

CLAIMS

1. A Cluster of Differentiation 70 (CD70)-specific chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single chain Fv fragment (scFv) binding to the extracellular domain of CD70, wherein the intracellular signaling domain comprises a 4-1BB signaling domain.

2. The CD70-specific CAR of claim 1 wherein the extracellular domain comprises a single chain Fv fragment (scFv) comprising a heavy chain variable (VH) region comprising three CDRs from the VH region comprising the sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379 or 381; and a light chain variable (VL) region comprising three CDRs from the VL region shown in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378 or 380.

3. The CD70-specific CAR of claim 1, wherein the VH region comprises the sequence shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379 or 381; and a light chain variable (VL) region comprising three CDRs from the VL region shown in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378 or 380, or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

4. The CD70-specific CAR of claim 1, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 97, 98, or 99; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 100 or 101; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 102; and a light chain variable region (VL) comprising the following CDRs: a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 217; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 218; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 219.

5. The CD70-specific CAR of claim 1, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 18 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 17.
6. The CD70-specific CAR of claim 1, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 145, 146, or 147; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 148 or 149; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 150; and a light chain variable region (VL) comprising the following CDRs: a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 241; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 242; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 243.
7. The CD70-specific CAR of claim 1, wherein the VH region comprises the amino acid sequence shown in SEQ ID NO: 34 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 33.
8. The CD70-specific CAR of claim 2 or 3, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the AbM definition, or the contact definition of CDR.
9. The CD70-specific CAR of any one of claims 1 to 8, wherein the intracellular signaling domain comprises a CD3 ζ signalling domain.
10. The CD70-specific CAR of any one of claims 1 to 9, wherein the intracellular signaling domain comprises a 4-1BB domain.
11. The CD70-specific CAR of any one of claims 1 to 10, further comprising a second intracellular signaling domain.
12. The CD70-specific CAR of claim 11, wherein the second intracellular signaling domain comprises a 4-1BB domain.
13. The CD70-specific CAR of any one of claims 1 to 12, further comprising a stalk domain between the extracellular ligand binding domain and the first transmembrane domain.

14. The CD70-specific CAR of claim 13, wherein the stalk domain is selected from the group consisting of: a human CD8 α hinge, an IgG1 hinge, and an Fc γ RIII α hinge.
15. The CD70-specific CAR of any one of claims 1 to 14, further comprising a CD20 epitope.
16. The CD70-specific CAR of claim 15 wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 293 or SEQ ID NO: 294 or SEQ ID NO: 609.
17. The CD70-specific CAR of claim 1, wherein the CD70-specific CAR comprises an amino acid sequence shown in SEQ ID NO: 311 to 334.
18. The CD70-specific CAR of claim 1, wherein the CD70-specific CAR comprises the amino acid sequence shown in SEQ ID NO: 319 or 327.
19. The CD70-specific CAR of any one of claims 1 to 18, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain.
20. The CD70-specific CAR of any one of claims 1 to 19, further comprising another extracellular ligand binding domain which is not specific for CD70.
21. The CD70-specific CAR of any one of claims 1 to 19, wherein the extracellular ligand-binding domain(s), the first transmembrane domain, and intracellular signaling domain(s) are on a single polypeptide.
22. The CD70-specific CAR of any one of claims 1 to 19, further comprising a second transmembrane domain, wherein the first transmembrane domain and the extracellular ligand-binding domain(s) are on a first polypeptide, and wherein the second transmembrane domain and the intracellular signaling domain(s) are on a second polypeptide, wherein the first transmembrane domain comprises a transmembrane domain from the α chain of the high-affinity IgE receptor (Fc ϵ RI) and the second transmembrane domain comprises a transmembrane domain from the γ or β chain of Fc ϵ RI.
23. The CD70-specific CAR of claim 22, further comprising a third polypeptide comprising a third transmembrane domain fused to an intracellular signaling domain from a co-stimulatory molecule, wherein the third transmembrane domain comprises a transmembrane domain from the γ or β chain of Fc ϵ RI.

- ~~24. A polynucleotide comprising a nucleic acid sequence encoding the CD70-specific CAR of any one of claims 1 to 23.~~
- ~~25. The polynucleotide of claim 24, wherein the polynucleotide comprises the nucleic acid sequence shown in SEQ ID NO: 336 or 337.~~
- ~~26. An expression vector comprising the polynucleotide of any one of claims 24 or 25.~~
- ~~27. An engineered immune cell expressing at its cell surface membrane a CD70-specific CAR of any one of claims 1 to 23.~~
- ~~28. The engineered immune cell of claim 27, further comprising another CAR which is not specific for CD70.~~
- ~~29. The engineered immune cell of claim 27 or 28, further comprising a polynucleotide encoding a suicide polypeptide.~~
- ~~30. The engineered immune cell of claim 29, wherein the suicide polypeptide is RQR8.~~
- ~~31. The engineered immune cell of any one of claims 27 to 30, wherein the immune cell is derived from an inflammatory T-lymphocyte, a cytotoxic T-lymphocyte, a regulatory T-lymphocyte, or a helper T-lymphocyte.~~
- ~~32. The engineered immune cell of claim any one of claims 27 to 31, further comprising a disruption one or more endogenous genes, wherein the endogenous gene encodes TCR α , TCR β , CD52, glucocorticoid receptor (GR), deoxycytidine kinase (dCK), CD70 or an immune checkpoint protein such as for example programmed death-1 (PD-1).~~
- ~~33. The engineered immune cell of claim any one of claims 27 to 31, further comprising a disruption of TCR α and CD52, or TCR α , CD52 and CD70.~~
- ~~34. The engineered immune cell of any one of claims 27 to 33, wherein the immune cell is obtained from a healthy donor.~~
- ~~35. The engineered immune cell of any one of claims 27 to 33, wherein the immune cell is obtained from a patient.~~

~~36. The engineered immune cell of any one of claims 27 to 35 for use as a medicament.~~

~~37. The engineered immune cell of claim 36, wherein the medicament is for use in treatment of a cancer.~~

~~38. The engineered immune cell of claim 37, wherein, the cancer is selected from the group consisting of Renal Cell Carcinoma, Glioblastoma, glioma such as low grade glioma, Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD), Waldenstrom's macroglobulinemia, Acute Myeloid Leukemia, Multiple Myeloma, diffuse large cell lymphoma, follicular lymphoma and Non-Small Cell Lung Cancer.~~

~~39. A population of cells according to any one of claims 27 to 38, wherein~~

~~a) said population of cells comprises a percentage of stem cell memory and central memory cells greater than 20%, 30% or 40%, and/or~~

~~b) said population of cells achieves a percentage of lysis of CD70-expressing cells at day 6 greater than 10%, 20%, 30% or 40% upon recursive CD70-expressing cells as measured using the assay disclosed in example 4.~~

~~40. The population of cells of claim 39, wherein, said population of cells achieves a percentage of lysis of CD70-expressing cells at day 6 greater than 20% upon recursive CD70-expressing cells as measured using the assay disclosed in example 4.~~

~~41. A method of engineering an immune cell comprising:~~

~~a) providing an immune cell; and~~

~~b) expressing at the surface of the cell at least one CD70-specific CAR according to any one of claims 1 to 23.~~

~~42. The method of engineering an immune cell of claim 41 comprising:~~

~~a) providing an immune cell;~~

~~b) introducing into the cell at least one polynucleotide encoding said CD70-specific CAR; and~~

~~c) expressing said polynucleotide into the cell.~~

~~43. The method of engineering an immune cell of claim 41 comprising:~~

- a) providing an immune cell;
 - b) introducing into the cell at least one polynucleotide encoding said CD70-specific CAR;
- and
- c) introducing at least one other CAR which is not specific for CD70.

44. An immune cell expressing at the surface a CD70-specific CAR according to any one of claims 1 to 23 for use as a medicament.

45. A pharmaceutical composition comprising the engineered immune cell of any one of claims 27 to 39.

46. Use of the pharmaceutical composition of claim 45 in the manufacture of a medicament for the treatment of a condition associated with malignant cells expressing CD70.

47. The use according to claim 46, wherein the condition is a cancer.

48. The use according to claim 47, wherein the cancer is selected from the group consisting of Renal Cell Carcinoma, Glioblastoma, glioma such as low grade glioma, Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD), Waldenstrom's macroglobulinemia, Acute Myeloid Leukemia, Multiple Myeloma, diffuse large-cell lymphoma, follicular lymphoma and Non-Small Cell Lung Cancer.

49. Use of the pharmaceutical composition of claim 45 in the manufacture of a medicament for the treatment of tumor growth or progression.

50. Use of the pharmaceutical composition of claim 45 in the manufacture of a medicament for the treatment of metastasis of malignant cells expressing CD70

51. Use of the pharmaceutical composition of claim 45 in the manufacture of a medicament for the treatment of a tumor.

52. A Cluster of Differentiation 70-specific chimeric antigen receptor (CD70-specific CAR) comprising an extracellular ligand-binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single-chain Fv fragment (scFv) binding to the extracellular domain of CD70 having a heavy chain variable (VH) region and a light chain variable (VL) region; wherein:

- a) the VH-region comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 18 and the VL-region comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 17; or

b) the VH region comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 34 and the VL region comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 33.

53. The CD70-specific CAR of claim 52, wherein the extracellular domain comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 319.

54. The CD70-specific CAR of claim 52, wherein the extracellular domain comprises an amino acid sequence that shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 327.

55. A polynucleotide encoding a CD70-specific CAR, wherein the polynucleotide comprises a nucleic acid sequence that:

a) shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 297 and shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 298; or

b) shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 307 and shares at least 95%, 96%, 97%, 98%, 99%, or 100% with SEQ ID NO: 308.

56. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule that specifically binds to CD70, wherein the antigen-binding molecule comprises at least one of:

a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 49-51, 55-57, 61-63, 67-69, 73-75, 79-81, 85-87, 91-93, 97-99, 103-105, 109-111, 115-117, 121-123, 127-129, 133-135, 139-141, 145-147, 151-153, 157-159, 163-165, 169-171, 175-177, 181-183, 187-189, 382-384, 388-390, 394-396, 400-402, 406-408, 412-414, 418-420, 424-426, 430-432, 436-438, 442-444, 448-450, 454-456, 460-462, 466-468, 472-474, 478-480, 484-486, 490-492, 496-498, 502-504, and 508-510;

b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs 52, 53, 58, 59, 64, 65, 70, 71, 76, 77, 82, 83, 88, 89, 94, 95, 100, 101, 106, 107, 112, 113, 118, 119, 124, 125, 130, 131, 136, 137, 142, 143, 148, 149, 154, 155, 160, 161, 166, 167, 172, 173, 178, 179, 184, 185, 190, 191, 385, 386, 391, 392, 397, 398, 403, 404, 409, 410, 415, 416, 421, 422, 427, 428, 433, 434, 439, 440, 445, 446, 451, 452, 457, 458, 463, 464, 469, 470, 475, 476, 481, 482, 487, 488, 493, 494, 499, 500, 505, 506, 511, and 512;

c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126, 132,

~~138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, and 513,~~

d) ~~variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 193, 196, 199, 202, 205, 208, 211, 214, 217, 220, 223, 226, 229, 232, 235, 238, 241, 244, 247, 250, 253, 256, 259, 262, 514, 517, 520, 523, 526, 529, 532, 535, 538, 541, 544, 547, 550, 553, 556, 559, 562, 565, 568, 571, 574, and 577,~~

e) ~~a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs. 194, 197, 200, 203, 206, 209, 212, 215, 218, 221, 224, 227, 230, 233, 236, 239, 242, 245, 248, 251, 254, 257, 260, 263, 515, 518, 521, 524, 527, 530, 533, 536, 539, 542, 545, 548, 551, 554, 557, 560, 563, 566, 569, 572, 575, and 578, and~~

f) ~~a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs. 195, 198, 201, 204, 207, 210, 213, 216, 219, 222, 225, 228, 231, 234, 237, 240, 243, 246, 249, 252, 255, 258, 261, 264, 516, 519, 522, 525, 528, 531, 534, 537, 540, 543, 546, 549, 552, 555, 558, 561, 564, 567, 570, 573, 576, and 579.~~

57. The CD70-specific CAR of claim 56, wherein the antigen binding molecule comprises:

a) ~~a variable heavy chain domain comprising amino acid sequences for CDRH1, CDRH2, and CDRH3, respectively, selected from one of SEQ ID NOs:~~

- ~~i) 49-51, 52-53, 54;~~
- ~~ii) 55-57, 58-59, 60;~~
- ~~iii) 61-63, 64-65, 66;~~
- ~~iv) 67-69, 70-71, 72;~~
- ~~v) 73-75, 76-77, 78;~~
- ~~vi) 79-81, 82-83, 84;~~
- ~~vii) 85-87, 88-89, 90;~~
- ~~viii) 91-93, 94-95, 96;~~
- ~~ix) 97-99, 100-101, 102;~~
- ~~x) 103-105, 106-107, 108;~~
- ~~xi) 109-111, 112-113, 114;~~
- ~~xii) 115-117, 118-119, 120;~~
- ~~xiii) 121-123, 124-125, 126;~~
- ~~xiv) 127-129, 130-131, 132;~~
- ~~xv) 133-135, 136-137, 138;~~

~~xvi) 139-141, 142-143, 144;~~
~~xvii) 145-147, 148-149, 150;~~
~~xviii) 151-153, 154-155, 156;~~
~~xix) 157-159, 160-161, 162;~~
~~xx) 163-165, 166-167, 168;~~
~~xxi) 169-171, 172-173, 174;~~
~~xxii) 175-177, 178-179, 180;~~
~~xxiii) 181-183, 184-185, 186;~~
~~xxiv) 187-189, 190-191, 192;~~
~~xxv) 382-384, 385-386, 387;~~
~~xxvi) 388-390, 391-392, 393;~~
~~xxvii) 394-396, 397-398, 399;~~
~~xxviii) 400-402, 403-404, 405;~~
~~xxix) 406-408, 409-410, 411;~~
~~xxx) 412-414, 415-416, 417;~~
~~xxxi) 418-420, 421-422, 423;~~
~~xxxii) 424-426, 427-428, 429;~~
~~xxxiii) 430-432, 433-434, 435;~~
~~xxxiv) 436-438, 439-440, 441;~~
~~xxxv) 442-444, 445-446, 447;~~
~~xxxvi) 448-450, 451-452, 453;~~
~~xxxvii) 454-456, 457-458, 459;~~
~~xxxviii) 460-462, 463-464, 465;~~
~~xxxix) 466-468, 469-470, 471;~~
~~xl) 472-474, 475-476, 477;~~
~~xli) 478-480, 481-482, 483;~~
~~xlii) 484-486, 487-488, 489;~~
~~xliii) 490-492, 493-494, 495;~~
~~xliv) 496-498, 499-500, 501;~~
~~xlv) 502-504, 505-506, 507; or~~
~~xlvi) 508-510, 511-512, 513; and~~

b) ~~a variable light chain domain comprising amino acid sequences for CDRL1, CDRL2, and CDRL3, respectively, selected from one of SEQ ID NOs:~~

- i) ~~193, 194, 195;~~
- ii) ~~196, 197, 198;~~
- iii) ~~199, 200, 201;~~
- iv) ~~202, 203, 204;~~
- v) ~~205, 206, 207;~~
- vi) ~~208, 209, 210;~~
- vii) ~~211, 212, 213;~~
- viii) ~~214, 215, 216;~~
- ix) ~~217, 218, 219;~~
- x) ~~220, 221, 222;~~
- xi) ~~223, 224, 225;~~
- xii) ~~226, 227, 228;~~
- xiii) ~~229, 230, 231;~~
- xiv) ~~232, 233, 234;~~
- xv) ~~235, 236, 237;~~
- xvi) ~~238, 239, 240;~~
- xvii) ~~241, 242, 243;~~
- xviii) ~~244, 245, 246;~~
- xix) ~~247, 248, 249;~~
- xx) ~~250, 251, 252;~~
- xxi) ~~253, 254, 255;~~
- xxii) ~~256, 257, 258;~~
- xxiii) ~~259, 260, 261;~~
- xxiv) ~~262, 263, 264;~~
- xxv) ~~514, 515, 516;~~
- xxvi) ~~517, 518, 519;~~
- xxvii) ~~520, 521, 522;~~
- xxviii) ~~523, 524, 525;~~
- xxix) ~~526, 527, 528;~~
- xxx) ~~529, 530, 531;~~

~~xxxi) 532, 533, 534;~~
~~xxxii) 535, 536, 537;~~
~~xxxiii) 538, 539, 540;~~
~~xxxiv) 541, 542, 543;~~
~~xxxv) 544, 545, 546;~~
~~xxxvi) 547, 548, 549;~~
~~xxxvii) 550, 551, 552;~~
~~xxxviii) 553, 554, 555;~~
~~xxxix) 556, 557, 558;~~
~~xl) 559, 560, 561;~~
~~xli) 562, 563, 564;~~
~~xlii) 565, 566, 567;~~
~~xliii) 568, 569, 570;~~
~~xliv) 571, 572, 573;~~
~~xlv) 574, 575, 576; and~~
~~xlvi) 577, 578, 579.~~

58. The CD70-specific CAR of claim 57, wherein the antigen binding molecule comprises amino acid sequences for CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, respectively, selected from one of SEQ ID NOs:

- a) ~~49-51, 52-53, 54, 193, 194, 195;~~
- b) ~~55-57, 58-59, 60, 196, 197, 198;~~
- c) ~~61-63, 64-65, 66, 199, 200, 201;~~
- d) ~~67-69, 70-71, 72, 202, 203, 204;~~
- e) ~~73-75, 76-77, 78, 205, 206, 207;~~
- f) ~~79-81, 82-83, 84, 208, 209, 210;~~
- g) ~~85-87, 88-89, 90, 211, 212, 213;~~
- h) ~~91-93, 94-95, 96, 214, 215, 216;~~
- i) ~~97-99, 100-101, 102, 217, 218, 219;~~
- j) ~~103-105, 106-107, 108, 220, 221, 222;~~
- k) ~~109-111, 112-113, 114, 223, 224, 225;~~
- l) ~~115-117, 118-119, 120, 226, 227, 228;~~
- m) ~~121-123, 124-125, 126, 229, 230, 231;~~

~~n) 127-129, 130-131, 132, 232, 233, 234;~~
~~o) 133-135, 136-137, 138, 235, 236, 237;~~
~~p) 139-141, 142-143, 144, 238, 239, 240;~~
~~q) 145-147, 148-149, 150, 241, 242, 243;~~
~~r) 151-153, 154-155, 156, 244, 245, 246;~~
~~s) 157-159, 160-161, 162, 247, 248, 249;~~
~~t) 163-165, 166-167, 168, 250, 251, 252;~~
~~u) 169-171, 172-173, 174, 253, 254, 255;~~
~~v) 175-177, 178-179, 180, 256, 257, 258;~~
~~w) 181-183, 184-185, 186, 259, 260, 261;~~
~~x) 187-189, 190-191, 192, 262, 263, 264;~~
~~y) 382-384, 385-386, 387, 514, 515, 516;~~
~~z) 388-390, 391-392, 393, 517, 518, 519;~~
~~aa) 394-396, 397-398, 399, 520, 521, 522;~~
~~bb) 400-402, 403-404, 405, 523, 524, 525;~~
~~cc) 406-408, 409-410, 411, 526, 527, 528;~~
~~dd) 412-414, 415-416, 417, 529, 530, 531;~~
~~ee) 418-420, 421-422, 423, 532, 533, 534;~~
~~ff) 424-426, 427-428, 429, 535, 536, 537;~~
~~gg) 430-432, 433-434, 435, 538, 539, 540;~~
~~hh) 436-438, 439-440, 441, 541, 542, 543;~~
~~ii) 442-444, 445-446, 447, 544, 545, 546;~~
~~jj) 448-450, 451-452, 453, 547, 548, 549;~~
~~kk) 454-456, 457-458, 459, 550, 551, 552;~~
~~ll) 460-462, 463-464, 465, 553, 554, 555;~~
~~mm) 466-468, 469-470, 471, 556, 557, 558;~~
~~nn) 472-474, 475-476, 477, 559, 560, 561;~~
~~oo) 478-480, 481-482, 483, 562, 563, 564;~~
~~pp) 484-486, 487-488, 489, 565, 566, 567;~~
~~qq) 490-492, 493-494, 495, 568, 569, 570;~~
~~rr) 496-498, 499-500, 501, 571, 572, 573;~~
~~ss) 502-504, 505-506, 507, 574, 575, 576; and~~

~~tt) 508-510, 511-512, 513, 577, 578, 579.~~

~~59. The CD70-specific CAR of claim 56, wherein the antigen-binding molecule comprises:~~

~~a) a variable light chain domain comprising an amino acid sequences for CDRH1, CDRH2, and CDRH3, respectively, selected from one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, and 380; and~~

~~b) a variable heavy chain domain comprising amino acid sequences for CDRL1, CDRL2, and CDRH3, respectively, selected from one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, and 381.~~

~~60. The CD70-specific CAR of claim 59, wherein the antigen-binding molecule comprises amino acid sequences for light chain variable domain and heavy chain variable domain, respectively, selected from one of SEQ ID NOs:~~

- ~~a) 1 and 2;~~
- ~~b) 3 and 4;~~
- ~~c) 5 and 6;~~
- ~~d) 7 and 8;~~
- ~~e) 9 and 10;~~
- ~~f) 11 and 12;~~
- ~~g) 13 and 14;~~
- ~~h) 15 and 16;~~
- ~~i) 17 and 18;~~
- ~~j) 19 and 20;~~
- ~~k) 21 and 22;~~
- ~~l) 23 and 24;~~
- ~~m) 25 and 26;~~
- ~~n) 27 and 28;~~
- ~~o) 29 and 30;~~
- ~~p) 31 and 32;~~
- ~~q) 33 and 34;~~
- ~~r) 35 and 36;~~

- s) ~~37 and 38;~~
- t) ~~39 and 40;~~
- u) ~~41 and 42;~~
- v) ~~43 and 44;~~
- w) ~~45 and 46;~~
- x) ~~47 and 48;~~
- y) ~~338 and 339;~~
- z) ~~340 and 341;~~
- aa) ~~342 and 343;~~
- bb) ~~344 and 345;~~
- cc) ~~346 and 347;~~
- dd) ~~348 and 349;~~
- ee) ~~350 and 351;~~
- ff) ~~352 and 353;~~
- gg) ~~354 and 355;~~
- hh) ~~356 and 357;~~
- ii) ~~358 and 359;~~
- jj) ~~360 and 361;~~
- kk) ~~362 and 363;~~
- ll) ~~364 and 365;~~
- mm) ~~366 and 367;~~
- nn) ~~368 and 369;~~
- oo) ~~370 and 371;~~
- pp) ~~372 and 373;~~
- qq) ~~374 and 375;~~
- rr) ~~376 and 377;~~
- ss) ~~378 and 379; and~~
- tt) ~~380 and 381.~~

61. The CD70-specific CAR of any one of claims 56 to 60, wherein the intracellular signaling domain comprises a CD3 ζ signalling domain.

~~62. The CD70-specific CAR of any one of claims 56 to 61, wherein the intracellular signaling domain comprises a 4-1BB domain.~~

~~63. The CD70-specific CAR of any one of claims 56 to 62, further comprising a second intracellular signaling domain.~~

~~64. The CD70-specific CAR of claim 63, wherein the second intracellular signaling domain comprises a 4-1BB domain.~~

~~65. The CD70-specific CAR of any one of claims 56 to 64, further comprising a stalk domain between the extracellular ligand binding domain and the first transmembrane domain.~~

~~66. The CD70-specific CAR of claim 65, wherein the stalk domain is selected from the group consisting of: a human CD8 α hinge, an IgG1 hinge, and an Fc γ RIII α hinge.~~

~~67. The CD70-specific CAR of any one of claims 56 to 66, further comprising a CD20 epitope.~~

~~68. The CD70-specific CAR of claim 67 wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 293 or SEQ ID NO: 294 or SEQ ID NO: 609.~~

~~69. The CD70-specific CAR of any one of claims 56 to 68, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain.~~

~~70. The CD70-specific CAR of any one of claims 56 to 69, further comprising another extracellular ligand binding domain which is not specific for CD70.~~

~~71. The CD70-specific CAR of any one of claims 56 to 70, wherein the extracellular ligand-binding domain(s), the first transmembrane domain, and intracellular signaling domain(s) are on a single polypeptide.~~

~~72. The CD70-specific CAR of any one of claims 56 to 70, further comprising a second transmembrane domain, wherein the first transmembrane domain and the extracellular ligand-binding domain(s) are on a first polypeptide, and wherein the second transmembrane domain and the intracellular signaling domain(s) are on a second polypeptide, wherein the first transmembrane domain comprises a transmembrane domain from the α chain of the high-affinity~~

~~IgE receptor (FcεRI) and the second transmembrane domain comprises a transmembrane domain from the γ or β chain of FcεRI.~~

~~73. The CD70-specific CAR of claim 72, further comprising a third polypeptide comprising a third transmembrane domain fused to an intracellular signaling domain from a co-stimulatory molecule, wherein the third transmembrane domain comprises a transmembrane domain from the γ or β chain of FcεRI.~~

~~74. A polynucleotide comprising a nucleic acid sequence encoding the CD70-specific CAR of any one of claims 56 to 73.~~

~~75. An expression vector comprising the polynucleotide of claim 74.~~

~~76. An engineered immune cell expressing at its cell surface membrane a CD70-specific CAR of any one of claims 56 to 73.~~

~~77. The engineered immune cell of claim 76, further comprising another CAR which is not specific for CD70.~~

~~78. The engineered immune cell of claim 76 or 77, further comprising a polynucleotide encoding a suicide polypeptide.~~

~~79. The engineered immune cell of claim 78, wherein the suicide polypeptide is RQR8.~~

~~80. The engineered immune cell of any one of claims 76 to 79, wherein the immune cell is derived from an inflammatory T-lymphocyte, a cytotoxic T-lymphocyte, a regulatory T-lymphocyte, or a helper T-lymphocyte.~~

~~81. The engineered immune cell of claim any one of claims 76 to 80, further comprising a disruption one or more endogenous genes, wherein the endogenous gene encodes TCR α , TCR β , CD52, glucocorticoid receptor (GR), deoxycytidine kinase (dCK), CD70 or an immune checkpoint protein such as for example programmed death-1 (PD-1).~~

~~82. The engineered immune cell of claim any one of claims 76 to 81, further comprising a disruption of TCR α and CD52, or TCR α , CD52 and CD70.~~

~~83. The engineered immune cell of any one of claims 76 to 82, wherein the immune cell is obtained from a healthy donor.~~

~~84. The engineered immune cell of any one of claims 76 to 82, wherein the immune cell is obtained from a patient.~~

~~85. The engineered immune cell of any one of claims 76 to 84 for use as a medicament.~~

~~86. The engineered immune cell of claim 85, wherein the medicament is for use in treatment of a cancer.~~

~~87. The engineered immune cell of claim 86, wherein, the cancer is selected from the group consisting of Renal Cell Carcinoma, Glioblastoma, glioma such as low grade glioma, Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD), Waldenstrom's macroglobulinemia, Acute Myeloid Leukemia, Multiple Myeloma, diffuse large cell lymphoma, follicular lymphoma and Non-Small Cell Lung Cancer.~~

~~88. A population of cells according to any one of claims 76 to 87, wherein~~

~~a) said population of cells comprises a percentage of stem cell memory and central memory cells greater than 20%, 30% or 40%, and/or~~

~~b) said population of cells achieves a percentage of lysis of CD70-expressing cells at day 6 greater than 10%, 20%, 30% or 40% upon recursive CD70-expressing cells as measured using the assay disclosed in example 4.~~

~~89. The population of cells of claim 88, wherein said population of cells achieves a percentage of lysis of CD70-expressing cells at day 6 greater than 20% upon recursive CD70-expressing cells as measured using the assay disclosed in example 4.~~

~~90. A method of engineering an immune cell, comprising:~~

~~a) providing an immune cell; and~~

~~b) introducing into the cell at least one polynucleotide encoding said CD70-specific CAR according to any one of claims 56 to 73.~~

~~91. The method of engineering an immune cell of claim 90, further comprising introducing at least one other CAR which is not specific for CD70.~~

92. An immune cell expressing at the surface a CD70-specific CAR according to any one of claims 56 to 73 for use as a medicament

93. A pharmaceutical composition comprising the engineered immune cell of any one of claims 76 to 87.

94. Use of the pharmaceutical composition of claim 93 in the manufacture of a medicament for the treatment of a condition associated with malignant cells expressing CD70.

95. The use according to claim 94, wherein the condition is a cancer.

96. The use according to claim 95, wherein the cancer is selected from the group consisting of Renal Cell Carcinoma, Glioblastoma, glioma such as low grade glioma, Non-Hodgkin's Lymphoma (NHL), Hodgkin's Disease (HD), Waldenstrom's macroglobulinemia, Acute Myeloid Leukemia, Multiple Myeloma, diffuse large-cell lymphoma, follicular lymphoma and Non-Small Cell Lung Cancer.

97. Use of the pharmaceutical composition of claim 93 in the manufacture of a medicament for the treatment of tumor growth or progression.

98. Use of the pharmaceutical composition of claim 93 in the manufacture of a medicament for the treatment of metastasis of malignant cells expressing CD70.

99. Use of the pharmaceutical composition of claim 93 in the manufacture of a medicament for the treatment of a tumor.

CLAIMS

1. A chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain that specifically binds to CD70, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular ligand-binding domain comprises a variable heavy chain domain comprising amino acid sequences for CDRH1, CDRH2, and CDRH3 and a variable light chain domain comprising amino acid sequences for CDRL1, CDRL2, and CDRL3, wherein:
 - the CDRH1 comprises an amino acid sequence selected from SEQ ID NOs: 97-99,
 - the CDRH2 comprises an amino acid sequence selected from SEQ ID NOs: 100-101,
 - the CDRH3 comprises the amino acid sequence of SEQ ID NO: 102,
 - the CDRL1 comprises the amino acid sequence of SEQ ID NO: 217,
 - the CDRL2 comprises the amino acid sequence of SEQ ID NO: 218, and
 - the CDRL3 comprises the amino acid sequence of SEQ ID NO: 219.
2. The CD70-specific CAR of claim 1, wherein the intracellular signaling domain comprises a CD3 ζ signaling domain.
3. The CD70-specific CAR of claim 1, wherein the intracellular signaling domain comprises a 4-1BB domain.
4. The CD70-specific CAR of claim 2, further comprising a second intracellular signaling domain.
5. The CD70-specific CAR of claim 4, wherein the second intracellular signaling domain comprises a 4-1BB domain.
6. The CD70-specific CAR of claim 1, further comprising a stalk domain between the extracellular ligand-binding domain and the first transmembrane domain.
7. The CD70-specific CAR of claim 6, wherein the stalk domain is selected from the group consisting of: a human CD8 α hinge, an IgG1 hinge, and an Fc γ RIII α hinge.
8. The CD70-specific CAR of claim 1, further comprising a CD20 epitope.
9. The CD70-specific CAR of claim 8 wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 293 or SEQ ID NO: 294 or SEQ ID NO: 609.
10. The CD70-specific CAR of claim 1, wherein the first transmembrane domain comprises a CD8 α chain transmembrane domain.

11. The CD70-specific CAR of claim 1, further comprising another extracellular ligand-binding domain which is not specific for CD70.
12. The CD70-specific CAR of claim 1, wherein the extracellular ligand-binding domain(s), the first transmembrane domain, and intracellular signaling domain(s) are on a single polypeptide.
13. A polynucleotide comprising a nucleic acid sequence encoding the CD70-specific CAR of claim 1.
14. An expression vector comprising the polynucleotide of claim 13.
15. An engineered immune cell expressing at its cell-surface membrane a CD70- specific CAR of claim 1.
16. The engineered immune cell of claim 15, further comprising another CAR which is not specific for CD70.
17. The engineered immune cell of claim 15, further comprising a polynucleotide encoding a suicide polypeptide.
18. The engineered immune cell of claim 17, wherein the suicide polypeptide is RQR8.
19. A population of cells of claim 15, wherein said population of cells comprises a percentage of stem cell memory and central memory cells greater than 20%, 30% or 40%.
20. The population of cells of claim 19, wherein the population of cells achieves lysis of greater than 20% of CD70 expressing cells at day 6 greater than 20% upon repeated exposure of the population of cells to CD70 expressing cells as measured using the assay disclosed in example 4.
21. A method of engineering an immune cell, comprising:
a) providing an immune cell; and
b) introducing into the cell at least one polynucleotide encoding the CD70-specific CAR of claim 1.
22. The method of engineering an immune cell of claim 21, further comprising introducing at least one other CAR which is not specific for CD70.
23. A pharmaceutical composition comprising the engineered immune cell of claim 15.
24. The CD70-specific CAR of claim 1, wherein the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 17 and the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 18.

25. The CD70-specific CAR of claim 1, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 619.
26. The CD70-specific CAR of claim 1, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 628.
27. An engineered immune cell expressing at its cell-surface membrane the CD70- specific CAR of claim 25.
28. An engineered immune cell expressing at its cell-surface membrane the CD70- specific CAR of claim 26.
29. An engineered immune cell expressing at its cell-surface membrane the CD70- specific CAR of claim 24.
30. The engineered immune cell of claim 29, wherein the engineered immune cell further comprises a polynucleotide encoding a suicide polypeptide.
31. The engineered immune cell of claim 30, wherein the suicide polypeptide comprises RSRQR or R2S.
32. The engineered immune cell of claim 17, wherein the suicide polypeptide comprises RSRQR or R2S.
33. A chimeric antigen receptor (CAR) comprising an extracellular ligand-binding domain that specifically binds to CD70, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular ligand-binding domain comprises a variable light chain domain comprising the amino acid sequence of SEQ ID NO: 18 and a variable light chain domain comprising the amino acid sequence of SEQ ID NO: 17.
34. An engineered immune cell expressing at its cell-surface membrane a CD70-specific CAR of claim 33.
35. The engineered immune cell of claim 34, wherein the engineered immune cell further comprises a polynucleotide encoding a suicide polypeptide.
36. The engineered immune cell of claim 35, wherein the suicide polypeptide comprises RSRQR or R2S.
37. The CD70-specific CAR of claim 1, further comprising a suicide polypeptide.
38. The CD70-specific CAR of claim 37, wherein the suicide polypeptide comprises RSRQR or R2S.

- 39. An engineered immune cell expressing at its cell-surface membrane a CD70- specific CAR of claim 38.
- 40. A pharmaceutical composition comprising the engineered immune cell of claim 27.
- 41. A pharmaceutical composition comprising the engineered immune cell of claim 28.
- 42. A pharmaceutical composition comprising the engineered immune cell of claim 29.
- 43. A pharmaceutical composition comprising the engineered immune cell of claim 31.
- 44. A pharmaceutical composition comprising the engineered immune cell of claim 32.
- 45. A pharmaceutical composition comprising the engineered immune cell of claim 34.
- 46. A pharmaceutical composition comprising the engineered immune cell of claim 36.
- 47. A pharmaceutical composition comprising the engineered immune cell of claim 39.