one of claims ~~75, 77-80, or 82-84~~73, 75-78, 80, or 81, or the use of any one of claims ~~76-79 or 81-84~~74-77, or 79-81, which is to be administered in combination with an agent that increases the efficacy of a cell expressing a CAR molecule, an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule, or an agent that treats the disease associated with CD19.

~~86~~83. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of any one of claims 73, 75-78, or 80-82~~75, 77-80, or 82-85~~, or the use of any one of claims ~~76-79 or 81-85~~74-77 or 79-82, which is to be administered in combination with a chemotherapeutic drug, immunosuppressive agent, therapy for CRS (cytokine release syndrome), or agent which inhibits ~~an inhibitory molecule, wherein the inhibitory molecule is~~

~~optionally chosen from~~ PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, and 2B4.

~~87~~84. The pharmaceutical composition, the CD19 binding domain, the CAR molecule, the nucleic acid molecule, the vector, or the cell for use of any one of claims 73, 75-78, or 80-83~~75, 77-80, or 82-86~~, or the use of any one of claims 74-77 or 79-83~~76-79 or 81-86~~, wherein:

the cell expressing a CAR molecule is to be administered at a dose of 10^4 to 10^9 cells/kg body weight, 10^5 to 10^6 cells/kg body weight, 1.4 x $l0^7$ to 1.1 x $l0^9$ cells per dose, up to 5 x10^7, 1 x 10^7 - 5 x 10^8, or l x 10^8 -5 x 10^8 cells per dose;

the use comprises one or more subsequent administrations of the cell, nucleic acid molecule, or CAR molecule; or

the use comprises more than one administration (e.g., 2, 3, or 4 administrations) in a week, of the cell, nucleic acid molecule, or CAR molecule.