

CLAIMS

What is claimed is:

1. An expression construct comprising sequence that encodes a CD70-specific engineered receptor and that encodes one or both of the following:
 - (a) a suicide gene; and
 - (b) a cytokine.
2. The construct of claim 1, wherein the CD70-specific engineered receptor is a chimeric antigen receptor (CAR) or a T cell receptor.
3. The expression construct of claim 2, wherein the CD70-specific CAR comprises a scFv having a heavy chain and a light chain, and wherein the heavy chain in the sequence that encodes the CAR is upstream of the light chain in a 5' to 3' direction.
4. The expression construct of claim 2, wherein the CD70-specific CAR comprises a scFv having a heavy chain and a light chain, and wherein the heavy chain in the sequence that encodes the CAR is downstream of the light chain in a 5' to 3' direction.
5. The expression construct of any one of claims 1-4, wherein the CD70-specific CAR comprises a codon optimized scFv.
6. The expression construct of any one of claims 1-4, wherein the CD70-specific CAR comprises a humanized scFv.
7. The expression construct of any one of claims 1-6, wherein the CD70-specific CAR comprises a signaling peptide.
8. The expression construct of claim 7, wherein the signaling peptide is from CD8alpha, Ig heavy chain, or granulocyte-macrophage colony-stimulating factor receptor or a signal peptide derived from one or more other surface receptors.
9. The expression construct of any one of claims 1-8, wherein the CD70-specific CAR comprises one or more costimulatory domains.

10. The expression construct of claim 9, wherein the costimulatory domain is selected from the group consisting of CD28, CD27, OX-40 (CD134), DAP10, DAP12, 4-1BB (CD137), CD40L, 2B4, DNAM, CS1, CD48, NKG2D, NKp30, NKp44, NKp46, NKp80, and a combination thereof.
11. The expression construct of any one of claims 1-10, wherein the CD70-specific CAR comprises CD3zeta.
12. The expression construct of any one of claims 1-11, wherein the CD70-specific CAR comprises a hinge between the scFv and a transmembrane domain.
13. The expression construct of claim 12, wherein the hinge is CD8-alpha hinge, the hinge comprises an artificial spacer comprised of Gly3, or the hinge comprises CH1, CH2, and/or CH3 domains of IgGs.
14. The expression construct of any one of claims 1-13, wherein the cytokine is IL-15, IL-12, IL-2, IL-18, IL-21, IL-7, or a combination thereof.
15. The expression construct of any one of claims 1-14, wherein the suicide gene is a mutant TNF-alpha, inducible caspase 9, HSV-thymidine kinase, CD19, CD20, CD52, or EGFRv3.
16. The expression construct of claim 14, wherein the mutant TNF-alpha is an engineered nonsecretable mutant TNF-alpha.
17. An expression construct of any one of claims 1-16, wherein the expression construct comprises any one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, or SEQ ID NO:13.
18. An immune cell, comprising the expression construct of any one of claims 1-17.
19. The immune cell of claim 18, wherein the immune cell is a natural killer (NK) cell, T cell, gamma delta T cells, invariant NKT (iNKT) cell, B cell, macrophage, MSCs, or dendritic cell.
20. The immune cell of claim 18 or 19, wherein the immune cell is a NK cell.

21. The immune cell of claim 19 or 20, wherein the NK cell is derived from cord blood, peripheral blood, induced pluripotent stem cells, bone marrow, or from a cell line.
22. The immune cell of claim 21, wherein the NK cell line is NK-92 cell line or another NK cell line derived from a tumor or from a healthy NK cell or a progenitor cell.
23. The immune cell of any one of claims 19-22, wherein the NK cell is a cord blood mononuclear cell.
24. The immune cell of any one of claims 19-23, wherein the NK cell is a CD56+ NK cell.
25. The immune cell of any one of claims 19-24, wherein the NK cells express one or more exogenously provided cytokines.
26. The immune cell of claim 25, wherein the cytokine is IL-15, IL-2, IL-12, IL-18, IL-21, IL-7, or a combination thereof.
27. The immune cell of any one of claims 18-26, wherein expression of one or more endogenous genes in the immune cell has been modified.
28. The immune cell of claim 27, wherein the expression has been partially or fully reduced in expression.
29. The immune cell of claim 27 or 28, wherein expression of the one or more gene has been modified using CRISPR.
30. The immune cell of any one of claims 27-29, wherein the gene is selected from the group consisting of NKG2A, SIGLEC-7, LAG3, TIM3, CISH, FOXO1, TGFBR2, TIGIT, CD96, ADORA2, NR3C1, PD1, PDL-1, PDL-2, CD47, SIRPA, SHIP1, ADAM17, RPS6, 4EBP1, CD25, CD40, IL21R, ICAM1, CD95, CD80, CD86, IL10R, CD5, CD7, CTLA-4, TDAG8, CD38, and a combination thereof.
31. A population of immune cells of any one of claims 18-30, said cells present in a suitable medium.
32. The population of claim 31, wherein the immune cells are NK cells.

33. A method of killing CD70-positive cells in an individual, comprising the step of administering to the individual an effective amount of cells harboring the expression construct of any one of claims 1-17.

34. The method of claim 33, wherein the cells are NK cells, T cells, gamma delta T cells, induced NKT (iNKT) cells, B cells, macrophages, gamma delta T cells, or dendritic cells.

35. The method of claim 34, wherein the NK cells are derived from cord blood, peripheral blood, induced pluripotent stem cells, bone marrow, or from a cell line.

36. The method of any one of claims 34-35, wherein the NK cells are derived from cord blood mononuclear cells.

37. The method of any one of claims 33-36, wherein the CD70-positive cells are not cancer cells.

38. The method of claim 37, wherein the CD70-positive cells are T regulatory cells.

39. The method of any one of claims 33-36, wherein the individual has acute myeloid leukemia, lymphoma, lung cancer, renal cancer, bladder cancer, melanoma, glioblastoma, breast cancer, head and neck cancer, mesothelioma, multiple myeloma, pancreatic cancer or a combination thereof.

40. The method of any one of claims 33-39, wherein the cells are allogeneic with respect to the individual.

41. The method of any one of claims 33-39, wherein the cells are autologous with respect to the individual.

42. The method of any one of claims 33-41, wherein the individual is a human.

43. The method of any one of claims 32-42, wherein the cells are administered to the individual once or more than once.

44. The method of claim 43, wherein the duration of time between administrations of the cells to the individual is 1-24 hours, 1-7 days, 1-4 weeks, 1-12 months, or one or more years.

45. The method of any one of claims 33-44, further comprising the step of providing to the individual an effective amount of an additional therapy.

46. The method of claim 45, wherein the additional therapy comprises surgery, radiation, gene therapy, immunotherapy, or hormone therapy.

47. The method of claim 45 or 46, wherein the additional therapy comprises one or more antibodies.

48. The method of any one of claims 33-47, wherein the cells are administered to the individual by injection, intravenously, intraarterially, intraperitoneally, intratracheally, intratumorally, intramuscularly, endoscopically, intralesionally, intracranially, percutaneously, subcutaneously, regionally, by perfusion, in a tumor microenvironment, or a combination thereof.

49. The method of any one of claims 33-48, further comprising the step of identifying CD70-positive cells in the individual.

50. The method of any one of claims 33-49, further comprising the step of producing the cells harboring the expression construct.

51. As a composition of matter, the sequences of SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13.