

What is claimed is:

1. A modified T lymphocyte comprising:
 - a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a first intracellular signaling domain, wherein said first polypeptide does not comprise a co-stimulatory domain; and
 - b. a second polypeptide comprising a second extracellular antigen binding domain binding a second antigen, or a receptor that binds said second antigen; and a second intracellular signaling domain;wherein said modified lymphocyte becomes maximally cytotoxic only when said first signaling domain and said second signaling domain are both activated by said first antigen and said second antigen, respectively.
2. The modified T lymphocyte of claim 1, wherein binding of said first antigen to said first antigen binding domain without binding of said second antigen to said second binding domain, or binding of said second antigen to said second antigen binding domain without binding of first second antigen to said first binding domain induces anergy of said modified T lymphocyte.
3. The modified T lymphocyte of claim 1, wherein said first antigen binding domain and said second antigen binding domain are independently an antigen-binding portion of a receptor or an antigen-binding portion of an antibody.
4. The modified T lymphocyte of claim 3, wherein either or both of said first antigen binding domain or said second antigen binding domain are scFv antibody fragments.
5. The modified T lymphocyte of claim 1, wherein said first polypeptide additionally comprises a transmembrane domain.
6. The modified T lymphocyte of claim 1, wherein said second polypeptide additionally comprises a transmembrane domain.
7. The modified T lymphocyte of any of claims 1-6, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.
8. The modified T lymphocyte of claim 1, wherein said first antigen is an antigen on a tumor cell.

9. The modified T lymphocyte of claim 8, wherein said tumor cell is a cell in a solid tumor.

10. The modified T lymphocyte of claim 8, wherein said antigen is a tumor-associated antigen or a tumor-specific antigen.

11. The modified T lymphocyte of claim 10, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), PSMA, BCMA, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostatein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

12. The modified T lymphocyte of claim 1, wherein said first antigen is integrin $\alpha\beta3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

13. The modified T lymphocyte of claim 1, wherein said first intracellular signaling domain comprises a polypeptide sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

14. The modified T lymphocyte of claim 13, wherein said polypeptide sequence is a CD3 ζ signaling domain.

15. The modified T lymphocyte of claim 1, wherein said second antigen is a growth factor, cytokine, or interleukin.

16. The modified T lymphocyte of claim 15, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

17. The modified T lymphocyte of claim 15, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

18. The modified T lymphocyte of claim 1, wherein signal transduction by said second polypeptide is induced by activation of a hypoxia-associated factor.

19. The modified T lymphocyte of claim 18, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

20. The modified T lymphocyte of claim 1, wherein said second antigen is an interleukin.

21. The modified T lymphocyte of claim 1, wherein said second antigen is a damage associated molecular pattern molecule (DAMP; also known as an alarmin).

22. The modified T lymphocyte of claim 21, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

23. The modified T lymphocyte of claim 1, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

24. The modified T lymphocyte of any of claims 1-23, wherein said second polypeptide comprises one or more co-stimulatory domains.

25. The modified T lymphocyte of claim 24, wherein said one or more co-stimulatory domains comprises one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

26. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is an angiogenic or vasculogenic factor, and one or more co-stimulatory molecule signaling motifs.

27. The modified T lymphocyte of claim 26, wherein said angiogenic factor is VEGF.

28. The modified T lymphocyte of claim 26, wherein said one or more co-stimulatory molecule signaling motifs comprise co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

29. The modified T lymphocyte of claim 28, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is VEGF, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

30. The modified T lymphocyte of claim 1, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

31. The modified T lymphocyte of claim 29, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

32. The modified T lymphocyte of claim 31, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGF β) receptor.

33. The modified T lymphocyte of claim 26, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is VEGF, an IL-7 receptor intracellular T cell survival motif, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

34. The modified T lymphocyte of claim 1, wherein said first antigen is a tumor-specific antigen or a tumor-associated antigen, and said first intracellular signaling domain comprises a CD3 ζ signaling domain; and wherein said second polypeptide comprises an antigen-binding domain that binds said second antigen, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

35. The modified T lymphocyte of claim 34, wherein said second polypeptide further comprises an intracellular T cell survival motif.

36. The modified T lymphocyte of claim 35, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an

intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGF β) receptor.

37. The modified T lymphocyte of claim 36, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7R.

38. The modified T lymphocyte of claim 34, wherein said second antigen is VEGF.

39. The modified T lymphocyte of claim 34, wherein said second antigen is IL-4.

40. The modified T lymphocyte of claim 36, wherein said second antigen is VEGF.

41. The modified T lymphocyte of claim 36, wherein said second antigen is IL-4.

42. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is an interleukin, and one or more co-stimulatory molecule signaling motifs.

43. The modified T lymphocyte of claim 42, wherein said interleukin is IL-4.

44. The modified T lymphocyte of claim 43, wherein said second antigen binding domain is an IL-4-binding portion of an IL-4 receptor.

45. The modified T lymphocyte of claim 44, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

46. The modified T lymphocyte of claim 45, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGF β) receptor.

47. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an IL-4-binding portion of an IL-4 receptor, an IL-7 receptor intracellular T cell survival motif, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

48. A modified T lymphocyte comprising:

a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a first intracellular signaling domain; and

b. a second polypeptide comprising a second extracellular antigen binding domain binding a second antigen, or a receptor that binds said second antigen; and a second intracellular signaling domain, wherein said second polypeptide does not comprise a co-stimulatory domain;

wherein said modified lymphocyte becomes maximally cytotoxic only when said first signaling domain and said second signaling domain are both activated by said first antigen and said second antigen, respectively.

49. The modified T lymphocyte of claim 48, wherein binding of said first antigen to said first antigen binding domain without binding of said second antigen to said second binding domain, or binding of said second antigen to said second antigen binding domain without binding of first second antigen to said first binding domain induces anergy of said modified T lymphocyte.

50. The modified T lymphocyte of claim 48, wherein said first antigen-binding domain and said antigen-binding domain are independently an antigen-binding portion of a receptor or an antigen-binding portion of an antibody.

51. The modified T lymphocyte of claim 50, wherein either or both of said first antigen binding domain or said second antigen binding domain are scFv antibody fragments.

52. The modified T lymphocyte of claim 48, wherein said first polypeptide additionally comprises a transmembrane domain.

53. The modified T lymphocyte of claim 48, wherein said second polypeptide additionally comprises a transmembrane domain.

54. The modified T lymphocyte of any of claims 48-53, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

55. The modified T lymphocyte of claim 43, wherein said first antigen is an antigen on a tumor cell.

56. The modified T lymphocyte of claim 55, wherein said tumor cell is a cell in a solid tumor.

57. The modified T lymphocyte of claim 55, wherein said first antigen is a tumor-associated antigen or a tumor-specific antigen.

58. The modified T lymphocyte of claim 57, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), PSMA, BCMA, alpha-

fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostatein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

59. The modified T lymphocyte of claim 48, wherein said first antigen is integrin $\alpha\beta 3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

60. The modified T lymphocyte of claim 48, wherein said second intracellular signaling domain comprises a polypeptide sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

61. The modified T lymphocyte of claim 60, wherein said polypeptide sequence is a CD3 ζ signaling domain.

62. The modified T lymphocyte of claim 48, wherein said second antigen is a growth factor, cytokine, or interleukin.

63. The modified T lymphocyte of claim 62, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

64. The modified T lymphocyte of claim 62, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

65. The modified T lymphocyte of claim 48, wherein signal transduction by said second chimeric receptor is induced by activation of a hypoxia-associated factor.

66. The modified T lymphocyte of claim 65, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

67. The modified T lymphocyte of claim 48, wherein said second antigen is an interleukin.

68. The modified T lymphocyte of claim 48, wherein said second antigen is a DAMP.

69. The modified T lymphocyte of claim 68, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

70. The modified T lymphocyte of claim 48, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

71. The modified T lymphocyte of any of claims 48-70, wherein said first polypeptide comprises one or more co-stimulatory domains.

72. The modified T lymphocyte of claim 71 or claim 72, wherein said one or more co-stimulatory domains comprises one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

73. The modified T lymphocyte of claim 48, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

74. The modified T lymphocyte of claim 73, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGF β) receptor.

75. A modified T lymphocyte comprising:

- a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, an intracellular signaling domain, and one or more co-stimulatory motifs; and

b. a second polypeptide comprising a second extracellular antigen binding domain that binds a second antigen, and a T cell survival motif, wherein said second polypeptide does not comprise an intracellular signaling domain or a co-stimulatory motif; wherein said modified lymphocyte survives only when said intracellular signaling domain and said T cell survival motif are both activated by said first antigen and said second antigen, respectively.

76. The modified T lymphocyte of claim 75, wherein said T cell survival motif is an IL-7 receptor intracellular T cell survival motif.

77. The modified T lymphocyte of claim 75, wherein said intracellular signaling domain is or comprises a CD3 ζ signaling domain.

78. The modified T lymphocyte of claim 75, wherein said one or more co-stimulatory motifs comprise one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

79. The modified T lymphocyte of claim 75, wherein said first antigen is an antigen on a tumor cell.

80. The modified T lymphocyte of claim 79, wherein said tumor cell is a cell in a solid tumor.

81. The modified T lymphocyte of claim 79, wherein said antigen is a tumor-associated antigen or a tumor-specific antigen.

82. The modified T lymphocyte of claim 81, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD19, CD22, CD27, CD30, CD70, GD2

(ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

83. The modified T lymphocyte of claim 75, wherein said first antigen is integrin $\alpha v \beta 3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

84. The modified T lymphocyte of claim 75, wherein said second antigen-binding domain is an IL-4-binding portion of an IL-4 receptor.

85. The modified T lymphocyte of claim 75, wherein said second antigen is a growth factor, cytokine, or interleukin.

86. The modified T lymphocyte of claim 83, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

87. The modified T lymphocyte of claim 86, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

88. The modified T lymphocyte of claim 75, wherein signal transduction by said second chimeric receptor is induced by activation of a hypoxia-associated factor.

89. The modified T lymphocyte of claim 88, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

90. The modified T lymphocyte of claim 75, wherein said second antigen is a damage associated molecular pattern molecule (DAMP; also known as an alarmin).

91. The modified T lymphocyte of claim 90, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

92. The modified T lymphocyte of claim 75, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

93. A modified T lymphocyte comprising:

a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a T cell survival motif, wherein said first polypeptide does not comprise an intracellular signaling domain or a co-stimulatory motif; and

b. a second polypeptide comprising a second extracellular antigen binding domain that binds a second antigen, an intracellular signaling domain and one or more co-stimulatory motifs;

wherein said modified lymphocyte survives only when said T cell survival motif and said intracellular signaling domain are both activated by said first antigen and said second antigen, respectively.

94. The modified T lymphocyte of claim 93, wherein said T cell survival motif is an IL-7 receptor intracellular T cell survival motif.

95. The modified T lymphocyte of claim 93, wherein said intracellular signaling domain is a CD3 ζ signaling domain.

96. The modified T lymphocyte of claim 93, wherein said one or more co-stimulatory motifs comprise one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

97. The modified T lymphocyte of claim 93, wherein said first antigen is an antigen on a tumor cell.

98. The modified T lymphocyte of claim 97, wherein said tumor cell is a cell in a solid tumor.

99. The modified T lymphocyte of claim 97, wherein said antigen is a tumor-associated antigen or a tumor-specific antigen.

100. The modified T lymphocyte of claim 99, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1,

muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

101. The modified T lymphocyte of claim 93, wherein said first antigen is integrin $\alpha v \beta 3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

102. The modified T lymphocyte of claim 93, wherein said second antigen-binding domain is an IL-4-binding portion of an IL-4 receptor.

103. The modified T lymphocyte of claim 93, wherein said second antigen is a growth factor, cytokine, or interleukin.

104. The modified T lymphocyte of claim 93, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

105. The modified T lymphocyte of claim 104, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

106. The modified T lymphocyte of claim 93, wherein signal transduction by said second chimeric receptor is induced by activation of a hypoxia-associated factor.

107. The modified T lymphocyte of claim 106, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

108. The modified T lymphocyte of claim 93, wherein said second antigen is a damage associated molecular pattern molecule (DAMP; also known as an alarmin).

109. The modified T lymphocyte of claim 108, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

110. The modified T lymphocyte of claim 93, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

Claims

1. A modified T lymphocyte comprising:

- a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a first intracellular signaling domain, wherein said first polypeptide does not comprise a co-stimulatory domain; and
- b. a second polypeptide comprising a second extracellular antigen binding domain binding a second antigen, or a receptor that binds said second antigen; and a second intracellular signaling domain;

wherein said second antigen is a growth factor, cytokine, or interleukin, or is a damage associated molecular pattern molecule, or wherein signal transduction by said second polypeptide is induced by activation of a hypoxia-associated factor, and wherein said modified lymphocyte becomes maximally cytotoxic only when said first signaling domain and said second signaling domain are both activated by said first antigen and said second antigen, respectively.

2. The modified T lymphocyte of claim 1, wherein binding of said first antigen to said first antigen binding domain without binding of said second antigen to said second binding domain, or binding of said second antigen to said second antigen binding domain without binding of first second antigen to said first binding domain induces anergy of said modified T lymphocyte.

3. The modified T lymphocyte of claim 1, wherein said first antigen binding domain and said second antigen binding domain are independently an antigen-binding portion of a receptor or an antigen-binding portion of an antibody.

4. The modified T lymphocyte of claim 3, wherein either or both of said first antigen binding domain or said second antigen binding domain are scFv antibody fragments.

5. The modified T lymphocyte of claim 1, wherein said first polypeptide additionally comprises a transmembrane domain.

6. The modified T lymphocyte of claim 1, wherein said second polypeptide additionally comprises a transmembrane domain.

7. The modified T lymphocyte of any of claims 1-6, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

8. The modified T lymphocyte of claim 1, wherein said first antigen is an antigen on a tumor cell.

9. The modified T lymphocyte of claim 8, wherein said tumor cell is a cell in a solid tumor.

10. The modified T lymphocyte of claim 8, wherein said antigen is a tumor-associated antigen or a tumor-specific antigen.

11. The modified T lymphocyte of claim 10, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), PSMA, BCMA, alpha-fetoprotein (AFP), carcino embryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T

lymphocytes; MART-1), myo-DI, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid

transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

12. The modified T lymphocyte of claim 1, wherein said first antigen is integrin $\alpha\text{v}\beta 3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

13. The modified T lymphocyte of claim 1, wherein said first intracellular signaling domain comprises a polypeptide sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

14. The modified T lymphocyte of claim 13, wherein said polypeptide sequence is a CD3 ζ signaling domain.

15. The modified T lymphocyte of claim [[15]] 1, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

16. The modified T lymphocyte of claim [[15]] 1, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

17. The modified T lymphocyte of claim [[18]] 1, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

18. The modified T lymphocyte of claim 1, wherein said second antigen is an interleukin.
19. The modified T lymphocyte of claim 1, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.
20. The modified T lymphocyte of claim 1, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.
21. The modified T lymphocyte of any of claims 1-20, wherein said second polypeptide comprises one or more co-stimulatory domains.
22. The modified T lymphocyte of claim 21, wherein said one or more co-stimulatory domains comprises one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD 134) polypeptide sequence, a co-stimulatory 4-1BB (CD 137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.
23. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is an angiogenic or vasculogenic factor, and one or more co-stimulatory molecule signaling motifs.
24. The modified T lymphocyte of claim 23, wherein said angiogenic factor is VEGF.
25. The modified T lymphocyte of claim 23, wherein said one or more co-stimulatory molecule signaling motifs comprise co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.
26. The modified T lymphocyte of claim 25, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is VEGF, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.
27. The modified T lymphocyte of claim 1, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.
28. The modified T lymphocyte of claim 26, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.
29. The modified T lymphocyte of claim 28, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling

domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGFB) receptor.

30. The modified T lymphocyte of claim 23, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is VEGF, an IL-7 receptor intracellular T cell survival motif, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

31. The modified T lymphocyte of claim 1, wherein said first antigen is a tumor-specific antigen or a tumor-associated antigen, and said first intracellular signaling domain comprises a CD3 ζ signaling domain; and wherein said second polypeptide comprises an antigen-binding domain that binds said second antigen, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

32. The modified T lymphocyte of claim 31, wherein said second polypeptide further comprises an intracellular T cell survival motif.

33. The modified T lymphocyte of claim 32, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGFB) receptor.

34. The modified T lymphocyte of claim 33, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7R.

35. The modified T lymphocyte of claim 31, wherein said second antigen is VEGF.

36. The modified T lymphocyte of claim 31, wherein said second antigen is IL-4.

37. The modified T lymphocyte of claim 33, wherein said second antigen is VEGF.

38. The modified T lymphocyte of claim 33, wherein said second antigen is IL-4.

39. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an antigen-binding domain wherein said antigen is an interleukin, and one or more co-stimulatory molecule signaling motifs.

40. The modified T lymphocyte of claim 39, wherein said interleukin is IL-4.

41. The modified T lymphocyte of claim 40, wherein said second antigen binding domain is an IL-4-binding portion of an IL-4 receptor.

42. The modified T lymphocyte of claim 41, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

43. The modified T lymphocyte of claim 42, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGFB) receptor.

44. The modified T lymphocyte of claim 1, wherein said first polypeptide comprises an extracellular tumor antigen-binding domain and a CD3 ζ signaling domain, and wherein said second polypeptide comprises an IL-4-binding portion of an IL-4 receptor, an IL-7 receptor intracellular T cell survival motif, and co-stimulatory signaling motifs from each of CD27, CD28, OX40, ICOS, and 4-1BB.

45. A modified T lymphocyte comprising:

a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a first intracellular signaling domain; and

b. a second polypeptide comprising a second extracellular antigen binding domain binding a second antigen, or a receptor that binds said second antigen; and a second intracellular signaling domain, wherein said second polypeptide does not comprise a co-stimulatory domain;

wherein said second antigen is a growth factor, cytokine, or interleukin, or is a DAMP, or wherein signal transduction by said second polypeptide is induced by activation of a hypoxia-associated factor, and wherein said modified lymphocyte becomes maximally cytotoxic only when said first signaling domain and said second signaling domain are both activated by said first antigen and said second antigen, respectively.

46. The modified T lymphocyte of claim 45, wherein binding of said first antigen to said first antigen binding domain without binding of said second antigen to said second binding domain, or binding of said second antigen to said second antigen binding domain without binding of first second antigen to said first binding domain induces anergy of said modified T lymphocyte.

47. The modified T lymphocyte of claim 45, wherein said first antigen-binding domain and said antigen-binding domain are independently an antigen-binding portion of a receptor or an antigen-binding portion of an antibody.

48. The modified T lymphocyte of claim 47, wherein either or both of said first antigen binding domain or said second antigen binding domain are scFv antibody fragments.
49. The modified T lymphocyte of claim 45, wherein said first polypeptide additionally comprises a transmembrane domain.
50. The modified T lymphocyte of claim 45, wherein said second polypeptide additionally comprises a transmembrane domain.
51. The modified T lymphocyte of any of claims 45-50, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.
52. The modified T lymphocyte of claim 45, wherein said first antigen is an antigen on a tumor cell.
53. The modified T lymphocyte of claim 52, wherein said tumor cell is a cell in a solid tumor.
54. The modified T lymphocyte of claim 52, wherein said first antigen is a tumor-associated antigen or a tumor-specific antigen.
55. The modified T lymphocyte of claim 54, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), PSMA, BCMA, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-DI, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor- 1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2- PK), CD 19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Spl7), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six- transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.
56. The modified T lymphocyte of claim 45, wherein said first antigen is integrin $\alpha v \beta 3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

57. The modified T lymphocyte of claim 45, wherein said second intracellular signaling domain comprises a polypeptide sequence comprising an immunoreceptor tyrosine-based activation motif (ITAM).

58. The modified T lymphocyte of claim 57, wherein said polypeptide sequence is a CD3 ζ signaling domain.

59. The modified T lymphocyte of claim 45, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

60. The modified T lymphocyte of claim 45, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

61. The modified T lymphocyte of claim 45, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

62. The modified T lymphocyte of claim 45, wherein said second antigen is an interleukin.

63. The modified T lymphocyte of claim 45, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

64. The modified T lymphocyte of claim 45, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

65. The modified T lymphocyte of any of claims 45-64, wherein said first polypeptide comprises one or more co-stimulatory domains.

66. The modified T lymphocyte of claim 64 or claim 65, wherein said one or more co-stimulatory domains comprises one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD 134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

67. The modified T lymphocyte of claim 45, wherein said first polypeptide or said second polypeptide comprises a T cell survival motif.

68. The modified T lymphocyte of claim 67, wherein said T cell survival motif is, or is derived from, an intracellular signaling domain of IL-7 receptor (IL-7R), an intracellular signaling

domain of IL-12 receptor, an intracellular signaling domain of IL-15 receptor, an intracellular signaling domain of IL-21 receptor, or an intracellular signaling domain of transforming growth factor β (TGFB) receptor.

69. A modified T lymphocyte comprising:
- a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, an intracellular signaling domain, and one or more co-stimulatory motifs; and
 - b. a second polypeptide comprising a second extracellular antigen binding domain that binds a second antigen, and a T cell survival motif, wherein said second polypeptide does not comprise an intracellular signaling domain or a co-stimulatory motif;

wherein said second antigen is a growth factor, cytokine, or interleukin, or is a DAMP, or wherein signal transduction by said second polypeptide is induced by activation of a hypoxia-associated factor, and wherein said modified lymphocyte survives only when said intracellular signaling domain and said T cell survival motif are both activated by said first antigen and said second antigen, respectively.

70. The modified T lymphocyte of claim 69, wherein said T cell survival motif is an IL-7 receptor intracellular T cell survival motif.

71. The modified T lymphocyte of claim 69, wherein said intracellular signaling domain is or comprises a CD3 ζ signaling domain.

72. The modified T lymphocyte of claim 69, wherein said one or more co-stimulatory motifs comprise one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD 134) polypeptide sequence, a co-stimulatory 4-1BB (CD 137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

73. The modified T lymphocyte of claim 69, wherein said first antigen is an antigen on a tumor cell.

74. The modified T lymphocyte of claim 73, wherein said tumor cell is a cell in a solid tumor.

75. The modified T lymphocyte of claim 73, wherein said antigen is a tumor-associated antigen or a tumor-specific antigen.

76. The modified T lymphocyte of claim 75, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1,

epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD 117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-DI, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor- 1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD 19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostatein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

77. The modified T lymphocyte of claim 69, wherein said first antigen is integrin $\alpha\beta3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

78. The modified T lymphocyte of claim 69, wherein said second antigen-binding domain is an IL-4-binding portion of an IL-4 receptor.

79. The modified T lymphocyte of claim 69, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

80. The modified T lymphocyte of claim 79, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

81. The modified T lymphocyte of claim 69, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

82. The modified T lymphocyte of claim ~~[[90]]~~ 69, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

83. The modified T lymphocyte of claim 69, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.

84. A modified T lymphocyte comprising:

a. a first polypeptide comprising a first extracellular antigen binding domain that binds a first antigen, and a T cell survival motif, wherein said first polypeptide does not comprise an intracellular signaling domain or a co-stimulatory motif; and

b. a second polypeptide comprising a second extracellular antigen binding domain that binds a second antigen, an intracellular signaling domain and one or more co-stimulatory motifs; wherein said second antigen is a growth factor, cytokine, or interleukin, or is a damage associated molecular pattern molecule, or wherein signal transduction by said second polypeptide is induced by activation of a hypoxia-associated factor, and wherein said modified lymphocyte survives only when said T cell survival motif and said intracellular signaling domain are both activated by said first antigen and said second antigen, respectively.

85. The modified T lymphocyte of claim 84, wherein said T cell survival motif is an IL-7 receptor intracellular T cell survival motif.

86. The modified T lymphocyte of claim 84, wherein said intracellular signaling domain is a CD3 ζ signaling domain.

87. The modified T lymphocyte of claim 84, wherein said one or more co-stimulatory motifs comprise one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD 134) polypeptide sequence, a co-stimulatory 4- IBB (CD 137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence.

88. The modified T lymphocyte of claim 84, wherein said first antigen is an antigen on a tumor cell.

89. The modified T lymphocyte of claim 88, wherein said tumor cell is a cell in a solid tumor.

90. The modified T lymphocyte of claim 88, wherein said antigen is a tumor- associated antigen or a tumor-specific antigen.

91. The modified T lymphocyte of claim 90, wherein said tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD34, CD45, CD99, CD 117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFF-15), HMB-45 antigen, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-DI, muscle-

specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysin, thyroglobulin, thyroid transcription factor- 1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), CD 19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostatein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein.

92. The modified T lymphocyte of claim 84, wherein said first antigen is integrin $\alpha\beta3$ (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene) or Ral-B.

93. The modified T lymphocyte of claim 84, wherein said second antigen-binding domain is an IL-4-binding portion of an IL-4 receptor.

94. The modified T lymphocyte of claim 84, wherein said second antigen is a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis.

95. The modified T lymphocyte of claim 94, wherein said second antigen is vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8).

96. The modified T lymphocyte of claim 84, wherein said hypoxia-associated factor is hypoxia-inducible factor-1 α (HIF-1 α), HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β .

97. The modified T lymphocyte of claim 84, wherein said DAMP is a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

98. The modified T lymphocyte of claim 84, wherein said second antigen is an antigen on an antibody that binds to an antigen presented by a tumor cell.