CLAIMS

WHAT IS CLAIMED IS:

1. A recombinant nucleic acid molecule comprising a sequence encoding a T cell receptor (TCR) fusion protein (TFP) wherein the TFP comprises:

   (a) a TCR subunit comprising:

   (i) at least a portion of a TCR extracellular domain, and

   (ii) a TCR transmembrane domain,

   (iii) a TCR intracellular domain, and

   (b) an antigen binding domain that specifically binds CD70; and

   wherein the TCR subunit and the antigen binding domain are operatively linked.

2. The recombinant nucleic acid molecule of claim 1, wherein the TFP functionally interacts with an endogenous TCR complex when expressed in a T cell.

3. The recombinant nucleic acid molecule of claim 1 or 2, wherein the TCR intracellular domain comprises a stimulatory domain from an intracellular signaling domain of CD3 gamma, CD3 delta, or CD3 epsilon.

4. The recombinant nucleic acid molecule of any one of claims 1-3, wherein a T cell expressing the TFP exhibits increased cytotoxicity to a human cell expressing CD70 compared to a T cell not containing the TFP.

5. The recombinant nucleic acid molecule of any one of claims 1-4, wherein the antigen binding domain is connected to the TCR extracellular domain by a linker sequence.

6. The recombinant nucleic acid molecule of claim 5, wherein the linker is 120 amino acids in length or less.

7. The recombinant nucleic acid molecule of claim 5, wherein the linker sequence comprises $(G_4S)_n$, wherein G is glycine, S is serine, and n is an integer from 1 to 10.

8. The recombinant nucleic acid molecule of claim 7, wherein n is an integer from 1 to 4.

9. The recombinant nucleic acid molecule of any one of claims 1-8, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from the same TCR subunit.

10. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR alpha, TCR beta, TCR gamma, TCR delta, CD3 epsilon, CD3 delta, or CD3 gamma.

~~11. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR beta.~~

~~12. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR gamma.~~

~~13. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from TCR delta.~~

~~14. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 epsilon.~~

~~15. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 delta.~~

~~16. The recombinant nucleic acid molecule of claim 9, wherein at least two of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 gamma.~~

~~17.~~11. The recombinant nucleic acid molecule of any one of claims 1-10~~9-16~~, wherein all three of the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from the same TCR subunit.

~~18.~~12. The recombinant nucleic acid molecule of claim 11~~17~~, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 epsilon, CD3 delta, or CD3 gamma.

~~19. The recombinant nucleic acid molecule of claim 17, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 delta.~~

~~20. The recombinant nucleic acid molecule of claim 17, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain are from CD3 gamma.~~

~~21.~~13. The recombinant nucleic acid molecule of claim 12~~17~~, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain comprise the constant domain of TCR alpha, the constant domain of TCR beta, the constant domain of TCR gamma, or the constant domain of TCR delta.

~~22.~~14. The recombinant nucleic acid molecule of claim 13~~21~~, wherein the constant domain of TCR alpha or the constant domain of TCR beta is murine.

~~23. The recombinant nucleic acid molecule of claim 17, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain comprise the constant domain of TCR beta.~~

~~24. The recombinant nucleic acid molecule of claim 23, wherein the constant domain of TCR beta is murine.~~

~~25. The recombinant nucleic acid molecule of claim 17, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain comprise the constant domain of TCR gamma.~~

~~26. The recombinant nucleic acid molecule of claim 17, wherein the TCR extracellular domain, the TCR transmembrane domain, and the TCR intracellular domain comprise the constant domain of TCR delta.~~

~~27.~~15. The recombinant nucleic acid molecule of any one of claims 1-14~~26~~, wherein the antigen binding domain is a camelid antibody or binding fragment thereof, a murine antibody or binding fragment thereof, or a human or humanized antibody or binding fragment thereof.

~~28. The recombinant nucleic acid molecule of any one of claims 1-26, wherein the antigen binding domain is a murine antibody or binding fragment thereof.~~

~~29. The recombinant nucleic acid molecule of any one of claims 1-26, wherein the antigen binding domain is a human or humanized antibody or binding fragment thereof.~~

~~30.~~16. The recombinant nucleic acid molecule of any one of claims 1-15,~~29~~ wherein the antigen binding domain is a single-chain variable fragment (scFv) or a single domain antibody (sdAb) domain.

~~31. The recombinant nucleic acid molecule of any one of claims 1-30, wherein the antigen binding domain is a single domain antibody (sdAb).~~

~~32.~~17. The recombinant nucleic acid molecule of claim 16~~31~~, wherein the sdAb is a V_{HH}.

~~33.~~18. The recombinant nucleic acid molecule of any one of claims 1-17~~32~~, wherein the antigen binding domain binds to human CD70 with a K_D value of 100 nM or less or from about 0.001 nM to about 100 nM.

~~34.~~19. The recombinant nucleic acid molecule of any one of claims 1-18~~33~~, wherein:

(i) the antigen binding domain does not compete with CD27 for binding to CD70, does not inhibit CD70 from interacting with CD27, and/or does not bind to the same epitope of CD70 to which CD27 binds; or

(ii) the antigen binding domain competes with CD27 for binding to CD70, inhibits CD70 from interacting with CD27, and/or binds to the same epitope of CD70 to which CD27 binds.

~~35. The recombinant nucleic acid molecule of any one of claims 1-33, wherein the antigen binding domain competes with CD27 for binding to CD70, inhibits CD70 from interacting with CD27, and/or binds to the same epitope of CD70 to which CD27 binds.~~

~~36.~~20. The recombinant nucleic acid molecule of any one of claims 1-18~~33~~, wherein the antigen binding domain specifically binds to an epitope that is within the amino acid sequence HRDGIYMVHIQVTLAICSSTTAS (SEQ ID NO:1230).

~~37.~~21. The recombinant nucleic acid molecule of claim ~~36~~20, wherein the antigen binding domain comprises a scFv having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 1207-1222, 1246, and 1247 , a scFv having at least about 90% sequence identity to residues 23-268 of SEQ ID NO: 1236, or a sdAb domain having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 618, 1224-1227.

~~38. The recombinant nucleic acid molecule of claim 36, wherein the antigen binding domain comprises a sdAb domain having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 1223-1227.~~

~~39.~~22. The recombinant nucleic acid molecule of any one of claims 1-20~~35~~, wherein the antigen binding domain comprises a variable domain comprising a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, and having at least 90% sequence identity to any one of SEQ ID NOs: 603-620 and 622-688.

~~40. The recombinant nucleic acid molecule of any one of claims 1-35 and39, wherein the antigen binding domain comprises a variable domain having at least 90% sequence identity to any one of SEQ ID NOs: 603-620 and 622-688.~~

~~41.~~23. The recombinant nucleic acid molecule of ~~any one of~~ claim~~s~~ 22~~1-35 and 39~~, wherein

(i) CDR1 comprises a sequence of any one of SEQ ID NOs: 87-104 and 107-172;

(ii) CDR2 comprises a sequence of any one of SEQ ID NOs: 259-276 and 279-344; and

(iii) CDR3 comprises a sequence of any one of SEQ ID NOs: 431-448 and 451-516.

~~42. The recombinant nucleic acid molecule of any one of claims 1-35 and 39, wherein the antigen binding domain comprises a variable domain having at least 90% sequence identity to SEQ ID NO: 618.~~

~~43. The recombinant nucleic acid molecule of claim 42, wherein the variable domain has at least 95% sequence identity to SEQ ID NO: 618.~~

~~44. The recombinant nucleic acid molecule of claim 43, wherein the variable domain comprises the sequence of SEQ ID NOs: 618.~~

~~45. The recombinant nucleic acid molecule of any one of claims 42-44, wherein CDR1 is SEQ ID NO: 102, CDR2 is SEQ ID NO: 274 and CDR3 is SEQ ID NO: 446.~~

~~46. The recombinant nucleic acid molecule of claim 42, wherein the antigen binding domain comprises a sdAb domain having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 1224-1227.~~

~~47.~~24. The recombinant nucleic acid molecule of any one of claims 1-21~~30~~, wherein the antigen binding domain is a single-chain variable fragment (scFv).

~~48.~~25. The recombinant nucleic acid molecule of claim 24~~47~~, wherein the scFv comprises a heavy chain variable (VH) domain having at least 90%, 95%, or 100% sequence identity to any one of SEQ ID NOs: 783-835, and/or a light chain variable (VL) domain having at least 90%, 95%, or 100% sequence identity to any one of SEQ ID NOs: 995-1047.

~~49. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a heavy chain variable (VH) domain having at least 95% sequence identity to any one of SEQ ID NOs: 783-835.~~

~~50. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a heavy chain variable (VH) domain having a sequence of any one of SEQ ID NOs: 783-835.~~

~~51. The recombinant nucleic acid molecule of any one of claims 47-50, wherein the scFv comprises a light chain variable (VL) domain having at least 90% sequence identity to any one of SEQ ID NOs: 995-1047.~~

~~52. The recombinant nucleic acid molecule of any one of claims 47-50, wherein the scFv comprises a light chain variable (VL) domain having at least 95% sequence identity to any one of SEQ ID NOs: 995-1047.~~

~~53. The recombinant nucleic acid molecule of any one of claims 47-50, wherein the scFv comprises a light chain variable (VL) domain having a sequence of any one of SEQ ID NOs: 995-1047.~~

~~54.~~26. The recombinant nucleic acid molecule of ~~any one of~~ claim~~s~~ 24 or 25~~48-53~~, wherein the VH domain comprises a heavy chain complementary determining region 1 (CDRH1) having a sequence of any one of SEQ ID NOs: 836-888, a CDRH2 having a sequence of any one of SEQ ID NOs: 889-941, and a CDRH3 having a sequence of any one of SEQ ID NOs: 942-994, and/or the VL domain comprises a light chain complementary determining region 1 (CDRL1) having a sequence of any one of SEQ ID NOs: 1048-1100, a CDRL2 having a sequence of any one of SEQ ID NOs: 1101-1153, and a CDRL3 having a sequence of any one of SEQ ID NOs: 1154-1206.

~~55. The recombinant nucleic acid molecule of any one of claims 48-54, wherein the VL domain comprises a light chain complementary determining region 1 (CDRL1) having a sequence of any one of SEQ ID NOs: 1048-1100, a CDRL2 having a sequence of any one of SEQ ID NOs: 1101-1153, and a CDRL3 having a sequence of any one of SEQ ID NOs: 1154-1206.~~

~~56.~~27. The recombinant nucleic acid molecule of claim 24~~47~~, wherein the scFv comprises a VH domain having at least 90%, 95%, or 100% sequence identity to any one of SEQ ID NOs:

1248, 1250, 1252, and 800, and/or a VL domain having at least 90%, 95%, or 100% sequence identity to any one of SEQ ID NO: 1249, 1251, 1253, or 1012.

~~57. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1248.~~

~~58. The recombinant nucleic acid molecule of any one of claims 47, 56, and 57, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1249.~~

~~59. The recombinant nucleic acid molecule of any one of claims 47, 56, and 57, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1249.~~

~~60.~~28. The recombinant nucleic acid molecule of claim 24 or 27~~47~~, wherein the scFv comprises:

(i) a VH domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1248, and a VL domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1249;

(ii) a VH domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1250, and a VL domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1251;

(iii) a VH domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1252, and a VL domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1253; or

(iv) a VH domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 800, and a VL domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1012.

~~61. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1248, and a VL domain of the sequence of SEQ ID NO: 1249.~~

~~62.~~29. The recombinant nucleic acid molecule of claim ~~61~~28, wherein:

(i) the VH domain of the sequence of SEQ ID NO: 1248 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1249

(ii) the VL domain of the sequence of SEQ ID NO: 1249 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1248,

(iii) the VH domain of the sequence of SEQ ID NO: 1250 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1251,

(iv) the VL domain of the sequence of SEQ ID NO: 1251 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1250,

(v) the VH domain of the sequence of SEQ ID NO: 1252 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1253,

(vi) the VL domain of the sequence of SEQ ID NO: 1253 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1252, or

(vii) the VH domain of the sequence of SEQ ID NO: 800 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1012, or

(viii) the VL domain of the sequence of SEQ ID NO: 1012 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 800.

~~63. The recombinant nucleic acid molecule of claim 61, wherein the VL domain of the sequence of SEQ ID NO: 1249 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1248.~~

~~64.~~30. The recombinant nucleic acid molecule of ~~any one of~~ claim~~s~~ 28 or 29~~56-63~~, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.

~~65.~~31. The recombinant nucleic acid molecule of claim 29 or 30~~62 or 63~~, wherein the VH domain~~of the sequence of SEQ ID NO: 1248~~ and the VL domain ~~of the sequence of SEQ ID NO: 1249~~ are operably linked via a linker sequence of SEQ ID NO: 1237, and wherein the VH and VL domains are the sequences of SEQ ID NOs: 1248 and 1249, respectively; the sequences of SEQ ID NOs: 1250 and 1251, respectively; or the sequences of SEQ ID NOs: 1252 and 1253, respectively.

~~66. The recombinant nucleic acid molecule of any one of claims 56-65, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1207 or SEQ ID NO: 1208.~~

~~67. The recombinant nucleic acid molecule of any one of claims 56-65, wherein the scFv comprises the sequence of SEQ ID NO: 1207 or SEQ ID NO: 1208.~~

~~68. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1250.~~

~~69. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1250.~~

~~70. The recombinant nucleic acid molecule of any one of claims 47, 68, and 69, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1251.~~

~~71. The recombinant nucleic acid molecule of any one of claims 47, 68, and 69, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1251.~~

~~72. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1250, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1251.~~

~~73. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1250, and a VL domain of the sequence of SEQ ID NO: 1251.~~

74. The recombinant nucleic acid molecule of claim 73, wherein the VH domain of the sequence of SEQ ID NO: 1250 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1251.

75. The recombinant nucleic acid molecule of claim 73, wherein the VL domain of the sequence of SEQ ID NO: 1251 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1250.

76. The recombinant nucleic acid molecule of any one of claims 68-75, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.

77. The recombinant nucleic acid molecule of claim 74 or 75, wherein the VH of the sequence of SEQ ID NO: 1250 and the VL domain of the sequence of SEQ ID NO: 1251 are operably linked via a linker sequence of SEQ ID NO: 1237.

78. The recombinant nucleic acid molecule of any one of claims 68-77, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1209 or SEQ ID NO: 1210.

79. The recombinant nucleic acid molecule of any one of claims 68-77, wherein the scFv comprises the sequence of SEQ ID NO: 1209 or SEQ ID NO: 1210.

80. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1252.

81. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1252.

82. The recombinant nucleic acid molecule of any one of claims 47, 80, and 81, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1253.

83. The recombinant nucleic acid molecule of any one of claims 47, 80, and 81, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1253.

84. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1252, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1253.

85. The recombinant nucleic acid molecule of claim 47, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1252, and a VL domain of the sequence of SEQ ID NO: 1253.

86. The recombinant nucleic acid molecule of claim 85, wherein the VH domain of the sequence of SEQ ID NO: 1252 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1253.

~~87. The recombinant nucleic acid molecule of claim 85, wherein the VL domain of the sequence of SEQ ID NO: 1253 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1252.~~

~~88. The recombinant nucleic acid molecule of any one of claims 80-87, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.~~

~~89. The recombinant nucleic acid molecule of claim 86 or 87, wherein the VH of the sequence of SEQ ID NO: 1252 and the VL domain of the sequence of SEQ ID NO: 1253 are operably linked via a linker sequence of SEQ ID NO: 1237.~~

~~90. The recombinant nucleic acid molecule of any one of claims 80-89, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1246 or SEQ ID NO: 1247.~~

~~91. The recombinant nucleic acid molecule of any one of claims 79-88, wherein the scFv comprises the sequence of SEQ ID NO: 1246 or SEQ ID NO: 1247.~~

~~92.~~32. The recombinant nucleic acid molecule of any one of claims 24-31~~47-91~~, wherein the antigen binding domain specifically binds to a second epitope is within the amino acid sequence ASRHHPTTLAVGICSPASRSISL (SEQ ID NO:1231).

~~93.~~33. The recombinant nucleic acid molecule of claim 32~~92~~, wherein the scFv comprises a VH domain that comprises a CDRH1 of SEQ ID NO: 853, a CDRH2 of SEQ ID NO: 906, and a CDRH3 of SEQ ID NO: 959, and a VL domain that comprises a CDRL1 of SEQ ID NO: 1065, a CDRL2 of SEQ ID NO: 1118, and a CDRL3 of SEQ ID NO: 1171.

~~94.~~34. The recombinant nucleic acid molecule of any one of claims 24-33~~47-93~~, wherein the scFv comprises a VH domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 800, and/or a VL domain having at least 90%, 95%, or 100% sequence identity to SEQ ID NO: 1012.

~~95. The recombinant nucleic acid molecule of any one of claims 47-93, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 800.~~

~~96. The recombinant nucleic acid molecule of any one of claims 47-93, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1012.~~

~~97. The recombinant nucleic acid molecule of any one of claims 47-93, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1012.~~

~~98. The recombinant nucleic acid molecule of any one of claims 47-93, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 800, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1012.~~

~~99. The recombinant nucleic acid molecule of any one of claims 47-93, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 800, and a VL domain of the sequence of SEQ ID NO: 1012.~~

~~100.~~35. The recombinant nucleic acid molecule of any one of claims 24-34~~47-99~~, wherein the scFv comprises a linker sequence of SEQ ID NO: 782.

~~101.~~36. The recombinant nucleic acid molecule of any one of claims 1-34~~100~~, wherein:

(i) a T cell expressing the TFP inhibits tumor growth when expressed in a T cell;

(ii) a T cell expressing the TFP has increased fratricide relative to a TFP having a different antigen binding domain; or

(iii) a T cell expressing the TFP has decreased fratricide relative to a TFP having a different antigen binding domain.

~~102. The recombinant nucleic acid molecule of any one of claims 1-100, wherein a T cell expressing the TFP has increased fratricide relative to a TFP having a different antigen binding domain.~~

~~103. The recombinant nucleic acid molecule of any one of claims 1-100, wherein a T cell expressing the TFP has decreased fratricide relative to a TFP having a different antigen binding domain.~~

~~104.~~37. The recombinant nucleic acid molecule of claim 1, wherein the recombinant nucleic acid molecule encodes any one of the amino acid sequences selected from SEQ ID NOs: 1233, 1236, 1240, and 1264.

~~105.~~38. A recombinant nucleic acid molecule comprising a sequence encoding an antibody or a fragment thereof that specifically binds CD70, wherein the antibody or fragment thereof is the antigen binding domain according to any one of claims 1-37.

~~106. The recombinant nucleic acid molecule of claim 105, wherein the antibody or antibody fragment is a camelid antibody or binding fragment thereof.~~

~~107. The recombinant nucleic acid molecule of claim 105, wherein the antibody or antibody fragment is a murine, human or humanized antibody or binding fragment thereof.~~

~~108. The recombinant nucleic acid molecule of any one of claims 105-107, wherein the antibody or antibody fragment is a single-chain variable fragment (scFv) or a single domain antibody (sdAb) domain.~~

~~109. The recombinant nucleic acid molecule of claim 108, wherein the antibody or antibody fragment is a single domain antibody (sdAb).~~

~~110. The recombinant nucleic acid molecule of claim 109, wherein the sdAb is a V_{HH}.~~

~~111. The recombinant nucleic acid molecule of any one of claims 105-110, wherein the antibody or antibody fragment binds to human CD70 with a K_D value of 100 nM or less or from about 0.001 nM to about 100 nM.~~

112. The recombinant nucleic acid molecule of any one of claims 105-111, wherein the antibody or antibody fragment does not compete with CD27 for binding to CD70, does not inhibit CD70 from interacting with CD27, and/or does not bind to the same epitope of CD70 to which CD27 binds.

113. The recombinant nucleic acid molecule of any one of claims 105-111, wherein the antibody or antibody fragment competes with CD27 for binding to CD70, inhibits CD70 from interacting with CD27, and/or binds to the same epitope of CD70 to which CD27 binds.

114. The recombinant nucleic acid molecule of any one of claims 105-111, wherein the antigen binding domain specifically binds to an epitope that is within the amino acid sequence HRDGIYMVHIQVTLAICSSTTAS (SEQ ID NO:1230).

115. The recombinant nucleic acid molecule of claim 114, wherein the antibody or antibody fragment comprises a scFv having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 1207-1222, 1246, and 1247.

116. The recombinant nucleic acid molecule of claim 114, wherein the antibody or antibody fragment comprises a sdAb domain having at least about 90% sequence identity to any one of sequence of SEQ ID NOs: 1223-1227.

117. The recombinant nucleic acid molecule of any one of claims 105-113, wherein the antibody or antibody fragment comprises a variable domain comprising a CDR1, a CDR2, and a CDR3.

118. The recombinant nucleic acid molecule of any one of claims 105-113 and 117, wherein the antibody or antibody fragment comprises a variable domain having at least 90% sequence identity to any one of SEQ ID NOs: 603-620 and 622-688.

119. The recombinant nucleic acid molecule of any one of claims 105-113 and 117, wherein
(i) CDR1 comprises a sequence of any one of SEQ ID NOs: 87-104 and 107-172;
(ii) CDR2 comprises a sequence of any one of SEQ ID NOs: 259-276 and 279-344; and (iii) CDR3 comprises a sequence of any one of SEQ ID NOs: 431-448 and 451-516.

120. The recombinant nucleic acid molecule of any one of 105-113 and 117, wherein the antibody or antibody fragment comprises a variable domain having at least 90% sequence identity to SEQ ID NO: 618.

121. The recombinant nucleic acid molecule of claim 120, wherein the variable domain has at least 95% sequence identity to SEQ ID NO: 618.

122. The recombinant nucleic acid molecule of claim 121, wherein the variable domain comprises the sequence of SEQ ID NOs: 618.

123. The recombinant nucleic acid molecule of any one of 120-122, wherein CDR1 is SEQ ID NO: 102, CDR2 is SEQ ID NO: 274 and CDR3 is SEQ ID NO: 446.

124. The recombinant nucleic acid molecule of claim 120, wherein the antibody or antibody fragment comprises a sdAb domain having at least about 80% sequence identity to any one of sequence of SEQ ID NOs: 1224-1227.

125. The recombinant nucleic acid molecule of any one of claims 105-108, wherein the antibody or antibody fragment is a scFv.

126. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a heavy chain variable (VH) domain having at least 90% sequence identity to any one of SEQ ID NOs: 783-835.

127. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a heavy chain variable (VH) domain having at least 95% sequence identity to any one of SEQ ID NOs: 783-835.

128. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a heavy chain variable (VH) domain having a sequence of any one of SEQ ID NOs: 783-835.

129. The recombinant nucleic acid molecule of any one of claims 125-128, wherein the scFv comprises a light chain variable (VL) domain having at least 90% sequence identity to any one of SEQ ID NOs: 995-1047.

130. The recombinant nucleic acid molecule of any one of claims 125-128, wherein the scFv comprises a light chain variable (VL) domain having at least 95% sequence identity to any one of SEQ ID NOs: 995-1047.

131. The recombinant nucleic acid molecule of any one of claims 125-128, wherein the scFv comprises a light chain variable (VL) domain having a sequence of any one of SEQ ID NOs: 995-1047.

132. The recombinant nucleic acid molecule of any one of claims 126-131, wherein the VH domain comprises a CDRH1 having a sequence of any one of SEQ ID NOs: 836-888, a CDRH2 having a sequence of any one of SEQ ID NOs: 889-941, and a CDRH3 having a sequence of any one of SEQ ID NOs: 942-994.

133. The recombinant nucleic acid molecule of any one of claims 126-132, wherein the VL domain comprises a CDRL1 having a sequence of any one of SEQ ID NOs: 1048-1100, a CDRL2 having a sequence of any one of SEQ ID NOs: 1101-1153, and a CDRL3 having a sequence of any one of SEQ ID NOs: 1154-1206.

134. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1248.

135. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1248.

136. The recombinant nucleic acid molecule of any one of claims 125, 134, and 135, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1249.

137. The recombinant nucleic acid molecule of any one of claims 125, 134, and 135, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1249.

138. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1248, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1249.

139. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1248, and a VL domain of the sequence of SEQ ID NO: 1249.

140. The recombinant nucleic acid molecule of claim 139, wherein the VH domain of the sequence of SEQ ID NO: 1248 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1249.

141. The recombinant nucleic acid molecule of claim 139, wherein the VL domain of the sequence of SEQ ID NO: 1249 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1248.

142. The recombinant nucleic acid molecule of any one of claims 134-141, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.

143. The recombinant nucleic acid molecule of claim 140 or 141, wherein the VH of the sequence of SEQ ID NO: 1248 and the VL domain of the sequence of SEQ ID NO: 1249 are operably linked via a linker sequence of SEQ ID NO: 1237.

144. The recombinant nucleic acid molecule of any one of claims 134-143, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1207 or SEQ ID NO: 1208.

145. The recombinant nucleic acid molecule of any one of claims 134-143, wherein the scFv comprises the sequence of SEQ ID NO: 1207 or SEQ ID NO: 1208.

146. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1250.

147. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1250.

148. The recombinant nucleic acid molecule of any one of claims 125, 146, and 147, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1251.

149. The recombinant nucleic acid molecule of any one of claims 125, 146, and 147, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1251.

150. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1250, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1251.

151. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1250, and a VL domain of the sequence of SEQ ID NO: 1251.

152. The recombinant nucleic acid molecule of claim 151, wherein the VH domain of the sequence of SEQ ID NO: 1250 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1251.

153. The recombinant nucleic acid molecule of claim 151, wherein the VL domain of the sequence of SEQ ID NO: 1251 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1250.

154. The recombinant nucleic acid molecule of any one of claims 146-153, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.

155. The recombinant nucleic acid molecule of claim 152 or 153, wherein the VH of the sequence of SEQ ID NO: 1250 and the VL domain of the sequence of SEQ ID NO: 1251 are operably linked via a linker sequence of SEQ ID NO: 1237.

156. The recombinant nucleic acid molecule of any one of claims 68-155, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1209 or SEQ ID NO: 1210.

157. The recombinant nucleic acid molecule of any one of claims 68-155, wherein the scFv comprises the sequence of SEQ ID NO: 1209 or SEQ ID NO: 1210.

158. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1252.

159. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1252.

160. The recombinant nucleic acid molecule of any one of claims 125, 158, and 159, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1253.

161. The recombinant nucleic acid molecule of any one of claims 125, 158, and 159, wherein the scFv comprises a VL domain of the sequence of SEQ ID NO: 1253.

162. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 1252, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1253.

163. The recombinant nucleic acid molecule of claim 125, wherein the scFv comprises a VH domain of the sequence of SEQ ID NO: 1252, and a VL domain of the sequence of SEQ ID NO: 1253.

164. The recombinant nucleic acid molecule of claim 163, wherein the VH domain of the sequence of SEQ ID NO: 1252 is operably linked via its C-terminus to the N-terminus of the VL domain of the sequence of SEQ ID NO: 1253.

165. The recombinant nucleic acid molecule of claim 163, wherein the VL domain of the sequence of SEQ ID NO: 1253 is operably linked via its C-terminus to the N-terminus of the VH domain of the sequence of SEQ ID NO: 1252.

166. The recombinant nucleic acid molecule of any one of claims 158-165, wherein the scFv comprises a linker sequence of SEQ ID NO: 1237.

167. The recombinant nucleic acid molecule of claim 164 or 165, wherein the VH of the sequence of SEQ ID NO: 1252 and the VL domain of the sequence of SEQ ID NO: 1253 are operably linked via a linker sequence of SEQ ID NO: 1237.

168. The recombinant nucleic acid molecule of any one of claims 158-167, wherein the scFv comprises a sequence having at least 90% sequence identity to SEQ ID NO: 1246 or SEQ ID NO: 1247.

169. The recombinant nucleic acid molecule of any one of claims 158-167, wherein the scFv comprises the sequence of SEQ ID NO: 1246 or SEQ ID NO: 1247.

170. The recombinant nucleic acid molecule of any one of claims 119-169, wherein the antibody or antibody fragment specifically binds to a second epitope is within the amino acid sequence ASRHHPTTLAVGICSPASRSISL (SEQ ID NO:1231).

171. The recombinant nucleic acid molecule of any one of claims 125-168, wherein the scFv comprises a VH domain that comprises a CDRH1 of SEQ ID NO: 853, a CDRH2 of SEQ ID NO: 906, and a CDRH3 of SEQ ID NO: 959, and a VL domain that comprises a CDRL1 of SEQ ID NO: 1065, a CDRL2 of SEQ ID NO: 1118, and a CDRL3 of SEQ ID NO: 1171.

172. The recombinant nucleic acid molecule of any one of claims 125-168, and 171, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 800.

173. The recombinant nucleic acid molecule of any one of claims 125-168, and 171, wherein the scFv comprises a VL domain having at least 90% sequence identity to SEQ ID NO: 1012.

174. The recombinant nucleic acid molecule of any one of claims 125-168, and 171, wherein the scFv comprises a VH domain having at least 90% sequence identity to SEQ ID NO: 800, and a VL domain having at least 90% sequence identity to SEQ ID NO: 1012.

175. The recombinant nucleic acid molecule of any one of claims 125-174, wherein the scFv comprises a linker sequence of SEQ ID NO: 782.

176. The recombinant nucleic acid molecule of any one of claims 105-175, wherein the recombinant nucleic acid molecule further comprises a sequence encoding a TCR constant domain.

~~177. The recombinant nucleic acid molecule of claim 176, wherein the antibody or antibody fragment is operatively linked to the sequence encoding a TCR constant domain, thereby forming a TFP.~~

~~178. The recombinant nucleic acid molecule of claim 176 or 177, wherein the TCR constant domain is a TCR alpha constant domain or portion thereof, a TCR beta constant domain or portion thereof, a TCR alpha constant domain or portion thereof and a TCR beta constant domain or portion thereof, a TCR gamma constant domain or portion thereof, a TCR delta constant domain or portion thereof, or a TCR gamma constant domain or portion thereof and a TCR delta constant domain or portion thereof.~~

~~179.~~39. The recombinant nucleic acid molecule of any one of claims 1-38~~105-178~~, further comprising a leader sequence, a promoter, a sequence encoding a poly(A) tail, and/or a 3'UTR sequence.

~~180. The recombinant nucleic acid molecule of any one of claims 1-179, wherein the nucleic acid is selected from the group consisting of a DNA and an RNA.~~

~~181. The recombinant nucleic acid molecule of claim 180, wherein the nucleic acid is a mRNA.~~

~~182. The recombinant nucleic acid molecule of claim 180, wherein the nucleic acid is a circRNA.~~

~~183. The recombinant nucleic acid molecule of any one of claims 1-182, wherein the nucleic acid comprises a nucleotide analog.~~

~~184. The recombinant nucleic acid molecule of claim 183, wherein the nucleotide analog is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA) modified, a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), a 1',5'-anhydrohexitol nucleic acid (HNA), a morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.~~

~~185. The recombinant nucleic acid molecule of any one of claims 1-184, further comprising a promoter.~~

~~186.~~40. The recombinant nucleic acid molecule of any one of claims 1-39~~185~~, wherein the nucleic acid is an *in vitro* transcribed nucleic acid.

~~187. The recombinant nucleic acid molecule of any one of claims 1-186, wherein the nucleic acid further comprises a sequence encoding a poly(A) tail.~~

~~188. The recombinant nucleic acid molecule of any one of claims 1-187, wherein the nucleic acid further comprises a 3'UTR sequence.~~

~~189. A polypeptide encoded by the recombinant nucleic acid molecule of any one of claims 1-188.~~

~~190.~~41. A vector comprising the recombinant nucleic acid molecule of any one of claims 1-~~104, 177, 178, and 179~~40.

~~191. A vector comprising the recombinant nucleic acid molecule of claims 105-176.~~

~~192. The vector of claim 190, further comprising a sequence encoding an siRNA, an shRNA, or an miRNA for reducing endogenous levels of CD70.~~

~~193. The vector of claim 190, further comprising a sequence encoding an inhibitory molecule 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.~~

~~194. The vector of claim 190, further comprising a sequence encoding a TCR constant domain.~~

~~195. The vector of claim 194, wherein the TCR constant domain is a TCR alpha constant domain or portion thereof, a TCR beta constant domain or portion thereof, a TCR alpha constant domain or portion thereof and a TCR beta constant domain or portion thereof, a TCR gamma constant domain or portion thereof, a TCR delta constant domain or portion thereof, or a TCR gamma constant domain or portion thereof and a TCR delta constant domain or portion thereof.~~

~~196. The vector of any one of claims 190-195, wherein the vector is selected from the group consisting of a DNA, a RNA, a plasmid, a lentivirus vector, adenoviral vector, a Rous sarcoma viral (RSV) vector, or a retrovirus vector.~~

~~197. The vector of any one of claims 190-196, further comprising a promoter.~~

~~198. The vector of any one of claims 190-197, wherein the vector is an *in vitro* transcribed vector.~~

~~199. The vector of any one of claims 190-198, wherein a nucleic acid sequence in the vector further comprises a poly(A) tail.~~

~~200. The vector of any one of claims 190-199, wherein a nucleic acid sequence in the vector further comprises a 3'UTR.~~

~~201.~~42. A cell comprising the recombinant nucleic acid molecule of any one of claims 1-~~188~~40~~, the polypeptide of claim 189~~, or the vector of ~~any one of~~ claim~~s~~ 41~~190-200~~.

~~202. A cell comprising a recombinant nucleic acid molecule comprising a sequence encoding a T cell receptor (TCR) fusion protein (TFP) wherein the TFP comprises:~~

~~(a) a TCR subunit comprising:~~

~~(i) at least a portion of a TCR extracellular domain, and~~

~~(ii) a TCR transmembrane domain,~~

~~(iii) a TCR intracellular domain, and~~

~~(b) an antigen binding domain that specifically binds CD70; and~~

~~wherein the TCR subunit and the antigen binding domain are operatively linked.~~

~~203. The cell of claim 201 or 202, wherein the cell is a T cell.~~

~~204. The cell of claim 203, wherein the T cell is a human T cell.~~

~~205. The cell of claim 203 or 204, wherein the T cell is a CD8+ or CD4+ T cell.~~

~~206. The cell of claim 203, wherein the T cell is a human αβ T cell.~~

~~207. The cell of claim 203, wherein the T cell is a human γδ T cell.~~

~~208. The cell of any one of claims 201 or 202, wherein the cell is a human NKT cell.~~

~~209. A T cell comprising the recombinant nucleic acid molecule of any one of claims 1-175, the polypeptide of claim 176, or the vector of any one of claims 177-187.~~

~~210.~~43. A T cell comprising a recombinant nucleic acid molecule of any one of claims 1-40, wherein the recombinant nucleic acid molecule comprises ~~comprising~~ a sequence encoding a T cell receptor (TCR) fusion protein (TFP), wherein the TFP comprises:

(a) a TCR subunit comprising:

(i) at least a portion of a TCR extracellular domain, and

(ii) a TCR transmembrane domain,

(iii) a TCR intracellular domain, and

(b) an antigen binding domain that specifically binds CD70; and

wherein the TCR subunit and the antigen binding domain are operatively linked.

~~211. The T cell of claim 209 or 210, wherein the T cell is a human T cell.~~

~~212. The T cell of claim 209 or 210, wherein the T cell is a CD8+ or CD4+ T cell.~~

~~213. The T cell of claim 209 or 210, wherein the T cell is a human αβ T cell.~~

~~214. The T cell of claim 209 or 210, wherein the T cell is a human γδ T cell.~~

~~215. The cell of claim 201 or 202 or the T cell of claim 209 or 210, further comprising a nucleic acid encoding an inhibitory molecule that comprises a first polypeptide comprising at least a portion of an inhibitory molecule, associated with a second polypeptide comprising a positive signal from an intracellular signaling domain.~~

~~216. The cell or T cell of claim 215, wherein the inhibitory molecule comprises the first polypeptide comprising at least a portion of PD-1 and the second polypeptide comprising a costimulatory domain and primary signaling domain.~~

~~217. The cell or T cell of claim 216, wherein the inhibitory molecule comprises the sequence of SEQ ID NO: 1239 or SEQ ID NO: 1244.~~

~~218. The cell or T cell of any one of claims 215-217, wherein the sequence encoding the TFP and the nucleic acid encoding an inhibitory molecule are included in a single nucleic acid molecule.~~

219. The cell or T cell of claim 215-217, wherein the sequence encoding the TFP and the nucleic acid encoding an inhibitory molecule are included in two separate nucleic acid molecules.

220. The cell of claim 201 or 202 or the T cell of claim 209 or 210, wherein the cell or the T cell further comprises a second nucleic acid sequence encoding an interleukin-15 (IL-15) polypeptide or a fragment thereof.

221. The cell or T cell of claim 220, wherein the sequence encoding the TFP and the second nucleic acid sequence are included in a single nucleic acid molecule.

222. The cell or T cell of claim 220, wherein the sequence encoding the TFP and the second nucleic acid sequence are included in two separate nucleic acid molecules.

223. The cell or T cell of claim 221, wherein the sequence encoding the TFP and the second nucleic acid sequence are operatively linked by a second linker.

224. The cell or T cell of claim 223, wherein the second linker comprises a protease cleavage site.

225. The cell or T cell of claim 224, wherein the protease cleavage site is a 2A cleavage site.

226. The cell or T cell of claim 225, wherein the 2A cleavage site is a T2A cleavage site.

227. The cell or T cell of any of claims 220-226, wherein expression of IL-15 increases persistence of the cells.

228. The cell or T cell of any one of claims 220-227, wherein the IL-15 polypeptide is secreted when expressed in the cell or T cell.

229. The cell or T cell of any one of claims 220-228, wherein the IL-15 polypeptide comprises a sequence of SEQ ID NO: 1242.

230. The cell or T cell of any one of claims 220-229, wherein the second nucleic acid sequence further encodes an IL-15 receptor (IL-15R) subunit or a fragment thereof.

231. The cell or T cell of claim 230, wherein the IL-15R subunit is IL-15R alpha (IL-15Rα).

232. The cell or T cell of claim 231, wherein IL-15 and IL-15Rα are operatively linked by a third linker.

233. The cell of claim 232, wherein the third linker is not a cleavable linker.

234. The cell or T cell of claim 233, wherein the third linker comprises a sequence comprising $(G_4S)_n$, wherein G is glycine, S is serine, and n is an integer from 1 to 10.

235. The cell or T cell of claim 234, wherein n is an integer from 1 to 4.

236. The cell or T cell of claim 235, wherein n is 3.

237. The cell or T cell of claim 236, wherein the third linker comprises a sequence of SEQ ID NO: 1243.

238. The cell or T cell of any one of claims 230-237, wherein the second nucleic acid sequence encodes a fusion protein comprising the IL-15 polypeptide linked to the IL-15Rα subunit.

239. The cell or T cell of claim 238, wherein the IL-15 polypeptide is linked to N-terminus of the IL-15Rα subunit.

240. The cell or T cell of claim 238, wherein the fusion protein comprises amino acids 30 – 162 of IL-15.

241. The cell or T cell of claim 238, wherein the fusion protein comprises amino acids 31 – 267 of IL-15Rα.

242. The cell or T cell of claim 238, wherein the fusion protein further comprises a sushi domain.

243. The cell or T cell of claim 238, wherein the fusion protein comprises a sequence of SEQ ID NO: 1244.

244. The cell or T cell of any one of claims 238-243, wherein the fusion protein is expressed on cell surface when expressed in the cell or T cell.

245. The cell or T cell of any one of claims 238-243, wherein the fusion protein is secreted when expressed in the cell or T cell.

246. The cell or T cell of any one of claims 220-245, wherein the cell or T cell further comprises a third nucleic acid sequence encoding a PD-1 polypeptide.

247. The cell or T cell of claim 246, wherein the PD-1 polypeptide is operably linked via its C-terminus to the N-terminus of an intracellular domain of a costimulatory polypeptide.

248. The cell or T cell of claim 246 or 247, wherein the third nucleic acid sequence is included in the same nucleic acid molecule as the first and second nucleic acid sequences.

249. The cell or T cell of any one of claims 247 or 248, wherein the PD-1 polypeptide is linked to the intracellular domain of the costimulatory polypeptide via a transmembrane domain of PD-1.

250. The cell or T cell of any one of claims 247-249, wherein the costimulatory polypeptide is chosen from a group comprising OX40, CD2, CD27, CDS, ICAM-1, ICOS (CD278), 4-1BB (CD137), GITR, CD28, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, CD226, FcγRI, FcγRII, and FcγRIII.

251. The cell or T cell of claim 247, wherein the intracellular domain of the costimulatory polypeptide comprises at least a portion of CD28.

252. The cell or T cell of claim 247, wherein an extracellular domain and the transmembrane domain of PD-1 are linked to an intracellular domain of CD28.

253. The cell or T cell of claim 246, wherein the cell or T cell comprises a fusion protein comprising an extracellular domain and a transmembrane domain of PD-1 linked to an intracellular domain of CD28 linked to IL-15Rα.

254. The cell or T cell of claim 253, wherein the fusion protein comprises a sequence of SEQ ID NO: 1254 or SEQ ID NO: 1262.

255. ~~The cell of claim 201 or 202 or the T cell of claim 209 or 210, wherein the cell or T cell further comprises a second nucleic acid sequence encoding an interleukin-15 receptor alpha (IL-15Rα) polypeptide or a fragment thereof.~~

256. ~~The cell or T cell of claim 255, wherein the sequence encoding the TFP and the second nucleic acid sequence are included in a single nucleic acid molecule.~~

257. ~~The cell or T cell of claim 255, wherein the sequence encoding the TFP and the second nucleic acid sequence are included in two separate nucleic acid molecules.~~

258. ~~The cell or T cell of claim 256, wherein the sequence encoding the TFP and the second nucleic acid sequence are operatively linked by a second linker.~~

259. ~~The cell or T cell of claim 258, wherein the second linker comprises a protease cleavage site.~~

260. ~~The cell or T cell of claim 259, wherein the protease cleavage site is a 2A cleavage site.~~

261. ~~The cell or T cell of claim 260, wherein the 2A cleavage site is a T2A cleavage site.~~

262. ~~The cell or T cell of any one of claims 255-261, wherein the second nucleic acid sequence further encodes PD-1 or a fragment thereof.~~

263. ~~The cell or T cell of claim 262, wherein the second nucleic acid sequence encodes the extracellular domain of PD-1.~~

264. ~~The cell or T cell of claim 262 or 263, wherein the second nucleic acid sequence encodes the extracellular and transmembrane domain of PD-1.~~

265. ~~The cell or T cell of any one of claims 262-264, wherein the second nucleic acid sequence further encodes CD28 or a fragment thereof.~~

266. ~~The cell or T cell of any one of claims 262-265, wherein the second nucleic acid sequence encodes the intracellular domain of CD28.~~

267. ~~The cell or T cell of any one of claims 262-266, wherein the second nucleic acid sequence encodes a fusion protein comprising the PD-1 extracellular domain and transmembrane domain linked to the CD28 intracellular domain linked to IL-15Rα.~~

268. ~~The cell or T cell of claim 267, wherein the CD28 intracellular domain is linked to the intracellular domain of IL-15Rα.~~

269. ~~The cell or T cell of any one of claims 262-268, wherein the second nucleic acid sequence comprises a sequence of SEQ ID NO: 1245.~~

270. ~~The cell or T cell of any one of claims 255-269, wherein the recombinant nucleic acid molecule further comprises a third nucleic acid sequence encoding an interleukin-15 (IL-15) polypeptide or a fragment thereof.~~

271. ~~The cell or T cell of claim 270, wherein the IL-15 polypeptide or a fragment thereof is secreted when expressed in the cell or T cell.~~

~~272. The cell or T cell of claim 271, wherein the cell or T cell secretes the IL-15 polypeptide in response to a T cell activation agent.~~

~~273. The cell or T cell of claim 220, wherein IL-15 signaling is increased in response to a T cell activation agent.~~

~~274. The cell or T cell of claim 273, wherein the T cell activation agent comprises anti-CD3 antibody or a fragment thereof, anti-CD28 antibody or a fragment thereof, a cytokine, an antigen that binds the antigen binding domain of the TFP, or any combinations thereof.~~

~~275. The cell or T cell of any one of claims 201-274, wherein the TFP functionally interacts with an endogenous TCR complex when expressed in a T cell.~~

~~276. The cell or T cell of any one of claims 201-274, wherein the cell or T cell comprises a functional disruption of an endogenous TCR.~~

~~277. The cell or T cell of any one of claims 201-276, wherein the cell or T cell is an allogeneic cell or T cell.~~

~~278.~~44. The cell or T cell of ~~any one of~~ claim~~s~~ 42 or 43~~201-277~~, wherein the cell or T cell comprises a functional disruption of the endogenous CD70 gene or a functional disruption of the endogenous CIITA gene.

~~279. The cell or T cell of any one of claims 201-277, wherein the cell or T cell comprises a functional disruption of the endogenous CIITA gene.~~

~~280. The cell or T cell of any one of claims 201-277, wherein the cell or T cell further comprises an antisense siRNA, an shRNA, or an miRNA for reducing endogenous levels of CD70.~~

~~281. The cell or T cell of any one of claims 201-277, wherein the cell or T cell further comprises an antisense siRNA, an shRNA, or an miRNA for reducing endogenous levels of CIITA.~~

~~282. The cell or T cell of any one of claims 201-277, wherein the cell or T cell further comprises a sequence encoding a fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.~~

~~283. The cell or T cell of any one of claims 201-277, wherein the recombinant nucleic acid comprises the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.~~

~~284. The cell or T cell of claim 283, wherein the sequence encoding the TFP and the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain are contained in the same operon.~~

~~285. The cell or T cell of claim 283 or 284, wherein the ER retention domain is encoded by any one of SEQ ID NOs: 756-779.~~

~~286. The cell or T cell of any one of claims 283-285, wherein the sequence encoding the fusion~~

protein further comprises a CD8 alpha transmembrane domain between the anti-CD70 antibody domain and the ER retention domain.

287. The cell or T cell of any one of claims 283-286, wherein the sequence encoding the fusion protein further comprises a sequence encoding a CD8 alpha signal peptide 5' to the sequence encoding the anti-CD70 antibody domain.

288. The cell or T cell of any one of claims 201-277, wherein the antibody domain comprises the recombinant nucleic acid of any one of claims 105-175.

289. The cell or T cell of any one of claims 201-277, wherein the cell or T cell comprises a cell-surface expressed CD70 bound to an anti-CD70 antibody.

290. The cell or T cell of claim 289, wherein the anti-CD70 antibody is the antibody or antigen binding fragment encoded by the recombinant nucleic acid of claims 105-175.

291. The cell or T cell of claim 289, wherein the anti-CD70 antibody has greater affinity for CD70 than the antibody or antigen binding fragment encoded by the recombinant nucleic acid of claims 105-175.

292. The cell or T cell of any one of claims 201-291, wherein the cell or T cell further comprises a heterologous sequence encoding an inhibitory molecule 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.

293. The cell or T cell of any one of claims 201-292, wherein the cell or T cell further comprises a heterologous sequence encoding a TCR constant domain.

294. The cell or T cell of claim 293, wherein the TCR constant domain is a TCR alpha constant domain or portion thereof, a TCR beta constant domain or portion thereof, a TCR alpha constant domain or portion thereof and a TCR beta constant domain or portion thereof, a TCR gamma constant domain or portion thereof, a TCR delta constant domain or portion thereof, or a TCR gamma constant domain or portion thereof and a TCR delta constant domain or portion thereof.

295. The cell or T cell of claim 294, wherein the TCR alpha constant domain or the TCR beta constant domain is murine.

296. The cell of claim 201 or 202 or the T cell of claim 209 or 210, wherein the cell or T cell comprises the recombinant nucleic acid molecule encoding any one of the amino acid sequences selected from SEQ ID NOs: 1233, 1236, 1240, and 1264.

297.45. A pharmaceutical composition comprising the cell or T cell of any one of claims 42-44201-296 and a pharmaceutically acceptable carrier for use in therapy.

~~298.~~46. A method of producing the cell or T cell of any one of claims 42-44 ~~278~~, the method comprising:

(A)

(i) disrupting an endogenous CD70 gene, thereby producing a cell or T cell containing a functional disruption of an endogenous CD70 gene; and

(ii) transducing the cell or T cell containing the functional disruption of the endogenous CD70 gene with the recombinant nucleic acid of any one of claims 1-40~~104, 177, 178, and 179~~, or the vector ~~of any one~~ of claim~~s~~ 41~~190 and 193-200~~

(B) (i) disrupting an endogenous CIITA gene, thereby producing a cell or T cell containing a functional disruption of an endogenous CIITA gene; and

(ii) transducing the cell or T cell containing the functional disruption of the endogenous CD70 gene or the functional disruption of the endogenous CIITA gene with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41;

(C) (i) transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41; and

(ii) contacting the cell or T cell with an anti-CD70 antibody that binds to CD70 on the cell surface; or

(D) transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-40, or the vector of claim 41, and a sequence encoding a fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.

~~299. The method of claim 298, wherein the disrupting comprises transducing the cell or T cell with a nuclease protein or a nucleic acid sequence encoding a nuclease protein that targets the endogenous CD70 gene.~~

~~300. The method of claim 298 or 299, wherein the method further comprises disrupting an endogenous TCR.~~

~~301. A method of producing the cell or T cell of claim 278, the method comprising transducing a cell or T cell comprising a disruption of an endogenous CD70 gene with the recombinant nucleic acid of any one of claims 1-104, 177, 178, and 179, or the vector of any one of claims 190 and 193-200.~~

~~302. The method of claim 301, wherein the cell or T cell further comprises a disruption of an endogenous TCR.~~

~~303. A method of producing the cell or T cell of any one of claims 201-277 and 289-291, the method comprising:~~

(i) transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-104, 177, 178, and 179, or the vector of any one of claims 190 and 193-200; and

(ii) contacting the cell or T cell with an anti-CD70 antibody that binds to CD70 on the cell surface.

304. The method of claim 303, wherein the anti-CD70 antibody is the antibody or antigen binding fragment encoded by the recombinant nucleic acid of claims 105-175.

305. The method of claim 304, wherein the anti-CD70 antibody has greater affinity for CD70 than the antibody or antigen binding fragment encoded by the recombinant nucleic acid of claims 105-175.

306. The method of any one of claims 303-305, wherein the contacting occurs prior to the transducing.

307. The method of claim 306, wherein the contacting occurs up to 1 day prior to the transducing.

308. The method of any one of claims 303-305, wherein the contacting occurs after the transducing.

309. The method of claim 308, wherein the contacting occurs up to 5 days after the transducing.

310. The method of any one of claims 303-305, further comprising sub-culturing the cells in media that does not comprise the anti-CD70 antibody 4 or more days after the transducing.

311. The method of claim 310, wherein the sub-culturing comprises sub-culturing the cells in media that does not comprise the anti-CD70 antibody 7 or more days after the transducing.

312.47. Use of a pharmaceutical composition comprising the cell or T cell of any one of claims 42-44 and a pharmaceutically acceptable carrier, or A method of treating a cancer in a subject in need thereof, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 45297 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject, thereby treating the cancer in the subject.

313. A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition comprising (a) the cell or T cell of any one of claims 201-296; and (b) a pharmaceutically acceptable carrier.

314. The method of claim 312 or 313, wherein the cancer is a cancer associated with elevated expression of CD70.

315. The method of any one of claims 312-314, further comprising administering to the subject an agent that increases levels of CD70 in the cancer cells.

316. The method of claim 315, wherein the agent that increases levels of CD70 is a hypomethylating agent.

317. The method of claim 316, wherein the hypomethylating agent is 5-azacitidine or decitabine.

318. The method of any one of claims 312-317, wherein the disease or the condition is selected from the group consisting of T cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), an Epstein-Barr virus (EBV) + cancer, and/or a human papilloma virus (HPV) + cancer.

319. The method of any one of claims 312-317, wherein the disease or the condition is selected from the group consisting of kidney cancer, renal cell carcinoma, lung cancer, pancreatic cancer, ovarian cancer, esophageal cancer, nasopharyngeal carcinoma, mesothelioma, glioblastoma, thymic carcinoma, breast cancer, head and neck cancer, and gastric cancer.

320. The method of any one of claims 312-319, wherein the subject is a human.

321. A method of producing the cell or T cell of claim 279, the method comprising:

(i) disrupting an endogenous CIITA gene, thereby producing a cell or T cell containing a functional disruption of an endogenous CIITA gene; and

(ii) transducing the cell or T cell containing the functional disruption of the endogenous CIITA gene with the recombinant nucleic acid of any one of claims 1-104, 177, 178, and 179, or the vector of any one of claims 190 and 193-200.

322. The method of claim 321, wherein the disrupting comprises transducing the cell or T cell with a nuclease protein or a nucleic acid sequence encoding a nuclease protein that targets the endogenous CIITA gene.

323. The method of claim 321 or 322, wherein the method further comprises disrupting an endogenous TCR.

324. A method of producing the cell or T cell of claim 279, the method comprising transducing a cell or T cell comprising a disruption of an endogenous CIITA gene with the recombinant nucleic acid of any one of claims 1-104, 177, 178, and 179, or the vector of any one of claims 190 and 193-200.

325. The method of claim 324, wherein the cell or T cell further comprises a disruption of an endogenous TCR.

326. A method of producing the cell or T cell of any one of claims 282-288, the method comprising transducing a cell or T cell with the recombinant nucleic acid of any one of claims 1-104, 177, 178, and 179, or the vector of any one of claims 190 and 193-200 and a sequence encoding a fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.

327. The method of claim 326, wherein the recombinant nucleic acid or vector and the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain are transduced simultaneously.

328. The method of claim 327, wherein the recombinant nucleic acid or vector comprises the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.

329. The method of claim 328, wherein the sequence encoding the TFP and the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain are contained in the same operon.

330. The method of claim 326, wherein the recombinant nucleic acid or vector are transduced before or after the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain.

331. The method of any one of claims 326-330, wherein the ER retention domain is encoded by any one of SEQ ID NOs: 756-779.

332. The method of any one of claims 326-331, wherein the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain further comprises a CD8 alpha transmembrane domain between the anti-CD70 antibody domain and the ER retention domain.

333. The method of any one of claims 326-332, wherein the sequence encoding the fusion protein comprising an anti-CD70 antibody domain and an ER retention domain further comprises a sequence encoding a CD8 alpha signal peptide 5' to the sequence encoding the anti-CD70 antibody domain.

334. The method of any one of claims 326-333, wherein the antibody domain comprises the anti-CD70 antibody of any one of claims 105-175.